Gabapentin for Neuropathic Pain

An application to the 21st meeting of the WHO Expert Committee on Selection and Use of Essential Medicines for the inclusion of gabapentin on the WHO Model List of Essential Medicines

Submitted by

International Association for the Study of Pain (IASP)
Neuropathic Pain Special Interest Group (NeuPSIG) of the IASP
International Association of Hospice and Palliative Care (IAHPC)

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Contents

General items

Summary statement of the proposal for inclusion.

We are applying for the ***inclusion of gabapentin as an analgesic agent for the management of neuropathic pain (central and peripheral) in adults***. The medicine has regulatory approval for the treatment of several neuropathic pain states in adults by numerous stringent regulatory bodies (including the Food and Drug Administration [1] and European Medicines Agency [2]). Furthermore, all recent evidence-based treatment guidelines recommend gabapentin as one of the first-line agents for the pharmacological management of neuropathic pain of central or peripheral origin [3–6]. A recent systematic review estimated the prevalence of neuropathic pain in the general, adult population to be between 7 and 10% [7], equating to over 518 million prevalent cases of adults with neuropathic pain globally. And, in certain chronic diseases that already impose or are predicted to impose a high burden of disease in low and middle income countries, such as HIV-AIDS, diabetes mellitus, leprosy, and low-back pain, the prevalence of neuropathic pain can be more than three times the population prevalence [8–10]. In addition, low and middle income countries are disproportionally affected by acute traumatic injuries (e.g., conflict-related trauma, motor vehicle injuries) that may cause nerve damage [11]. Neuropathic pain has a major negative impact on health-related quality of life, and places a significant human and economic burden on health resources [12,13]. Neuropathic pain is difficult to treat, and requires specific classes of medication for its management. Evidence-based recommendations list three classes of medicines as first-line agents: tricyclic antidepressants (TCAs), $\alpha_2\delta$ calcium channel ligands (gabapentin and pregabalin), and serotonin and noradrenaline re-uptake inhibitors (SNRIs, duloxetine and venlafaxine). The number needed to treat (NNT) to achieve 50% pain relief non-attributable to placebo for these effective medications ranges between 4 and 9 [amitriptyline: 4.3 (95% CI: 3.6 to 5.3), gabapentin 6.3 (95% CI: 5.0 to 8.3)] [3,4,6]. Failure to respond adequately to initial monotherapy necessitates switching to another class of agent, or using combination therapy. Thus, management of neuropathic pain requires an adequate armamentarium of medications that have proven efficacy and may be used in combination. The WHO recently urged member states to ensure, *"the availability of essential medicines for the management of symptoms, including pain,"* and *"[the] education and training of healthcare professionals, in order to ensure adequate responses to palliative care needs."* [14]. Yet for neuropathic pain, the WHO Model List of Essential Medicines [15,16] is deficient in medicines with proven efficacy in treating neuropathic pain, such that only one medicine recommended as first-line therapy (amitriptyline) is included in the document. Of the other analgesics currently included in the Model List, evidence-based recommendations for neuropathic pain place morphine as third-line treatment, and non-streoidal anti-inflammatory drugs are not recommended at all. In addition, the WHO Model Formulary [17] is not consistent with current evidence-based critical analysis and guidelines on appropriate medications to use for treating neuropathic pain. These deficiencies are echoed in the national essential medicines lists of low and middle income countries [18]. Given its proven efficacy, good cost-utility, and global availability, we are therefore applying for inclusion of gabapentin as an additional treatment for neuropathic pain on the Model Essential Medicines List. *Please note that our request to include gabapentin is complementary to the continued inclusion of morphine and amitriptyline on the Model List; both these agents are essential components of the suite of pharmacological agents required for the management of pain.*

Name of the WHO technical department and focal point supporting the application (where relevant).

Dr Tarun Dua
Co-ordinator: Evidence, Research and Action on Mental and Brain Disorders (MER)
Department of Mental Health and Substance Abuse

Name of organization(s) consulted and/or supporting the application.

Proposing organizations

- International Association for the Study of Pain (IASP);
- Neuropathic Pain Special Interest Group (NeuPSIG) of the IASP;
- International Association for Hospice and Palliative Care (IAHPC)

Supporting organizations

(see Appendix 1 for copies of the letters of support)

- International Society for Physical and Rehabilitative Medicine (ISPRM)
- World Federation of Societies of Anaesthesiology (WFSA)
- World Medical Association (WMA)
- National Chapters of the IASP
  - American Pain Society
  - Asociación Chilena para el Estudio del Dolor [Chile]
  - Asociacion Dominicana para el Estudio y Tratamiento del Dolor y Cuidados Paliativos [Dominican Republic]
  - Asociación Istmeña para el Estudio del Dolor [Panama]
  - Australian Pain Society
  - Bangladesh Society for Study of Pain
  - Belgian Pain Society
  - British Pain Society
  - Chinese Association for the Study of Pain
  - Croatian Pain Society
  - Dutch Pain Society
  - German Pain Society
  - Hong Kong Pain Society
  - Indian Society for Study of Pain
  - Iranian Pain Society
  - Irish Pain Society
  - Lebanese Society for the Study of Pain
  - Lithuanian Pain Society

- Malaysian Association for the Study of Pain
- New Zealand Pain Society
- Österreichische Schmerzgesellschaft [Austria]
- Pain Society of the Philippines
- PainSA [South Africa]
- Professional Health Association – Pain Section, Kosovo
- Saudi Society of Pain Medicine
- Serbian Pain Association of Pain Research and Treatment
- Sociedad Española Del Dolor [Spain]
- Society for the Study of Pain, Nigeria
- Sri Lanka Association for the Study of Pain
- Thai Association for the Study of Pain

International Nonproprietary Name (INN) and Anatomical Therapeutic Chemical (ATC) code of the medicine.

Table 1: *Drug classification*

Taxonomic.system	Name
International Nonproprietary Name (INN)	Gabapentin
Anatomical Therapeutic Chemical (ATC)	N03AX12

Formulation(s) and strength(s) proposed for inclusion; including adult and paediatric (if appropriate).

Gabapentin is only approved for use in managing neuropathic pain in adults.[2]

Core List

- Solid oral dose forms (tablets and capsules): 100mg, 200mg, 300mg, 400mg, 600mg, 800mg

International availability

Table 2 lists countries, trade names, formulations, and manufacturers of gabapentin obtained from Martindale: The Complete Drug Reference [19] via Micromedex Solutions (Micromedex Inc., http://micromedex.com). The source listed 206 unique manufacturers of gabapentin across 42 countries, marketing the medicine under 241 proprietary names. Of these, 17 countries, 161 manufacturers, and 177 proprietary names were listed under countries classified as low or middle income countries by the International Monetary Fund [20].

[2] *While not approved for the management of neuropathic pain in children, gabapentin is approved for seizure control in children as young as three-years old, and has case reports and clinical consensus to support its use in neuropathic pain in children and youths.*

The 17 low and middle income countries where gabapentin was listed as being available constitute about 53% of the global population [21].

All listed products were for the tablet and capsule formulations of gabapentin.

Table 2: *International availability of gabapentin (low and middle income countries are highlighted)*

Country	Trade name	Available formulations	Manufacturer
Argentina	Abaglin	capsules / tablets	Teva Tuteur
Argentina	Alidial	capsules / tablets	Filaxis
Argentina	Arapentin	capsules / tablets	Ariston
Argentina	Elifer	capsules / tablets	Casasco
Argentina	Ganavan	capsules / tablets	Lafedar
Argentina	Logistic	capsules / tablets	Craveri
Argentina	Neurontin	capsules / tablets	Pfizer
Argentina	Ultraneural	capsules / tablets	Raffo
Australia	Gabacor	capsules / tablets	Pharmacor
Australia	Gabahexal	capsules / tablets	Sandoz
Australia	Gabaran	capsules / tablets	Ranbaxy
Australia	Gabatine	capsules / tablets	Aspen
Australia	Gantin	capsules / tablets	Pfizer
Australia	Neurontin	capsules / tablets	Pfizer
Australia	Nupentin	capsules / tablets	Alphapharm
Australia	Pendine	capsules / tablets	Alphapharm
Austria	Gabarex	capsules / tablets	Torrex
Austria	Gabatal	capsules / tablets	Pharmaselect
Austria	Neurontin	capsules / tablets	Pfizer
Belgium	Neurontin	capsules / tablets	Pfizer
Brazil	Gabaneurin	capsules / tablets	Sigma
Brazil	Neurontin	capsules / tablets	Pfizer
Brazil	Progresse	capsules / tablets	Biosintetica
Canada	Neurontin	capsules / tablets	Pfizer
Chile	Dineurin	capsules / tablets	Recalcine
Chile	Gabacross	capsules / tablets	Biocross
Chile	Gabex	capsules / tablets	Andromaco
Chile	Gabictal	capsules / tablets	Tecnofarma
Chile	Neugabin	capsules / tablets	Mepro
Chile	Normatol	capsules / tablets	Pfizer
Chile	Ritmenal	capsules / tablets	Sanitas
China	Die Li	capsules / tablets	Nhwa
China	Neurontin	capsules / tablets	Parke Davis
China	Pai Ting	capsules / tablets	Hengrui
China	Wei Nuo Ding	capsules / tablets	Guangdong
Czech Republic	Apo-Gab	capsules / tablets	Apotex
Czech Republic	Gabagamma	capsules / tablets	Worwag
Czech Republic	Gabalept	capsules / tablets	Pliva
Czech Republic	Gabanox	capsules / tablets	Sandoz
Czech Republic	Gabatem	capsules / tablets	Temapharm
Czech Republic	Gabator	capsules / tablets	Chiesi
Czech Republic	Gabenta	capsules / tablets	Stichting

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Czech Republic	Gordius	capsules / tablets	Gedeon Richter
Czech Republic	Grimodin	capsules / tablets	Egis
Czech Republic	Neurontin	capsules / tablets	Pfizer
Czech Republic	Nurabax	capsules / tablets	Ranbaxy
Denmark	Cenegab	capsules / tablets	Teva
Denmark	Desigaba	capsules / tablets	Tiefenbacher
Denmark	Gabadoz	capsules / tablets	Sandoz
Denmark	Gabalept	capsules / tablets	Hexal
Denmark	Gabalix	capsules / tablets	Ratiopharm
Denmark	Gabamed	capsules / tablets	Generics
Denmark	Gabanicht	capsules / tablets	Sandoz
Denmark	Gabaratio	capsules / tablets	Teva
Denmark	Gabastad	capsules / tablets	Stada
Denmark	Gabatifin	capsules / tablets	Generics
Denmark	Neuril	capsules / tablets	Alternova
Denmark	Neurontin	capsules / tablets	Pfizer
Denmark	Pentagab	capsules / tablets	Generics
Finland	Gabaseis	capsules / tablets	Masterfarm
Finland	Gabrion	capsules / tablets	Orion
Finland	Geabatan	capsules / tablets	Gea
Finland	Neuril	capsules / tablets	Alternova
Finland	Neurontin	capsules / tablets	Pfizer
France	Neurontin	capsules / tablets	Pfizer
Germany	Gabagamma	capsules / tablets	Worwag
Germany	GabaLich	capsules / tablets	Winthrop
Germany	Gabax	capsules / tablets	Temmler
Germany	Neurontin	capsules / tablets	Parke Davis
Greece	Belgabin	capsules / tablets	Alapis
Greece	Brilian	capsules / tablets	Gerolymatos
Greece	Gabantin	capsules / tablets	Iasis
Greece	Gabaront	capsules / tablets	Alet
Greece	Gabental	capsules / tablets	Pharmanel
Greece	Gabiton	capsules / tablets	Qualia
Greece	Gapenten	capsules / tablets	Aenorasis
Greece	Medivapom	capsules / tablets	Rafarm
Greece	Neurontin	capsules / tablets	Pfizer
Greece	Neuros	capsules / tablets	Santa
Greece	Pentin	capsules / tablets	Specifar
Greece	Peronten	capsules / tablets	Pharmathen
Greece	Seni-Ven	capsules / tablets	Integris
Hong Kong	Gabenil	capsules / tablets	Remedica
Hong Kong	Neurontin	capsules / tablets	Pfizer
Hong Kong	Vultin	capsules / tablets	Unison
Hungary	Gabagamma	capsules / tablets	Worwag
Hungary	Gordius	capsules / tablets	Gedeon Richter
Hungary	Grimodin	capsules / tablets	Egis
Hungary	Neuroba	capsules / tablets	Medico Uno
Hungary	Neurontin	capsules / tablets	Pfizer
India	Alcobal	capsules / tablets	Obsurge
India	Alnacob-G	capsules / tablets	Alna
India	Armet G	capsules / tablets	Armour

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India	Bigvin Forte	capsules / tablets	Bestochem
India	Capin-G	capsules / tablets	Kamakshi
India	Chiny-GP	capsules / tablets	Positif
India	Cobalvit-GT	capsules / tablets	Intra-Labs
India	Cobanerve-G	capsules / tablets	Invision
India	Cobaver-M	capsules / tablets	Evershine
India	Cobsa-G	capsules / tablets	Arvincare
India	Doloneuron	capsules / tablets	Pulse
India	Electa-GP	capsules / tablets	Positif
India	Encentin	capsules / tablets	East West
India	Encentin Plus	capsules / tablets	East West
India	Encentin-AM	capsules / tablets	East West
India	Encentin-M	capsules / tablets	East West
India	G-Care	capsules / tablets	H & Care
India	G-Neuro	capsules / tablets	Indoco
India	Gaba	capsules / tablets	Hanburys
India	Gaba-MC	capsules / tablets	Mediez
India	Gabacap	capsules / tablets	Zydus
India	Gabacent	capsules / tablets	Crescent
India	Gabafact	capsules / tablets	Medico
India	Gabalept	capsules / tablets	Micro
India	Gabaneuron	capsules / tablets	Aristo
India	Gabanez-M	capsules / tablets	Wintech
India	Gabantin	capsules / tablets	Sun
India	Gabastar M	capsules / tablets	Lupin
India	Gabata	capsules / tablets	Alkem
India	Gabatin	capsules / tablets	Neon
India	Gabator	capsules / tablets	Torrent
India	Gabator M	capsules / tablets	Torrent
India	Gabaz	capsules / tablets	Ritz
India	Gabil	capsules / tablets	Biocon
India	Gabin-M	capsules / tablets	Ind-Swift
India	Gabion-M	capsules / tablets	Zenon
India	Gabsoft-M	capsules / tablets	Elnova
India	Gaby	capsules / tablets	Siomond
India	Game	capsules / tablets	Dyota
India	Gamet	capsules / tablets	Constant
India	GBN-M	capsules / tablets	Xieon
India	Gelina-M	capsules / tablets	Aronex
India	Gentin	capsules / tablets	Psyco Remedies
India	Gentin-MC	capsules / tablets	Psyco Remedies
India	Gibi Forte	capsules / tablets	Triton
India	Gic-M	capsules / tablets	Vensat
India	Goben	capsules / tablets	CMG
India	Hyteron-M	capsules / tablets	Hos & Ins
India	Indcobal	capsules / tablets	Ind Biosciences
India	Magic-M	capsules / tablets	Vensat
India	Malzix-GB	capsules / tablets	Aamorb
India	Marinol-GB	capsules / tablets	Scoshia
India	Me-Gab	capsules / tablets	Sykocure
India	Mecobal-GB	capsules / tablets	Uniroyal

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India	Mecoday-G	capsules / tablets	Invision
India	Mecoriv-G	capsules / tablets	East African
India	Melife-G	capsules / tablets	Life Line
India	Mericobal-G	capsules / tablets	Merion
India	Methipas-GP	capsules / tablets	Daniel Pasteur
India	Mewin-GB	capsules / tablets	Winsome
India	Miko G	capsules / tablets	Genesis
India	Mokia-G	capsules / tablets	Orion
India	Motrin GB	capsules / tablets	Apotex
India	Mycovit-GB	capsules / tablets	Solitaire
India	Mygaba	capsules / tablets	Gentech
India	Neogaba	capsules / tablets	Symbiosis
India	Nervic-G	capsules / tablets	Unimarck
India	Nervicin-G	capsules / tablets	Cinerea
India	Nervimax-G	capsules / tablets	Cruise
India	Nervon-GM	capsules / tablets	Laksun
India	Nervoptin	capsules / tablets	Abbott
India	Nervuptin	capsules / tablets	Piramal
India	Nervz-G	capsules / tablets	Intas
India	Nerwin-GT	capsules / tablets	Arrowin
India	Neupent AF	capsules / tablets	Ranbaxy
India	Neuro-GM	capsules / tablets	Cyno
India	Neuroage GF	capsules / tablets	Allenge
India	Neurocap-G	capsules / tablets	Biosync
India	Neurogab	capsules / tablets	Emgen
India	Neuromas-G	capsules / tablets	Cosmas
India	Neuromed-GF	capsules / tablets	Daksh
India	Neurontin	capsules / tablets	Pfizer
India	Neuropill	capsules / tablets	Ordain
India	Neurotop-G	capsules / tablets	Novaduo
India	Nexcob-G	capsules / tablets	Nitro Cadineur
India	Novomine-GB	capsules / tablets	Novogen
India	NTOmec-G	capsules / tablets	Sanify
India	Nuroclad-GB	capsules / tablets	Symbiotic
India	Nurokind-G	capsules / tablets	Mankind
India	Nuthyl-GB	capsules / tablets	Zubit
India	Orogab-M	capsules / tablets	Rishab
Indonesia	Alpentin	capsules / tablets	Actavis
Indonesia	Epiven	capsules / tablets	Novell
Indonesia	Gabasant	capsules / tablets	Pyridam
Indonesia	Gabexal	capsules / tablets	Sandoz
Indonesia	Galepsi	capsules / tablets	Guardian
Indonesia	Ganin	capsules / tablets	Ferron
Indonesia	Nepatic	capsules / tablets	Kalbe
Indonesia	Neurontin	capsules / tablets	Pfizer
Indonesia	Repligen	capsules / tablets	Pharos
Indonesia	Sipentin	capsules / tablets	Mersifarma
Indonesia	Tineuron	capsules / tablets	Lapi
Ireland	Gabin	capsules / tablets	Rowex
Ireland	Gabture	capsules / tablets	Milpharm
Ireland	Neurontin	capsules / tablets	Pfizer

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Ireland	Neurostil	capsules / tablets	Teva
Ireland	Rangabax	capsules / tablets	Ranbaxy
Israel	Neurontin	capsules / tablets	Pfizer
Italy	Aclonium	capsules / tablets	SmithKline Beecham
Italy	Apentin	capsules / tablets	Biomedica
Italy	Gabexine	capsules / tablets	Chiesi
Italy	Neurontin	capsules / tablets	Pfizer
Italy	Semerial	capsules / tablets	Mediolanum
Italy	Yalipent	capsules / tablets	CT
Japan	Gabapen	capsules / tablets	Pfizer
Malaysia	Neurontin	capsules / tablets	Pfizer
Mexico	Aconeuba	capsules / tablets	Accord
Mexico	Bapex	capsules / tablets	Probiomed
Mexico	Blugat	capsules / tablets	Landsteiner
Mexico	Clozepaxel	capsules / tablets	Pisa
Mexico	Compulxine	capsules / tablets	Armstrong
Mexico	Darbentin	capsules / tablets	Darier
Mexico	Gabantin	capsules / tablets	Sun
Mexico	Gapridol	capsules / tablets	Psicofarma
Mexico	Gavindo	capsules / tablets	Merck
Mexico	Microleptin	capsules / tablets	Micro
Mexico	Neurontin	capsules / tablets	Pfizer
Mexico	Nopatic	capsules / tablets	Rayere
Mexico	Nyepzyl	capsules / tablets	Ultra
Mexico	Tremecox	capsules / tablets	Rimsa
Mexico	Tremepen	capsules / tablets	Rimsa
Mexico	Wermy	capsules / tablets	Wermar
Netherlands	Neurontin	capsules / tablets	Pfizer
Norway	Neurontin	capsules / tablets	Pfizer
New Zealand	Neurontin	capsules / tablets	Pfizer
New Zealand	Nupentin	capsules / tablets	Mylan
Philippines	Aforpen	capsules / tablets	Merck
Philippines	Calmpent	capsules / tablets	Lloyd
Philippines	Gabalept	capsules / tablets	Brown & Burk
Philippines	Gabalion	capsules / tablets	Stallion
Philippines	Gabapen	capsules / tablets	Shine
Philippines	Gabaron	capsules / tablets	Shin Poong
Philippines	Gabatin	capsules / tablets	InnoGen
Philippines	Gabatrex	capsules / tablets	Intas
Philippines	Gabix	capsules / tablets	Getz
Philippines	Garbapia	capsules / tablets	Daewoong
Philippines	Gonnaz	capsules / tablets	XL
Philippines	Neurontin	capsules / tablets	Pfizer
Philippines	Reinin	capsules / tablets	Medichem
Poland	Gabagamma	capsules / tablets	Worwag
Poland	Gabatem	capsules / tablets	Temapharm
Poland	Gabax	capsules / tablets	Norton
Poland	Neuran	capsules / tablets	Ranbaxy
Poland	Neurontin	capsules / tablets	Pfizer
Poland	Symleptic	capsules / tablets	SymPhar
Portugal	Anabix	capsules / tablets	Helm

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Portugal	Aneptir	capsules / tablets	Helm
Portugal	Gabacalma	capsules / tablets	Arrowblue
Portugal	Gabamox	capsules / tablets	Pentafarma
Portugal	Gatiraban	capsules / tablets	Mylan
Portugal	Mengaptrix	capsules / tablets	Helm
Portugal	Molnarux	capsules / tablets	Helm
Portugal	Neurontin	capsules / tablets	Pfizer
Russia	Convalis	capsules / tablets	Lekko
Russia	Egipentin	capsules / tablets	Egis
Russia	Eplyrontin	capsules / tablets	Micro
Russia	Gabagamma	capsules / tablets	Worwag
Russia	Gapentek	capsules / tablets	Actavis
Russia	Katena	capsules / tablets	Belupo
Russia	Lepsitin	capsules / tablets	Pliva
Russia	Neurontin	capsules / tablets	Pfizer
Russia	Tebantin	capsules / tablets	Gedeon Richter
South Africa	Epleptin	capsules / tablets	Litha
South Africa	Neurexal	capsules / tablets	Sandoz
South Africa	Neurontin	capsules / tablets	Pfizer
Singapore	Neurontin	capsules / tablets	Pfizer
Singapore	Nupentin	capsules / tablets	Alphapharm
Spain	Equipax	capsules / tablets	Parke Davis
Spain	Gabamerck	capsules / tablets	Merck
Spain	Gabatur	capsules / tablets	Cantabria
Spain	Gabmylan	capsules / tablets	Mylan
Spain	Neurontin	capsules / tablets	Parke Davis
Spain	Oxaquin	capsules / tablets	Rubio
Sweden	Neurontin	capsules / tablets	Pfizer
Switzerland	Gabantine	capsules / tablets	Spirig
Switzerland	Neurontin	capsules / tablets	Pfizer
Thailand	Gabantin	capsules / tablets	M & H
Thailand	Gabutin	capsules / tablets	Siam Bheasach
Thailand	Neurontin	capsules / tablets	Pfizer
Thailand	Neverpentin	capsules / tablets	Daewoong
Thailand	Rontin	capsules / tablets	Biolab
Thailand	Vultin	capsules / tablets	Unison
Turkey	As-Gabapen	capsules / tablets	Apotex
Turkey	Eveptin	capsules / tablets	Aset
Turkey	Gabaset	capsules / tablets	Biofarma
Turkey	Gabateva	capsules / tablets	Med
Turkey	Gabenyl	capsules / tablets	Bilim
Turkey	Gabtin	capsules / tablets	Zentiva
Turkey	Gemuda	capsules / tablets	Sanovel
Turkey	Nepitin	capsules / tablets	Ali
Turkey	Neruda	capsules / tablets	Sanovel
Turkey	Neurontin	capsules / tablets	Pfizer
Turkey	Patyca	capsules / tablets	Abdi
United Kingdom	Neurontin	capsules / tablets	Pfizer
Ukraine	Gabagamma	capsules / tablets	Worwag
Ukraine	Gabalept	capsules / tablets	Micro Labs
Ukraine	Gabantin	capsules / tablets	Pharma Start

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Ukraine	Gatonin	capsules / tablets	Teva
Ukraine	Meditan	capsules / tablets	Farmak
Ukraine	Tebantin	capsules / tablets	Gedeon Richter
USA	Gabarone	capsules / tablets	Ivax
USA	Gralise	capsules / tablets	Depomed
USA	Neurontin	capsules / tablets	Pfizer
Venezuela	Neurontin	capsules / tablets	Pfizer

Whether listing is requested as an individual medicine or as representative of a pharmacological class.

We are requesting the inclusion of gabapentin as an individual medicine.

Treatment details, public health relevance and evidence appraisal and synthesis

Treatment details (requirements for diagnosis, treatment and monitoring)

Diagnosis and monitoring

The diagnosis of neuropathic pain can be established using a history and clinical examination, and without the need for specialised equipment or facilities [22–24]. Figure 1 outlines the diagnostic process and how each step informs the level of diagnostic certainty [22]. Like the diagnosis, monitoring of treatment outcome can be performed without specialised equipment or facilities. Readily available clinical screening tools such as the Douleur Neuropathique en 4 questions (DN4), Leeds Assessment of Neuropathic Symptoms and Signs (LANSS), and painDETECT can be used to assist in diagnosing pain of neuropathic origin. These tools have been translated and validated into numerous languages [25].

Treatment

The information on treatment was obtained from regulatory documents available from the Food and Drug Administration (FDA) [1], and European Medicines Agency (EMA) [2] for Neurontin (gabapentin, Pfizer Inc). Full product information from both the FDA and EMA can be located in Appendix 4 and Appendix 5, respectively. Here we summarise key aspects of the aforementioned documents.

Dosage and administration

Usual dosage range:

- *Adults:* 900-1800mg/day in three divided doses.

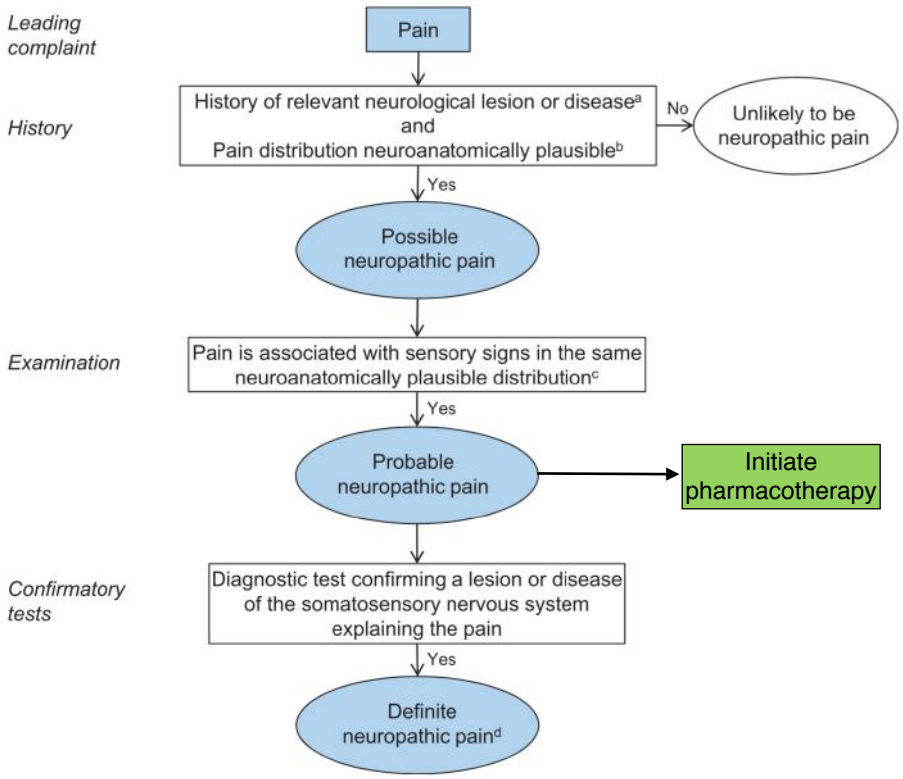

Figure 1: *Diagnosis and grading of diagnostic certainty of neuropathic pain. The level of "probable" is usually sufficient to initiate treatment according to neuropathic pain guidelines. The level "definite" is useful in specialist contexts and when a causal treatment of the underlying lesion or disease is an option.* [a] *History, including pain descriptors, the presence of non-painful sensory symptoms, and aggravating and alleviating factors, suggestive of pain being related to a neurological lesion. The suspected lesion or disease is reported to be associated with neuropathic pain, including a temporal and spatial relationship representative of the condition.* [b] *The pain distribution reported by the patient is consistent with the suspected lesion or disease.* [c] *The area of sensory changes may extend beyond, be within, or overlap with the area of pain. Sensory loss is generally required but touch-evoked or thermal allodynia may be the only finding at bedside examination.* [d] *The term "definite" in this context means "probable neuropathic pain with confirmatory tests". Adapted from: Finnerup et al., 2016 [22].*

- *Children:* Gabapentin is not approved for the management of neuropathic pain in children.

  We are cognisant of the lack of therapeutic choices for children, and that gabapentin is indicated for paediatric use for epilepsy by major regulatory bodies. But, while gabapentin has demonstrative evidence of tolerability and safety in children there is insufficient data on the use of the medicine for the treatment of neuropathic pain in children to draw evidence-based recommendations. Based on case-reports and expert consensus, doses from 15-50 mg/kg per day, in three or four divided doses, are recommended.

  A recent review of neuropathic pain in children provides an excellent summary of our knowledge of neuropathic pain and its treatment in children: *"The most common neuropathic pain conditions seen in adults are rare in children. Some neuropathic conditions are becoming increasingly recognized in children and adolescents, including complex regional pain syndromes, phantom limb pain, spinal cord injury, trauma and postoperative neuropathic pain, autoimmune and degenerative neuropathies (eg, Guillain-Barré syndrome, Charcot-Marie-Tooth disease), and the effects of cancer disease processes and treatment. Some neuropathic pain syndromes are relatively unique to the pediatric population, including toxic and metabolic neuropathies (eg, lead, mercury, alcohol, infection), hereditary neurodegenerative disorders (eg, Fabry disease), mitochondrial disorders, and primary erythromelalgia. All these cause significant suffering to children and their caregivers and steps need to be taken to alleviate this suffering. In some countries, gabapentin has been approved for the use of paediatric neuropathic pain. However, the amount of evidence available on the effectiveness and safety of gabapentin in pediatric neuropathic pain is too weak for the authors to make a recommendation at this time. Additional studies are recommended and needed."* [26].

  Unfortunately, the evidence-base for treatments of neuropathic pain in children has not advanced significantly since the writing of the review. But hopefully if recent activity in this area continues [27], the evidence for the use of gabapentin for neuropathic pain in children can be reassessed for future editions of the Essential Medicines List for Children.

Treatment typically is started at 300mg once daily, escalating by 300mg per day until reaching 900mg daily (t.i.d). Thereafter, if required, the dose can be increased in 300mg/day increments every 2 to 3 days up to a maximum dose of 1800mg/day. Gabapentin can be administered with or without food, and should be swallowed whole with sufficient fluid (e.g. a glass of water).

Any additional benefit of increasing the dose past 1800mg/day (up to 3600mg/day) has not been demonstrated. In clinical trials, the clinical effect (separation from placebo) typically was evident by the end of first week of treatment.

If the gabapentin dose is reduced or discontinued the dose should be gradually reduced over a minimum of one week.

Special populations

Dosing adjustments and risk-benefit assessments are required in the following populations: individuals with renal impairment, older persons, and pregnant and nursing women. Although no formal studies have been conducted, neither sex, race, nor hepatic impairment have been reported to affect the pharmacokinetics of gabapentin.

Pharmacokinetics

Gabapentin bio-availability is not dose proportional, such that bio-availability decreases as dose increases. Less than 3% of gabapentin circulates bound to plasma protein, and it is eliminated from the systemic circulation by renal excretion as an unchanged molecule.

Long-term use and overdose

The efficacy and safety of gabapentin has not been examined in clinical studies for treatment periods longer than five months, and the treating physician should assess the patient's clinical status and need should longer periods of treatment be required.

Acute oral overdoses of gabapentin up to 49,000mg have been reported, and in all cases patients recovered with supportive care. Coma, resolving with dialysis, has been reported in patients with chronic renal failure who were treated with gabapentin.

Drug interactions

In vitro studies indicate that gabapentin has no or negligible effect on major cytochrome P450 enzymes, while *in vivo* interaction studies for gabapentin showed no interaction with: carbamazepine, naproxen, phenobarbital, phenytoin, probenecid, valproic acid, and zolpidem.

Nor does gabapentin have any known interactions with treatments recommended for:

- HIV infection in adults or children (lamivudine, abacavir, zidovudine, tenofovir, stavudine, lopinavir/ritonavir, darunavir, dolutegravir, efavirenz, emtricitabine, nevirapine) [28]
- tuberculosis infection (isoniazid, rifampicin, streptomycin, ethambutol, pyrazinamide) [29],
- diabetes mellitus (insulin, metformin, sulfonylureas) [14].
- malaria (amodiaquine, artemether/lumefantrine, artesunate, dihydroartemisinin, meoquine, piperaquine, sulfadoxine–pyrimethamine) [30]
- leprosy (clofazimine, dapsone, minocycline, ofloxacin, rifampicin) [31]

Gabapentin has been shown to interact with: antacids, cimetidine, felbamate, hydrocodone, morphine, and oral contraceptives.

Substance abuse and dependence

Gapentin in not an internationally controlled medication.

The dependence and abuse potential of gabapentin has not been formally evaluated in human studies.

Abuse: Gabapentin does not exhibit affinity for benzodiazepine (GABA), opioid, or cannabinoid-1 receptor sites. A small number of post-marketing cases report gabapentin

misuse and abuse. The FDA recommendation is consistent with a review of the literature by Schifano [32], which concluded that the risk of misuse of $\alpha_2\delta$ calcium channel ligands is low when the agents are administered at therapeutic doses to individuals with no history of substance misuse.

Dependence: There are rare post-marketing reports of individuals experiencing mild withdrawal symptoms shortly after discontinuing higher than recommended doses of gabapentin used to treat illnesses for which the medicine is not approved.

Increased seizure frequency may occur in patients with seizure disorders if gabapentin is abruptly discontinued

Guideline recommendations

We are unaware of any WHO guidelines for the treatment of neuropathic pain, but several reputable organizations that are independent of the WHO have developed evidence-based guidelines. These include:

- Pharmacotherapy for Neuropathic Pain in Adults: A Systematic Review and Meta-analysis, Association for the Study of Pain (IASP) [3] *(Please note that N Finnerup, S Haroutounian, PR Kamerman, SN Raja, ASC Rice and BH Smith were involved in the development of this guideline)*;
- Neuropathic Pain: The Pharmacological Management of Neuropathic Pain in Adults in Non-Specialist Settings, National Institute for Health and Care Excellence (NICE), UK [4];
- EFNS Guidelines on the Pharmacological Treatment of Neuropathic Pain: 2010 Revision, European Federation of Neurological Societies [6].

All three guidelines agree that tricyclic antidepressants, $\alpha_2\delta$ calcium channel ligands (gabapentin and pregabalin), and selective serotonin and noradrenaline re-uptake inhibitors should be considered first-line therapy. With the choice of medicine being guided by clinical and therapeutic factors (e.g., contraindications, interactions), and medicine availability and affordability.

Information supporting the public health relevance

Neuropathic pain is defined as *"Pain caused by a lesion or disease of the somatosensory nervous system"* [33,34]. It is commonly associated with back pain (e.g., lumbar or cervical radiculopathy), diabetes (painful diabetic neuropathy), post-surgical pain, HIV-AIDS, and herpes zoster (post-herpetic neuralgia), but can also arise through many other diseases or injuries. Specific clinical features include symptoms such as paraesthesia, burning or shooting pains, altered sensation (numbness, allodynia or hyperalgesia), and locally altered autonomic function [35].

In the absence of a 'gold standard' for defining cases and a clinical code for routine healthcare use, it is impossible to identify the precise prevalence of neuropathic pain, for example through the Global Burden of Disease 2013 study [36]. However, a recent systematic review

found that between 7 and 10% of the adult population are affected by pain with neuropathic characteristics (identified through validated questionnaires) [7]. With a global population of approximately 7.4 billion people, this means that some 518 to 740 million individuals are estimated to currently be affected by neuropathic pain. This includes (but is not restricted to) people with:

- diabetes mellitus (410 million prevalent cases globally, increasing by 133% since 1990 [36], and projected to rise further [37]). Approximately 26% of those with diabetes mellitus have painful polyneuropathy [7,38], equating to 107 million individuals. Figure 2 shows estimates and projected prevalence data for diabetes mellitus from 1985 to 2030 [37,39], with the estimated number of coincident cases of painful polyneuropathy [40].

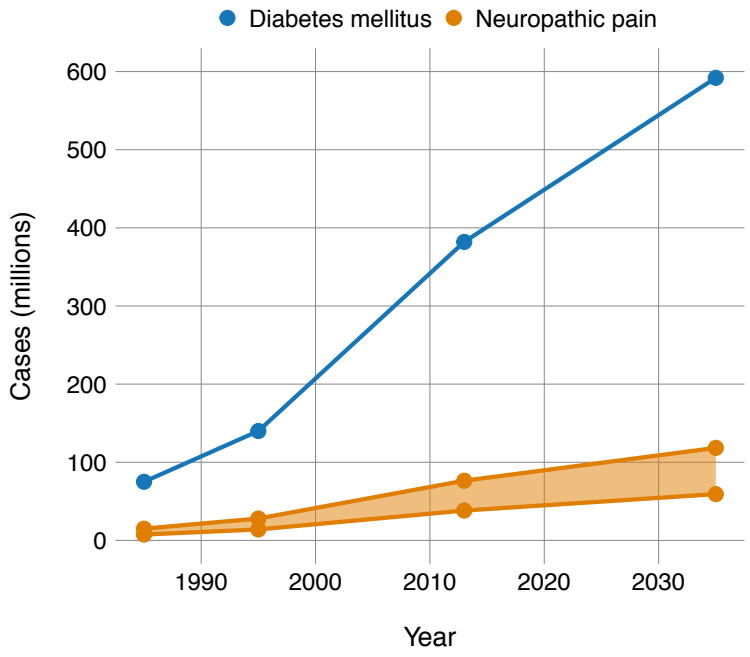

Figure 2: *Estimated and projected number of cases of diabetes mellitus (blue) between 1985 and 2035, and the number of cases of painful diabetic polyneuropathy (orange) over the same period based on conservative estimates of between 10 and 20% of individuals with diabetes developing a painful neuropathy. Data sources: [37,39,40].*

- HIV/AIDS (29 million prevalent cases globally, increasing by 275% since 1990 [36]). Approximately 35% of people with HIV/AIDS have painful neuropathy [8], equating to 10 million individuals. The incidence [41,42] and prevalence [43] of the neuropathy has decreased since the introduction of newer antiretroviral regimens that forego neurotoxic medicines such as stavudine, but remains high [44].
- Chronic low back pain (651 million prevalent cases globally, increasing by 57% since 1990 [36]). Approximately 37% of those with chronic low back pain have been shown to experience neuropathic pain [45], equating to 228 million individuals;

Trauma also a major cause of nervous system injury, and hence neuropathic pain. Data from the Global Burden of Disease initiative indicate that physical injury is more common in low and middle income countries than in high income countries [36], and thus those with the least

resources are likely to face a greater burden of trauma-related neuropathic pain. This greater burden is superimposed on the already greater risk for neuropathic pain in these regions associated with increasing prevalence of diabetes, and a disproportionate share of conditions such as HIV/AIDS and leprosy (Figure 3).

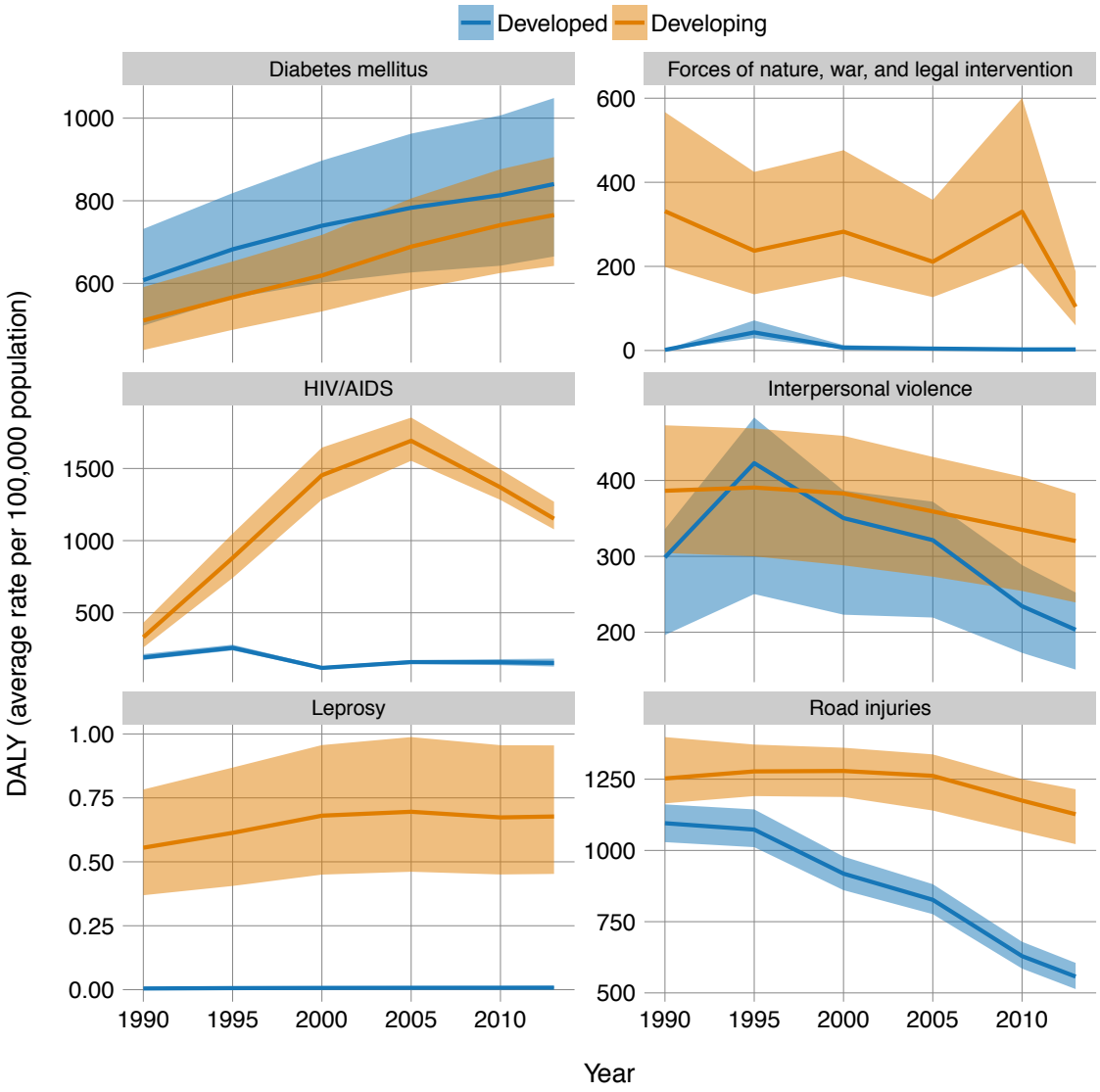

Figure 3: *Disability Adjusted Life Years (DALY) in high income (orange), and low and middle income (blue) countries associated with diabetes mellitus, HIV/AIDS, leprosy, road injuries, interpersonal violence, and forces of nature, war, and legal intervention for the period 1990 and 2013. The shaded areas show uncertainty estimates. Data were downloaded from Global Health Data Exchange: GHDx on 20 July 2016.*

Older age is one of the most important risk factors for neuropathic pain [46]. The ageing population worldwide, as well as the separate rising prevalence of underlying conditions such as diabetes mellitus [36,37] mean that neuropathic pain is likely to increase in prevalence and importance in the future.

Neuropathic pain has a significant adverse impact on all measured aspects of life, health and function [47]. This impact is greater than the impact of chronic, non-neuropathic pain, even when adjusting for pain intensity [48], and is irrespective of the underlying diagnosis [12]. In one study, 17% of people reporting neuropathic pain rated their quality of life as ‘worse

than death', according to the validated EQ5D measure [13]. Average quality of life scores in the presence of neuropathic pain are comparable to those in severe depression, in poorly-controlled DM, and after recent myocardial infarction [48].

In general, neuropathic pain responds poorly to treatment with conventional analgesics (there is no evidence for effectiveness of medicines such as non-steroidal anti-inflammatory drugs [49]), and specific classes of medication are required. Gabapentin is recommended as a first-line treatment for neuropathic pain in many national and international guidelines [3–6,50]. Tricyclic antidepressants (TCAs) are also recommended first-line treatments in these guidelines, and are already widely available, and cheaper than gabapentin [18]. The target population for gabapentin use is therefore all those with neuropathic pain who have not responded, or not responded sufficiently to TCAs, or for whom TCAs are contra-indicated (e.g., glaucoma, cardiovascular disorders, epileptic seizures, symptomatic urinary retention associated with benign prostatic hypertrophy, poly-pharmacy) or not tolerated. The target population excludes those in whom gabapentin is contraindicated (e.g., in renal failure) or have a known intolerance to gabapentin.

The effectiveness of medicines used in neuropathic pain was recently reviewed systematically and comprehensively [3]. In this study, gabapentin (excluding extended release preparations and the pro-drug enacarbil) had a demonstrated number needed to treat (NNT) of 6.3 to achieve at least 50% reduction in pain severity scores relative to placebo. If, as above, 518 million people have neuropathic pain worldwide, the use of gabapentin will potentially lead to this successful treatment outcome for around 82 million people. Excluding the 144 million people who could potentially achieve 50% reduction in pain from TCAs (with an NNT of 3.6 [3], there remain approximately 59 million individuals who could potentially achieve this outcome from gabapentin.

The actual number who could benefit will be higher because (a) many more will achieve important reductions in pain severity, though less than 50%; (b) TCAs are contraindicated in many people – for example, they are not recommended for use in older adults [51]; (c) combination of gabapentin and TCA are effective and recommended [4,5]; and (d) these NNTs are calculated after adjusting for placebo and other non-specific effects, so the actual effectiveness is greater than they suggest.

Our review of national essential medicine lists for medications recommended as first- or second-line treatments for neuropathic pain[3] identified that most countries reviewed only had one class of first-line treatment listed (typically a TCA), and about 40% had no second-line treatments listed (Figure 4. Of the countries listing two or more first-line medications, the most commonly listed agent was gabapentin (30% of all countries) [18]. Most of the countries did, however, list morphine (95%), a medication on the Model List with evidence supporting its use in the treatment of neuropathic pain. But, the evidence supporting the use of morphine and other strong opioids in neuropathic pain is of low quality [6,52], and this information, together with questions about the safety of strong opioids (e.g., high rates of adverse effects and study withdrawal due to adverse effects, and dependency concerns) means that strong opioids typically are recommended as third-line treatments for neuropathic pain [3,4,6]. Thus, most of the 104 low and middle income countries' essential medicine lists had a very limited scope of first- and second-line treatments for neuropathic pain. This limitation is counter to WHO Resolution EB134.R7 of 2014 [14], which urges member states to ensure, *"the availability of*

[3] First-line medications include: tricyclic antidepressants (TCAs), $\alpha_2\delta$ calcium channel ligands (gabapentin and pregabalin), and serotonin and noradrenaline re-uptake inhibitors (SNRIs, duloxetine and venlafaxine); second-line medications include: tramadol, 8% capsaicin patch, and 5% lidocaine patch. From: Finnerup et al. 2015 [3].

essential medicines for the management of symptoms, including pain,", as well as the United Nations Sustainable Development Goal 3.8 which advocates for, *"access to safe, effective, quality and affordable essential medicines and vaccines for all"* [53,54].

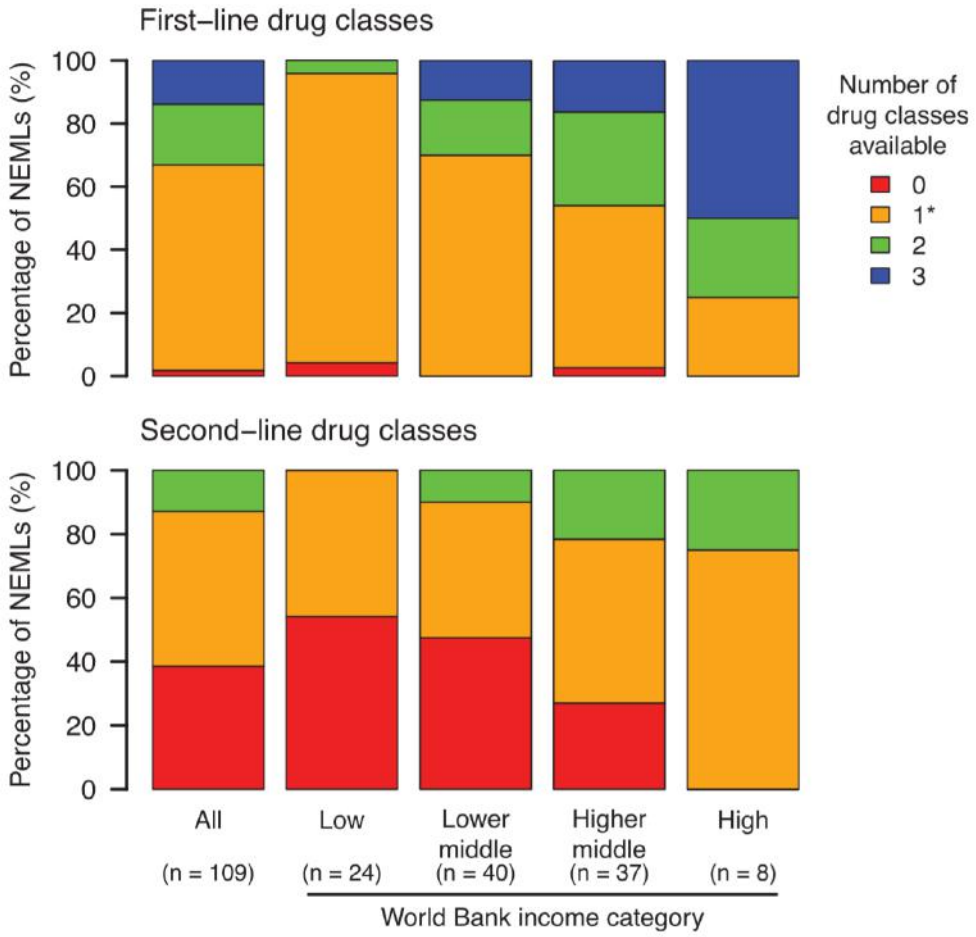

Figure 4: *Percentage of national essential medicine lists (NEMLs) that included 0, 1, 2, or 3 medicine classes recommended for the treatment of neuropathic pain. Data are shown grouped according to World Bank income category and for all countries (n = 109, data from the Cook Islands, Nauru, and Niue were not included because the World Bank does not index them). The top panel shows medicine-classes recommended as first-line treatment, and the bottom panel shows second-line medicine classes. First-line medicine classes include: tricyclic antidepressants, serotonin and noradrenaline re-uptake inhibitors, and $\alpha 2\delta$ calcium channel ligands. Second-line medicine classes include: tramadol (weak opioid), 8% capsaicin patch, and 5% lidocaine patch (topical agents). There was a positive association between income category and the number of first-line and second-line medicine classes listed on NEMLs (corrected $P < 0.001$). $*$ The tricyclic antidepressant amitriptyline was the only first-line medicine listed on the NEMLs of 32% of low-income countries, 36% of lower-middle income countries, 28% of higher-middle income countries and 4% of high-income countries. From: Kamerman et al., 2015 [18].*

Review of benefits: summary of comparative effectiveness in a variety of clinical settings.

The treatment of neuropathic pain is pharmacologically based as there is scant evidence from high-quality placebo-controlled trials supporting the use of invasive procedures [55] or psy-

chological or behaviour-based therapies.

For pharmacological interventions, the evidence supporting this application is based upon our recent systematic review, meta-analysis and GRADE-based clinical guideline formulation [3]. The systematic review of the literature used a standardised review and data extraction protocol *(for the full protocol and detailed results see: Finnerup et al., 2015 [3]; Appendix 2):*

- Full reports of randomized, controlled, double-blind studies published in peer-reviewed journals between January, 1966, and April, 2013, were identified by searches of PubMed, Medline, the Cochrane Central Register of Controlled Trials, and Embase. An additional search up to Jan 31, 2014, retrieved papers from PubMed. Additional papers were identified from published reviews and the reference lists of selected papers.
- To identify unpublished trials, studies reporting results were searched in all primary registries in the WHO Registry Network and in registries approved by the International Committee of Medical Journal Editors in April, 2013. Only ClinicalTrials.gov had relevant data. An additional search up to Jan 31, 2014, retrieved studies the ClinicalTrials.gov website. Data from a search in May, 2009, of the Pharmaceutical Research and Manufacturers of America (PhRMA) clinical study results website were also included.
- For the purposes of this application a supplementary search of PubMed was conducted on February 26, 2016. Search terms included: *[medicine name]* pain (randomised or randomized); neuropathic pain and (randomised or randomized); neuralgia and (randomised or randomized); neuropathy pain and (randomised or randomized); not neuropathic. Figure 5 shows the combined flow chart for study selection from the original search and the update.

The target population was patients of any age with neuropathic pain according to the International Association for the Study of Pain definition (i.e., pain caused by a lesion or disease of the somatosensory nervous system) [33]:[4]

The interventions considered were systemic or topical treatments (oral, sublingual, oropharyngeal, intranasal, topical, subcutaneous, intradermal, and smoking) with at least 3 weeks of treatment. Single-administration treatments with long-term efficacy (high-concentration capsaicin 8% patches, botulinum toxin) were included if there was a minimum follow-up of 3 weeks. Studies in which intramuscular, intravenous, or neuroaxial routes of administration were used and those of pre-emptive analgesia were excluded.

We included randomized, double-blind, placebo controlled studies with parallel group or crossover study designs that had at least ten patients per group. We separately summarised enriched-enrolment, randomized withdrawal trials. We excluded studies published only as abstracts and included double-blind, active comparator trials of medicines generally proposed

[4] Post-herpetic neuralgia, diabetic and non-diabetic painful polyneuropathy, post-amputation pain, post-traumatic or post-surgical neuropathic pain including plexus avulsion and complex regional pain syndrome type II (which was generally subsumed into post-traumatic or post-surgical neuropathic pain), central post-stroke pain, spinal cord injury pain, and multiple-sclerosis-associated pain. Neuropathic pain pertaining to different causes was also included. Neuropathic pain associated with nociceptive components (e.g., neuropathic cancer-related pain and radiculopathy) was included if the primary outcome of the study was related to neuropathic pain. Disorders such as complex regional pain syndrome type I, low-back pain without radicular pain, fibromyalgia, and atypical facial pain were not included because they do not meet the current definition of neuropathic pain. Trigeminal neuralgia was assessed separately because the response to pharmacological management is generally distinct from other neuropathic pains.

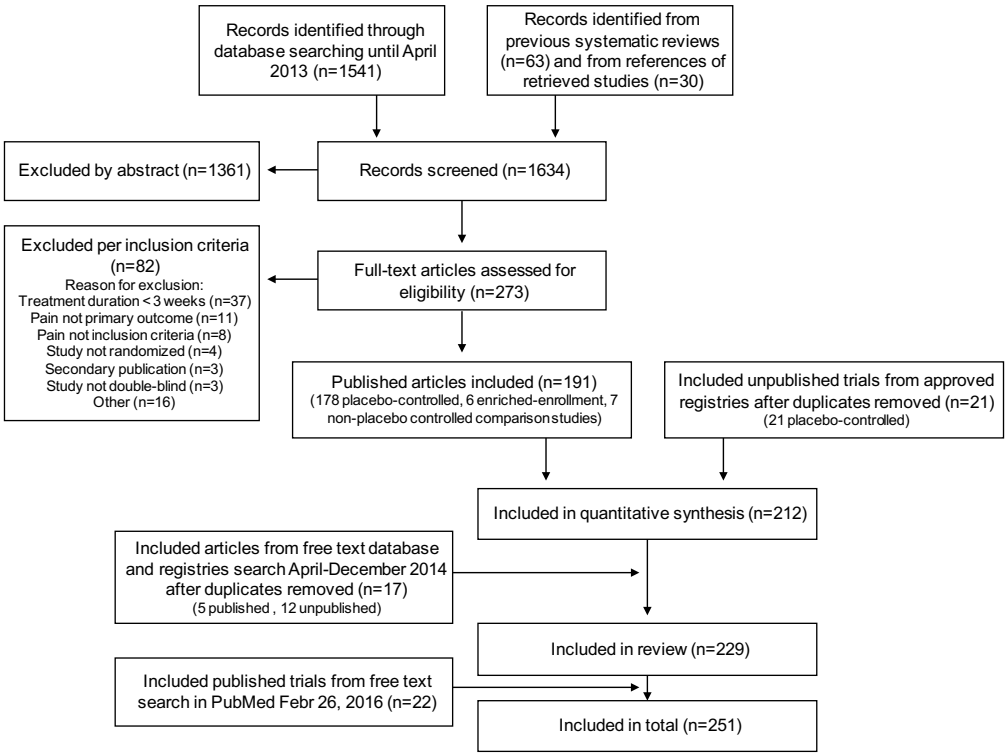

Figure 5: *Flow chart of study selection. Updated from Finnerup et al., 2015 [3] on 26 February 2016.*

as first-line or second-line treatments. The study outcome (positive or negative) was based on the effect on the primary outcome measure (i.e, neuropathic pain intensity). **We excluded studies in which the primary outcome measure was not pain**, including those studies that used a composite score of pain and paraesthesia or paraesthesia only (e.g., Rao et al., 2007 DOI: 10.1002/cncr.23008).

Studies were assessed for methodological quality by using the five-point Oxford Quality Scale [56]. A minimum score of 2 of 5 (randomized and double-blind study) was required for inclusion [56]. We also assessed the serious risk of bias relating to absence of allocation concealment, incomplete accounting of outcome events, selective outcome reporting, stopping early for benefit, use of invalidated outcome measures, carry-over effects in crossover trials, and inadequate sample size. We followed the 23-item Appraisal of Guidelines for Research and Evaluation (AGREE II) for developing and reporting recommendations [57].

Number needed to treat (NNT) for 50% pain intensity reduction (or 30% pain reduction or at least moderate pain relief), calculated using the fixed-effects Mantel-Haenszel method, was the primary effect measure. NNT and NNH were calculated as the reciprocal values. Susceptibility to risk of publication bias was assessed by funnel plots [58], Egger's regression [59], and Duval and Tweedie's non-parametric trim-and-fill approach [60]. Heterogeneity in trials was presented as a L'Abbé plot [61] and as the Iˆ2 statistic, and heterogeneity, particularly that which was not easily explained by differences in medicine dose, diagnosis, and size of placebo response, was included in the GRADE recommendation.

Evidence summary and reporting

The GRADE classification system was used to summarise the evidence and formulate clinical guidelines [62,63] with final quality of evidence rated as strong or weak from the summary of available data (appraisal of quality, outcome measures, summary of results).

A total of 229 reports, across a number of agents, were included in the published meta-analysis [3].[5] One hundred and twenty-seven (55%) of 229 trials were in patients with diabetic painful polyneuropathy or post-herpetic neuralgia. NNT could be calculated in 176 (77%) of 229 published placebo-controlled trials.

The mean Oxford Quality Scale (Jadad) score was 4.1 (SD: 0.87, range: 2 to 5). Funnel plots and Egger regression identified asymmetry. Computing theoretical missing studies using the *'trim-and-fill'* method suggested about a 10% overstatement of treatment effects across all medicines assessed in the meta-analysis [Figure 6; 34 theoretical missing studies, which adjusted the effect size from an odds ratio of 1.8 (95% CI 1.7 to 1.9), to 1.6 (95% CI: 1.5 to 1.7)]. Susceptibility to bias analysis of individual medicines/medicine classes confirmed that publication bias was unlikely to be a major confound of this evidence (Figure 7).[6]

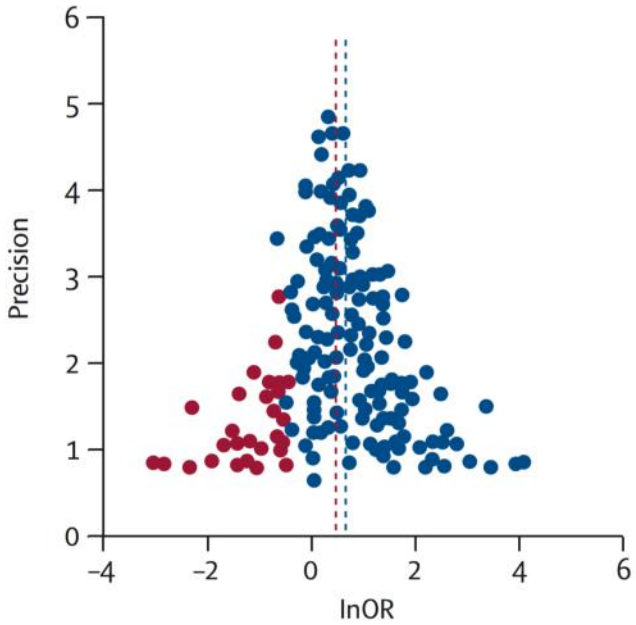

Figure 6: *Funnel plot showing the precision (inverse of standard error) against the effect size (natural log of the odds ratio, LnOR). Blue circles are individual studies. Missing studies imputed by trim and fill are shown in red. The blue vertical line indicates the uncorrected estimate of the effect size, while the red vertical line indicates the possible summary if the theoretical missing studies included. Adapted from: Finnerup et al., 2015 [3].*

Using the GRADE process, we identified that tricyclic antidepressants (TCAs; mainly

[5] Tricyclic antidepressants (TCAs), serotonin-noradrenaline re-uptake inhibitor antidepressants (SNRIs), other antidepressants, pregabalin, gabapentin or gabapentin extended release and enacarbil, other anti-epileptics, tramadol, opioids, cannabinoids, lidocaine 5% patch, capsaicin high concentration patch and cream, botulinum toxin A, NMDA antagonists, mexiletine, miscellaneous topical treatments, newer systemic medicines, and combination therapies.

[6] The grouping of gabapentin with gabapentin extended release /enacarbil and the updating of the literature in February 2016 means that NNT data reported in Figure 7 are not directly comparable to those reported elsewhere in the document.

	Comparisons*	Participants†	Active pain relief	Placebo	Number needed to treat (95% CI)	Susceptibility to bias‡
Tricyclic antidepressants	15	948	217/473	85/475	3·6 (3·0–4·4)	1973
Serotonin-noradrenaline reuptake inhibitors	10	2541	676/1559	278/982	6·4 (5·2–8·4)	1826
Pregabalin	25	5940	1359/3530	578/2410	7·7 (6·5–9·4)	2534
Gabapentin§	14	3503	719/2073	291/1430	7·2 (5·9–9·1)	1879

Figure 7: *Analysis of susceptibility to bias in published and unpublished trials. Data are number, unless otherwise indicated. ∗ Number of comparisons with placebo in published trials and unpublished trials included in the meta-analysis; results from registries were included if they reported numbers of responders. † Total number of patients treated with active treatment and placebo; patients were counted twice if the study had a crossover design. ‡ Number of patients needed to be treated in a new study showing no effect to make the number needed to treat (NNT) greater than 11, which is the cut-off for clinical relevance; susceptibility to publication bias implies that a new study with fewer than 400 participants with no effect might increase the NNT to greater than 11. § Includes gabapentin extended release and enacarbil. NNT was calculated for 50% pain intensity reduction (or 30% pain reduction or at least moderate pain relief where 50% relief were not available). Adapted from: Finnerup et al., 2015 [3].*

amitriptyline),[7] serotonin–adrenaline re-uptake inhibitors (SNRIs; mainly duloxetine),[8] pregabalin[9] and gabapentin could be considered as first-line medicines (Figure 8, and Figure 9). Amitriptyline, a TCA, already features strongly on the WHO Model List of Essential Medicines, and shares its analgesic mechanism of action with other TCAs and SNRIs. Accordingly, all TCAs and SNRIs are contraindicated for use with each other, and this contraindication precludes combination therapy with these medications should patients not respond adequately to monotherapy. Because of the incompatibility of these first-line medicine classes, the evidence-base for the use of TCAs and SNRIs is not evaluated further in this section of the application.[10] Instead, we provide updated information (based on our supplementary search in February 2016) only on the efficacy of the $\alpha 2\delta$ calcium channel ligands gabapentin and pregabalin. This class of medicines is not contraindicated for use with TCAs or SNRIs, and so may be used alone or in combination therapy with the other two first-line classes of medications, as well as recommended second- and third-line therapies *(note: morphine increases the AUC of gabapentin)*. Indeed, combinations therapy is often used in the management of neuropathic pain in clinical practice [65], and using two or more agents with proven efficacy, and which have complementary actions, has the potential to enhance efficacy and reduce side effects (through lower dosing of the individual agents) [66]. Only a few high-quality clinical trials of combination therapy for neuropathic pain have been conducted, and therefore GRADE evaluation was inconclusive [3]. Nevertheless, Gilron and colleagues reported that gabapentin used in combination with nortriptyline [67] or morphine [68] achieved better efficacy and at lower doses than when the agents were used as monotherapy. Thus, the ability to use gabapentin together with the the other classes of evidence-based pharmacological therapies, provides clinicians with the scope to trial empirical combination therapy should monotherapy fail.

Updated evidence-base for $\alpha 2\delta$ calcium channel ligands

Pregabalin

Eight new reports were identified in the 2016 supplementary search of which one was an enriched-enrolment trial and five provided dichotomous data for NNT calculation. In a mixed peripheral neuropathy population, Holbech and colleagues [69] showed modest analgesic effects for pregabalin (300mg/day) versus placebo and Liu et al 2015 [70] found an effect in PHN. The other studies (Simpson et al 2014 [71], Huffman et al. 2015 [72], Raskin et al. 2016 [73], Chappell et al. 2014 [74], and Ziegler et al. 2015 [75]) failed to find an effect of pregabalin in painful polyneuropathy due to diabetes or HIV. All the negative studies except the study in HIV neuropathy [71] used a 300mg daily dose of pregabalin. In total, 32 randomized controlled trials of pregabalin for neuropathic pain were identified after our updated search.

[7] In 18 placebo-controlled trials [20 comparisons with placebo, of which seven comparisons had active placebos; 12 trials assessed amitriptyline (25–150mg/day)], 16 comparisons were positive. The final quality of evidence was moderate (Appendix 2). There was no evidence of a dose-response effect. Combined NNT for 15 studies was 3.6 (95% CI: 3.0 to 4.4).

[8] 14 studies of serotonin-noradrenaline re-uptake inhibitors with available results: nine with duloxetine (20–120 mg, seven positive), four with venlafaxine (doses 150–225 mg/day, two positive, and two negative with low doses), one with venlafaxine (negative; Appendix 2). The final quality of evidence was high. Combined NNT was 6.4 (95% CI: 5.2 to 8.4).

[9] 18 of 25 placebo-controlled randomized trials of pregabalin (150–600mg/day) were positive, with high final quality of evidence (Appendix 2). There was a dose response gradient (higher response with 600mg daily than with 300mg daily; data not shown). Combined NNT was 7.7 (95% CI: 6.5 to 9.4). The combined NNT is 8.8 (95% CI: 7.5 to 10.8) when the 5 new studies identified in the 2016 search are included.

[10] The supplementary literature search in 2016 identified one new report on amitriptyline: Dinat et al., 2015 [64]. Dinat and colleagues compared amitriptyline and placebo in HIV-associated sensory neuropathy, and the outcome, which was associated with high placebo responses, was negative for amitriptyline.

	First-line drugs		
	Serotonin-noradrenaline reuptake inhibitors duloxetine and venlafaxine	Tricyclic antidepressants	Pregabalin, gabapentin, gabapentin extended release or enacarbil
Quality of evidence	High	Moderate	High
Balance between desirable and undesirable effects			
Effect size	Moderate	Moderate	Moderate
Tolerability and safety*	Moderate	Low-moderate	Moderate-high
Values and preferences	Low-moderate	Low-moderate	Low-moderate
Cost and resource allocation	Low-moderate	Low	Low-moderate
Strength of recommendation	Strong	Strong	Strong
Neuropathic pain conditions	All	All	All

Figure 8: *Summary of the GRADE recommendations by Finnerup et al., 2015 [3] for first-line medications for managing neuropathic pain.*

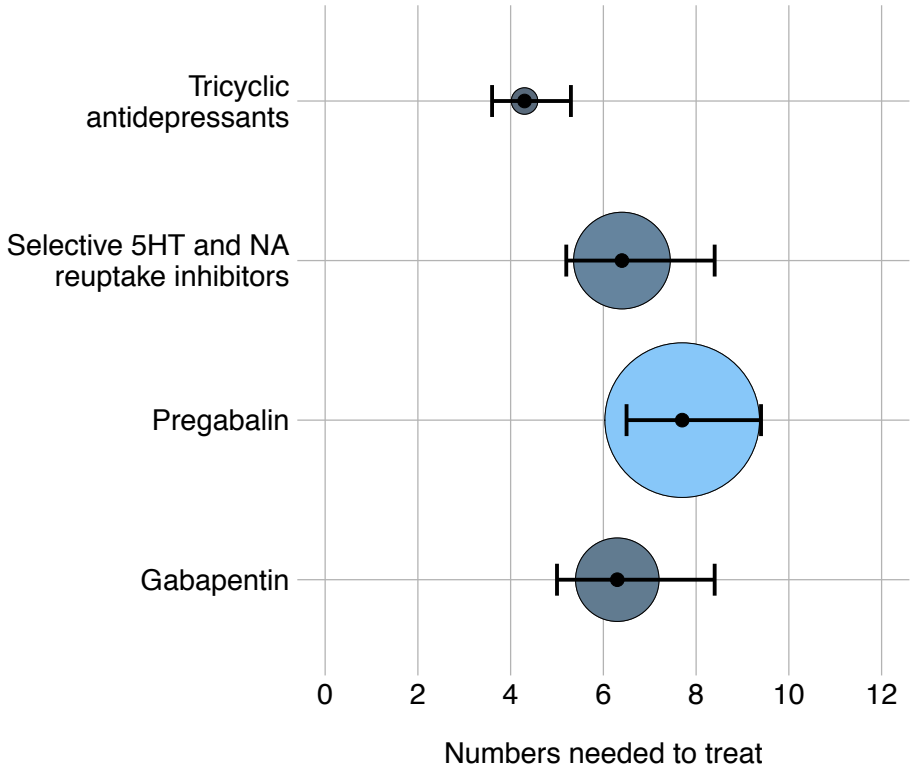

Figure 9: *Mean (95% CI) numbers needed to treat (NNT) for first-line medications recommended by Finnerup et al., 2015 [3]. The size of the coloured circles indicate the relative number of individuals randomized in trials for a particular medication. Data from Finnerup et al., 2015 were updated to include two new trials in the tricyclic antidepressant class, and gabapentin extended release and enacarbil were excluded from the gabapentin group.*

Thirty of these studies provided dichotomous data, and the updated combined NNT for pregabalin was 8.8 (95% CI: 7.5 to 10.8). There was a dose response gradient (higher response with 600 mg daily than with 300 mg daily).

Gabapentin

No additional studies using gabapentin for neuropathic pain were identified in our supplementary search. In total, our assessment was based on 14 randomized controlled trials of gabapentin (900 to 3600 mg/day; nine positive) [68,76–88]. The trials were predominantly conducted in patients with post-herpetic neuralgia, painful polyneuropathy (mainly diabetic), spinal cord injury, post-amputation pain, and peripheral nerve injury. Detailed descriptions of individual studies, along with bias assessments (including statistical power) are provided in Appendix 2. A summary of the GRADE assessment of the evidence is provided in Table 4. A summary of the bias assessment, derived from a 2014 Cochrane review of gabapentin for neuropathic pain and fibromyalgia by Moore and colleagues [89]) is shown in Figure 10. There is no evidence of systematic bias across the 14 studies; concerns over sample size, defined by Moore et al using a rigid cut-off of $<$200 participants, are mitigated by evidence that most studies classified as unclear or high risk for bias based on small sample size met or exceeded the minimum sample size calculated for the study (Backonja 1998 [76], Bone 2002 [77], Gilron 2005 [68], Gordh 2008 [79], Gorson 1999 [80], and Levendoglu 2004 [82]; Appendix 2).

The combined NNT for gabapentin across the 14 studies was 6.3 (95% CI: 5.0 to 8.3), and there was no evidence of a dose-response effect. Figure 11 shows absolute risk differences between gabapentin and placebo arms in individual studies reporting dichotomous pain relief data (n = 8), and the pooled absolute risk difference across the 8 studies. Studies shown in the figure are grouped as low risk for allocation bias or unclear risk of allocation bias based on the assessment of allocation bias by Moore and colleagues in their 2014 Cochrane review [89]. Figure 11 clearly shows no significant effect of allocation bias on the effect size. Efficacy data for each of the 14 studies data is provided in Appendix 3.

Unlike our GRADE analysis, which ignored the aetiology of the neuropathic pain, the Cochrane review by Moore and colleagues [89] partitioned the analysis according to pain aetiology. Despite this difference in approach, our data are largely concordant with that of the Cochrane review, whose authors concluded (based on second tier evidence) that gabapentin was efficacious in post-herpetic neuralgia (NNT 8.0, 95% CI: 6.0 to 12) and painful diabetic neuropathy (NNT 5.9, 95% CI: 4.6 to 8.3). The authors concluded that there were insufficient data in other pain conditions, including fibromyalgia, to reach any reliable conclusion.

Head-to-head trials of gabapentin and tricyclic antidepressants

There are very few high-quality head-to-head trials of gabapentin against TCAs, and the results are conflicting. Rintala and coworkers [84] reported that gabapentin had lower efficacy than amitriptyline in the management of neuropathic pain resulting from spinal cord injury (no dichotomous pain data reported), while Chandra *et al.* [90] and Morello *et al.* [91] reported no difference in treatment efficacy between gabapentin and nortriptyline or amitriptyline. The latter two studies reported dichotomous pain data, and the data are shown in Figure 12.

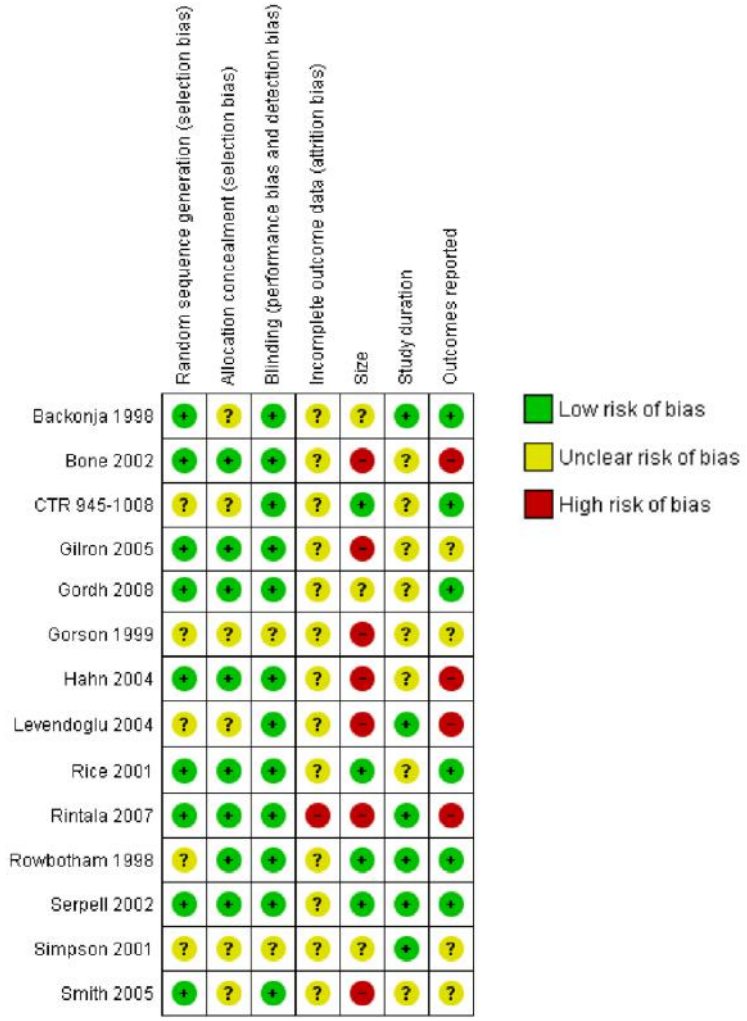

Figure 10: *Summary of the methodological quality of 14 studies of gabapentin for the management of neuropathic pain included in the GRADE analysis. The summaries are derived from a 2014 Cochrane review of the evidence for the use of gabapentin for neuropathic pain and fibromyalgia by Moore and colleagues [49]. Studies by Backonja 1998 [74], Bone 2002 [75], Gilron 2005 [66], Gordh 2008 [77], Gorson 1999 [78], and Levendoglu 2004 [80] all met or exceeded the calculated sample size for the study; Appendix 2*

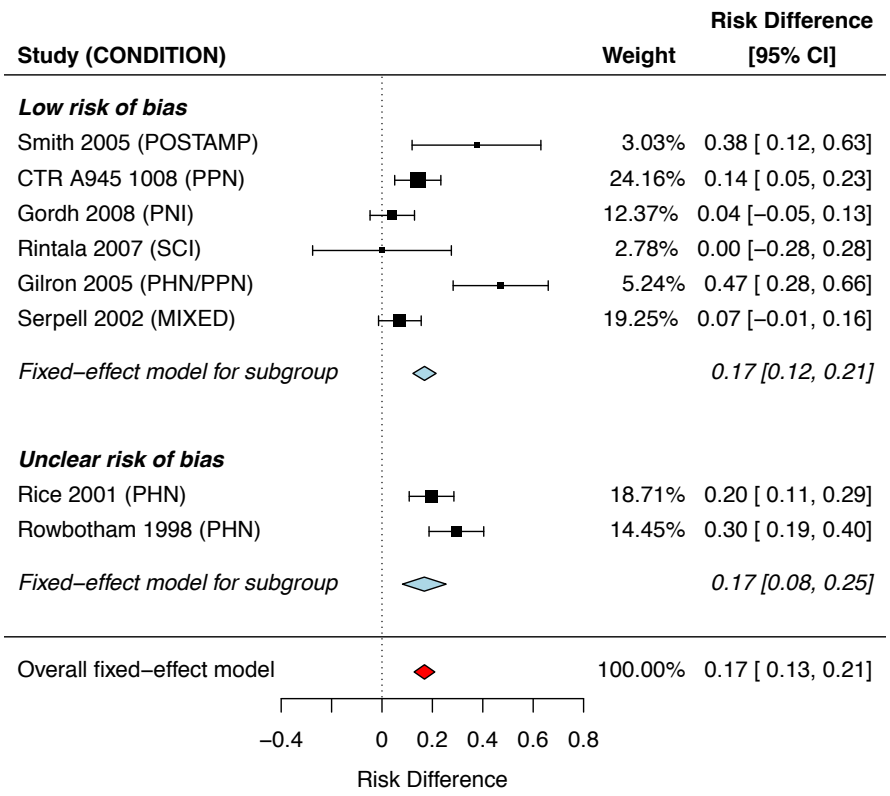

Figure 11: *Absolute risk difference (95% CI) between gabapentin and placebo for the management of neuropathic pain. Positive values indicate greater benefit for gabapentin over placebo. Data are shown for individual studies (black squares), subgroup effects (low and unclear risk of allocation bias; blue diamonds), and the overall effect (red diamond). The size of the filled squares indicate the relative number of individuals randomized in each trial. Only data from 8/14 studies reporting dichotomous pain relief data are shown. MIXED: various causes of neuropathic pain, PHN: post-herpetic neuralgia, POSTAMP: post-amputation pain, PNI: peripheral nerve injury, PPN: painful polyneuropathy, SCI: spinal cord injury. Data sources: [3,49].*

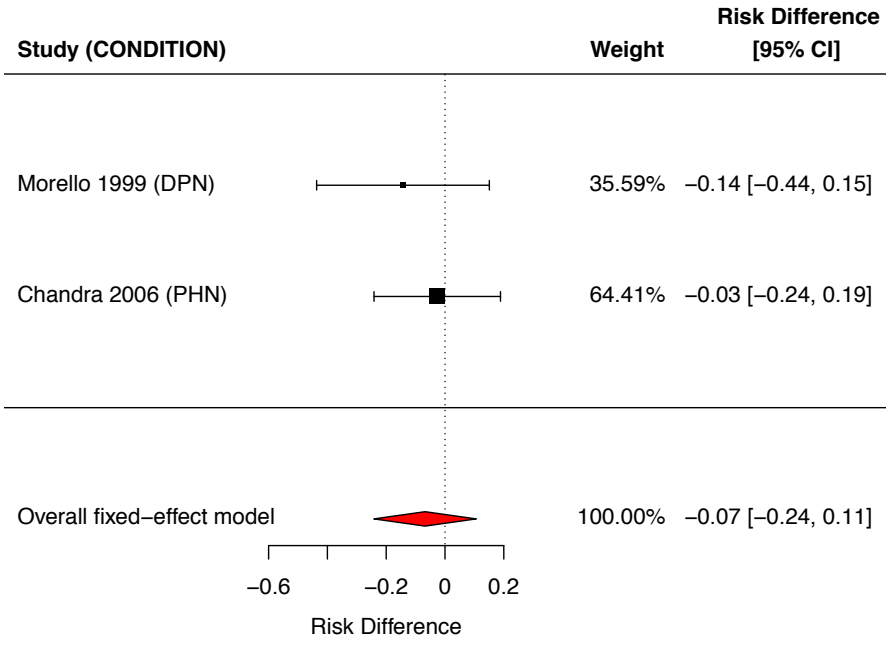

Figure 12: *Absolute risk difference (95% CI) between gabapentin and amitriptyline (Morello 1999 [89]), and gabapentin and nortriptyline (Chandra 2006 [88]) for the management of neuropathic pain. Positive values indicate greater benefit for gabapentin over the TCAs. Data are shown for individual studies (black squares), and the overall effect (red diamond). The size of the filled squares indicate the relative number of individuals randomized in each trial. Only data from 2 studies reporting dichotomous pain relief data are shown. DPN: painful diabetic polyneuropathy, PHN: post-herpetic neuralgia. Data sources: [3,49].*

Review of harms and toxicity: summary of evidence on safety.

The information on harms and toxicity was obtained from regulatory documents available from the Food and Drug Administration (FDA) [1], and European Medicines Agency (EMA) [2] for Neurontin (gabapentin, Pfizer Inc). Please refer to Appendices 6 and 7 for detailed information.

Contraindications

Gabapentin is contraindicated in patients who have demonstrated hypersensitivity to the medicine or its ingredients.

Warnings and precautions

Drug reaction with eosinophilia and systemic symptoms (DRESS), anaphylaxis and angioedema, driving and operating heavy machinery, somnolence and dizziness, withdrawal precipitated seizure, suicidal behaviour and ideation, tumorigenic potential, sudden and unexplained death in patients with epilepsy.

Adverse events in trials for neuropathic pain

Our analysis of adverse effects in trials of gabapentin for neuropathic pain was based on the 14 studies included in the meta-analysis by Finnerup and colleagues [3] as our supplementary literature search in February 2016 did not identify additional studies. Of the 14 studies, one study used only a low dose of gabapentin (900mg) [80] and two studies did not provide comparative numbers of drop-outs due to side effect [68,77], thus the combined number needed to harm (NNH) was based on 11 studies (see Figure 13 for absolute risk differences). The NNH was calculated as the number of patients who needed to be treated for one patient to drop out because of adverse effects. The 95% confidence intervals (CIs) of the NNH were calculated as the reciprocal values of the 95% CIs for the absolute risk difference using the normal approximation. The combined NNH for gabapentin was 25.6 (95% CI: 15.3 to 78.6) [3].

When examining specific adverse events, dizziness, somnolence (or drowsiness or sedation), and in a few studies peripheral oedema and confusion, had a prevalence $>$ 10% and a higher prevalence than in the placebo group. The NNH for dizziness was 5.1 (95% CI: 4.3 to 6.3) and for somnolence 7.1 (95% CI: 5.7 to 9.4) (see Figures 14 and 15 for absolute risk differences).

In a Cochrane review of gabapentin in fibromyalgia and neuropathic pain [89], 62% during gabapentin and 50% during placebo experienced at least one adverse event in 17 studies with 4002 participants. The risk ratio for adverse events was 1.25 (95% CI: 1.2 to 1.3), and the NNH was 8.6 (95% CI: 6.8 to 12). Serious adverse events were not more common for gabapentin than for placebo (risk ratio = 1.2, 95% CI: 0.8 to 1.7) [89]. The NNH for somnolence, drowsiness, or sedation was 11 (95% CI: 9.4 to 14; 4125 participants), for dizziness 7.6 (95% CI: 6.6 to 8.8; 4125 participants), and for peripheral oedema 21 (95% CI: 16 to 30; 3220 participants). Gabapentin was associated with an increased risk of ataxia or gait disturbance with and NNH of 13 (95% CI: 9 to 24; 544 participants) [89].

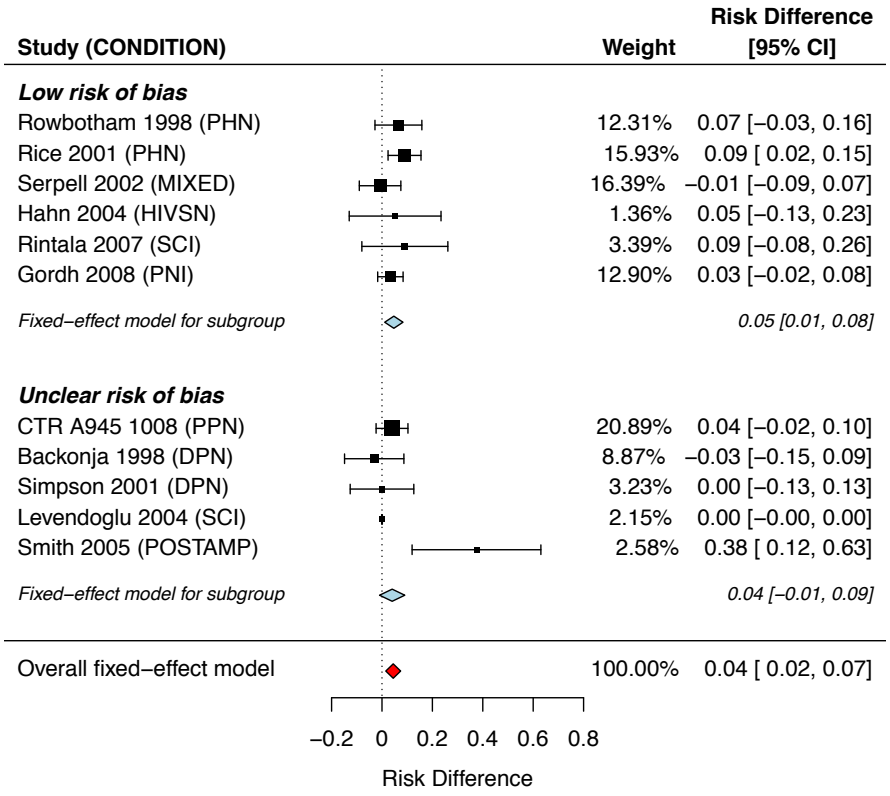

Figure 13: *Withdrawal due to adverse reactions: Absolute risk difference (95% CI) between gabapentin and placebo for study drop-outs because of adverse events. Positive values indicate greater harm for gabapentin over placebo. Data are shown for individual studies (black squares), subgroup effects (low and unclear risk of allocation bias; blue diamonds), and the overall effect (red diamond). The size of the filled squares indicate the relative number of individuals randomized in each trial. Only data from 11/14 studies reporting withdrawal events due to adverse events are shown. DPN: painful diabetic polyneuropathy, HIVSN: painful HIV-associated sensory neuropathy, MIXED: various causes of neuropathic pain, PHN: post-herpetic neuralgia, POSTAMP: post-amputation pain, PNI: peripheral nerve injury, PPN: painful polyneuropathy, SCI: spinal cord injury. Data sources: [3,49].*

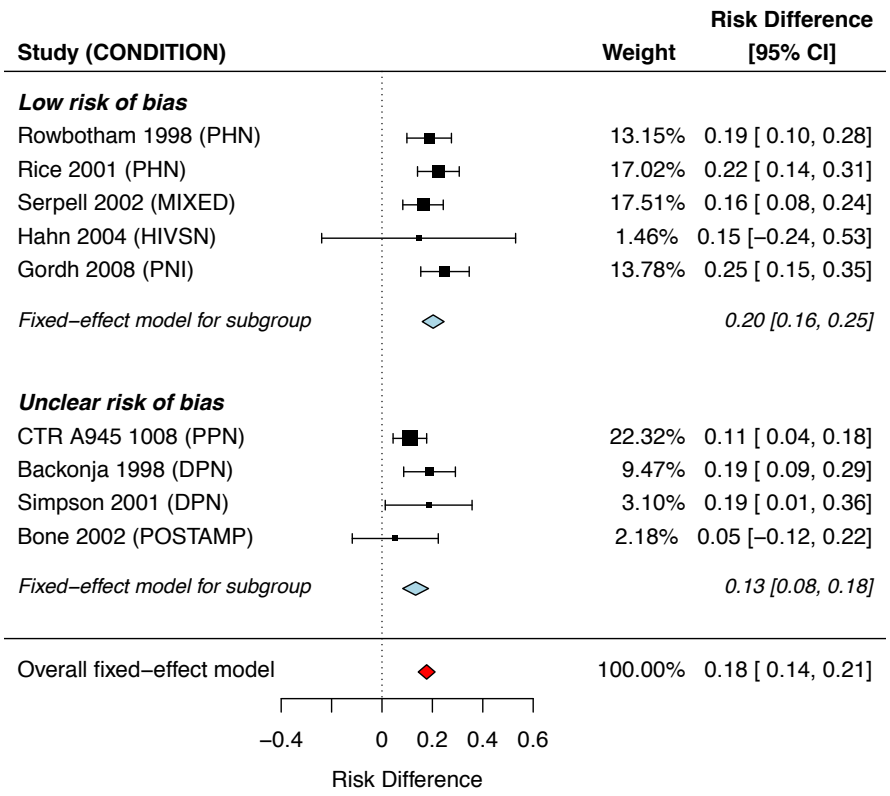

Figure 14: *Dizziness: Absolute risk difference (95% CI) between gabapentin and placebo for participants reporting dizziness. Positive values indicate greater harm for gabapentin over placebo. Data are shown for individual studies (black squares), subgroup effects (low and unclear risk of allocation bias; blue diamonds), and the overall effect (red diamond). The size of the filled squares indicate the relative number of individuals randomized in each trial. Only data from 9/14 studies reporting dizziness data are shown. DPN: painful diabetic polyneuropathy, MIXED: various causes of neuropathic pain, PHN: postherpetic neuralgia, POSTAMP: post-amputation pain, PNI: peripheral nerve injury, PPN: painful polyneuropathy, SCI: spinal cord injury. Data source: [49].*

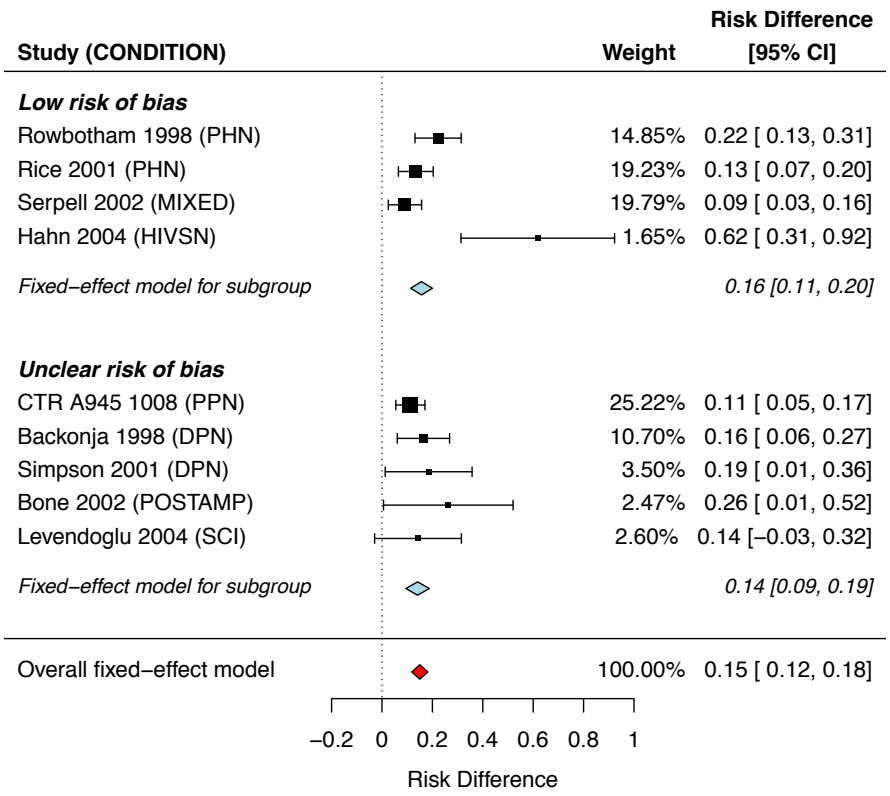

Figure 15: *Somnolence: Absolute risk difference (95% CI) between gabapentin and placebo for participants reporting somnolence. Positive values indicate greater harm for gabapentin over placebo. Data are shown for individual studies (black squares), subgroup effects (low and unclear risk of allocation bias; blue diamonds), and the overall effect (red diamond). The size of the filled squares indicate the relative number of individuals randomized in each trial. Only data from 9/14 studies reporting somnolence data are shown. DPN: painful diabetic polyneuropathy, MIXED: various causes of neuropathic pain, PHN: post-herpetic neuralgia, POSTAMP: post-amputation pain, PNI: peripheral nerve injury, PPN: painful polyneuropathy, SCI: spinal cord injury. Data source: [49].*

Summary of efficacy and safety across first-line medications

Tables 3 summarises the benefits and harms of gabapentin based on our systematic review and meta-analysis. For comparison, we have also included the data for other medicines we recommended as first-line [3] (a more granular summary of the GRADE analysis for gabapentin only is provided in Table 4). Based on the balance of the evidence, we recommended gabapentin, pregabalin, TCAs and SNRIs as first-line treatments; the updated literature search in 2016 did not change our recommendation. When making our original recommendations, we stated that there was no evidence for any of the agents having superior efficacy in general, or for specific causes of neuropathic pain; and nor did the updated search not alter our position on these issues. Therefore, our recommendations applied to neuropathic pain in general. However, we also noted the paucity of clinical trials on cancer-related neuropathic pain, and the absence of trials in children.

Table 3: *Summary of efficacy and adverse events reported by Finnerup et al., 2015 [3]*

	Number needed to treat (50% / 30% / moderate pain relief)	Number needed to harm			
		Major*	Dizziness	Somnolence	Dry mouth
TCA	4.3	13.4	10.3	9.5	4.8
Gabapentin†	6.3	25.6	5.1	7.1	-
Pregabalin	8.8	13.9	-	-	-
SNRI	6.4	11.8	-	-	-

TCA: Tricyclic antidepressants; SNRI: Serotonin and noradrenaline re-uptake inhibitors;
∗ : Withdrawal from study because of adverse events;
† : Excluding gabapentin extended release / enacarbil

In their guideline on the management of neuropathic pain, NICE generated a heat-map of relative benefits and harms of the medications they assessed [4]. Figure 16 presents a summary of that figure that only includes medications recommended as first-line therapy by NICE [4] and others [3,5,6].

Summary of available data on comparative cost and cost-effectiveness within the pharmacological class or therapeutic group.

Comparative costs

Comparative pricing data were obtained from the Management Sciences for Health (MSH) International Drug Price Indicator Guide [92]. Tables 5 to 7 report comparative prices of gabapentin and two other medications on the WHO Model Essential Medicines List, amitriptyline and carbamazepine. Amitriptyline was included because it is recommended, along with gabapentin as a first-line pharmacological treatment for neuropathic pain [3–6]. Carbamazepine falls into the same therapeutic class as gabapentin (anticonvulsants), and it is recommended for the treatment of trigeminal neuralgia [6][11]. The data are reported as unit price of the medications (Table 5), price when prescribed at the defined daily dose for each

[11] In our recent meta-analysis and GRADE analysis [3] there was inconclusive evidence for the use of carbamazepine in the management of neuropathic pains outside of trigeminal neuralgia, and thus carbamazepine was *not* recommended for use in the pharmacological management of neuropathic pain. Even in the case of trigeminal neuralgia, the data supporting the use of carbamazepine is old and of low quality [6].

Table 4: *Summary of the GRADE assessment and recommendation for gabapentin*

Category	Summary
GRADE questions	i) In patients with neuropathic pain, is treatment with gabapentin for at least 3 weeks more likely to result in a reduction in pain intensity (primary outcome) as compared to placebo? ii) In patients with neuropathic pain, is treatment with gabapentin for at least 3 weeks more likely to result in side effects and dropouts due to side effects as compared to placebo?
Number of placebo-controlled trials	14
Number of patients included	1728
Comparison groups	Inert placebo: 14; Active placebo: 2
Number needed to treat (95% CI)	6.3 (5.0 to 8.3)
Number needed to harm (95% CI)	25.6 (15.3 to 78.6)
Initial GRADE quality rating	High *(all randomized, controlled trials)*
Study limitations	No systematic or serious limitations *(overall risk of bias was low; see Appendix 2)*
Inconsistency of results	No important inconsistency *(9 positive trials and 5 negative trials, but no major discrepencies in effect sizes; see Figure 11 and Appendix 2)*
Imprecision	Moderate imprecision
Indirectness	Direct
Publication bias	Low risk of publication bias *(see Figure 6 and 7)*
Large effect size	No *(effect size was moderate)*
Dose response	Not studied
Serious adverse events	Low risk of serious harm
Overall quality of evidence	High quality evidence
Desirable versus undesirable effects	Desirable > Undesirable
Variability in values and preferences	Low to moderate
Cost	Low to moderate
GRADE RECOMMENDATION	**Strong recommendation for gabapentin**

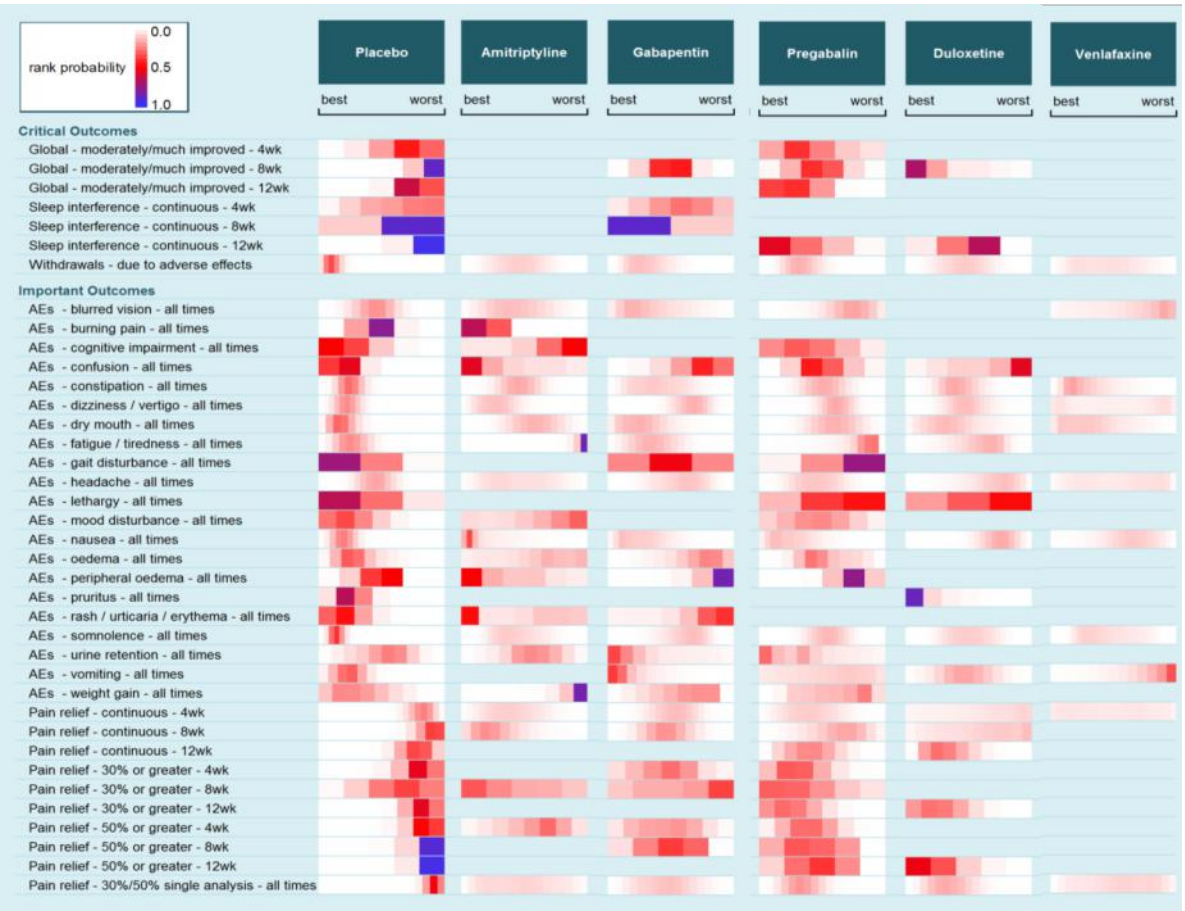

Figure 16: *Graphical table showing the probability that each first-line treatment is the best option for which evidence is available, the worst available option, or any point in between. The probabilities are indicated by intensity of colour (see legend). All outcomes presented on a standardised scale, from best (left) to worst (right). Thus, where the outcome is desirable (e.g., pain relief) the treatments with most intense colour in the left-hand part of the scale are those with the highest estimated probability of achieving that result. Where results are for an undesirable outcome (e.g., nausea) a concentration of colour on the left-hand part of the scale implies a lower probability of the event. Relatively pale colours across a broad spread of the scale are indicative of substantial uncertainty, while an intense concentration of colour at one point on the scale reflects unambiguous results. Adapted from: NICE CG173 [4].*

medication (Table 6), and price when prescribed at the maximum recommended daily dose of the medications (Table 7).

Analysis of comparative pricing for gabapentin was limited by the absence of price data from suppliers, and price data was only available from one buyer source each for the 100mg and 400mg doses of gabapentin, and three sources for the 300mg dose.

Table 5: *Price based on the unit cost of gabapentin (amitriptyline and carbamazepine are shown for comparison)*

Drug	Strength (mg)	Type	Number of price comparator sources	Median price per unit (US$)	High:Low price ratio
Gabapentin	100	buyer	1	0.13	1.00
Gabapentin	300	buyer	3	0.06	11.04
Gabapentin	400	buyer	1	0.30	1.00
Amitriptyline	10	buyer	1	0.02	1.00
Amitriptyline	25	buyer	6	0.03	3.45
Amitriptyline	25	supplier	9	0.01	4.13
Amitriptyline	50	buyer	1	0.03	1.00
Carbamazepine	200	buyer	5	0.02	6.83
Carbamazepine	200	supplier	10	0.02	3.92

Table 6: *Price based on the defined daily dose (DDD) of gabapentin (amitriptyline and carbamazepine are shown for comparison)*

Drug	Strength (mg)	Type	Number of price comparator sources	Median price based on DDD (US$)	High:Low DDD price ratio
Gabapentin	100	buyer	1	2.31	1.00
Gabapentin	300	buyer	3	0.36	11.04
Gabapentin	400	buyer	1	1.33	1.00
Amitriptyline	10	buyer	1	0.17	1.00
Amitriptyline	25	buyer	6	0.09	3.45
Amitriptyline	25	supplier	9	0.02	4.13
Amitriptyline	50	buyer	1	0.05	1.00
Carbamazepine	200	buyer	5	0.11	6.83
Carbamazepine	200	supplier	10	0.10	3.92

Cost-utility analysis

The National Institute of Health and Care Excellence, UK (NICE), recently completed a cost-utility analysis across treatments typically recommended as first-line for neuropathic pain [4]. In brief, their methodology included:[12]

- A literature search of published cost-utility analyses, which yielded 3353 unique citations, 3340 of which were excluded after review, leaving 13 articles (all for peripheral

[12] For full details on the methodology, please see NICE CG173 guideline [4]: Appendix F.

Table 7: *Price based on the maximum daily dose (MDD) of gabapentin (amitriptyline and carbamazepine are shown for comparison)*

Drug	Strength (mg)	Type	Number of price comparator sources	Median price based on MDD (US$)	High:Low MDD price ratio
Gabapentin	100	buyer	1	4.62	1.00
Gabapentin	300	buyer	3	0.72	11.04
Gabapentin	400	buyer	1	2.66	1.00
Amitriptyline	10	buyer	1	0.34	1.00
Amitriptyline	25	buyer	6	0.17	3.45
Amitriptyline	25	supplier	9	0.04	4.13
Amitriptyline	50	buyer	1	0.10	1.00
Carbamazepine	200	buyer	5	0.13	6.83
Carbamazepine	200	supplier	10	0.12	3.92

neuropathic pain) for inclusion in the analysis;

- For a medicine to be included in the modelling process, at least one estimate of dichotomous pain relief (30% and/or 50% relief compared with baseline) and data on withdrawal due to adverse effects was required;
- Medicine prices were taken from the National Health Service, UK Electronic Drug Tariff register for March 2013, and health benefit was valued in quality-adjusted life-year (QALY).
- Based on the available trial data, a time horizon of 20 weeks was used in the model. And, to take into account the uncertainty associated with each input parameter, the model was built probabilistically using Bayesian Markov-chain Monte-Carlo sampling.

The results of the cost-utility analysis are summarised in Tables 8 to 10. Gabapentin compared favourably with other medications recommended as first-line in the management of neuropathic pain in terms of cost (Table 8), and in terms of the probability that it would be considered the most cost-effective option based on an assumed QALY value of £ 20,000 and £ 30,000 (Tables 9 and 10).

Table 8: *NICE health economic model: daily dosages and prices of drugs [4] (amitriptyline, pregabalin, duloxetine, and venlafaxine are shown for comparison)*

Medicine	Average trial dosage (mg/day)	Most efficient dosage delivery	140-day cost (£)
Amitriptyline	95	2 x 50mg	8.20
Gabapentin	2572	6 x 400mg + 2 x 100mg	46.73
Pregabalin	398	2 x 200mg	332.00
Duloxetine	78	1 x 60mg + 1 x 30mg	250.60
Venlafaxine	119	4 x 37.5mg	25.30

Based on the outcome of the cost-utility analysis, the NICE Guideline Development Group recommended gabapentin and amitriptyline as initial treatment options for neuropathic pain.

Table 9: *NICE health economic model: Probabilistic sensitivity analysis when* ***1 QALY is valued at £ 20,000*** *[4] (amitriptyline, pregabalin, duloxetine, and venlafaxine are shown for comparison)*

Medicine	Net monetary benefit (NMB)	Probability of greatest NMB (%)	Probability of NMB being $>$ placebo (%)
Amitriptyline	2575	13.3	84.7
Gabapentin	2608	9.5	94.3
Pregabalin	2485	1.0	98.3
Duloxetine	2428	1.3	84.8
Venlafaxine	2391	6.5	64.9

Table 10: *NICE health economic model: Probabilistic sensitivity analysis when* ***1 QALY is valued at £ 30,000*** *[4] (amitriptyline, pregabalin, duloxetine, and venlafaxine are shown for comparison)*

Medicine	Net monetary benefit (NMB)	Probability of greatest NMB (%)	Probability of NMB being $>$ placebo (%)
Amitriptyline	3908	10.7	86.0
Gabapentin	3978	7.6	95.8
Pregabalin	3904	2.0	100.0
Duloxetine	3800	2.1	94.3
Venlafaxine	3656	5.6	68.4

The results of the NICE cost-utility analysis, combined with similar efficacy and safety profiles for the molecules, informed our decision to apply for inclusion of gabapentin on the Model List, and not pregabalin, the other agent in the $\alpha 2\delta$-calcium channel ligand class. Although pregabalin, unlike gabapentin, demonstrates a linear absorption profile and has a universal indication for treatment of neuropathic pain by stringent regulatory bodies, we concluded that, on the balance of the core GRADE indicators of cost, efficacy, and safety gabapentin was the more suitable agent for widespread recommendation at present.

Regulatory information

Summary of regulatory status of the medicine.

Gabapentin has regulatory approval as a **prescription only medicine** from the following stringent regulatory bodies: US Federal Drug Administration (FDA), European Medicines Agency (EMA), Australian Therapeutic Goods Administration (TGA), Japanese Pharmaceuticals and Medical Devices Agency (PMDA), and Health Canada (see Table 11 for registered neuropathic pain indications[13]). There are discrepancies between the regulatory bodies with regards to gabapentin being registered for the treatment of neuropathic pain. The EMA and

[13] All four regulatory authorities indicate gabapentin as adjunctive therapy in the treatment of partial seizures with and without secondary generalization in adults and children. The PMDA and EMA also indicate gabapentin as mono-therapy for partial seizures with and without secondary generalization in adults and children.

TGA provide broad registration of gabapentin for the treatment of neuropathic pain, while the FDA indication is limited to post-herpetic neuralgia, and the PMDA and Health Canada only indicate gabapentin for the treatment of epilepsy. These discordant registrations are at odds with the body of evidence that indicates that gabapentin is effective in the treatment of neuropathic pain of various aetiologies. Given the evidence base, possible reasons for the discordant registrations include: i) absence of a general neuropathic pain indication within a regulatory framework (e.g., FDA), and ii) an attempt by the developer (Parke-Davis/Pfizer) to differentiate, where possible, gabapentin and pregabalin, both of which are recommended first-line for the treatment of neuropathic pain.

None of these agencies have registered gabapentin as a controlled substance.

While gabapentin (and other medicines) have regulatory approval for the treatment of neuropathic pain, the International Classification of Diseases (ICD) revision 10 does not provide adequate coding for neuropathic pain [93]. This deficiency in the ICD-10 hampers the collection of accurate epidemiological data on adverse reactions, as well as prescribing, dispensing, and billing information related to the treatment of neuropathic pain. However, the revised ICD-11 coding system, which is currently in beta version (ICD-11 Beta Draft), specifically codifies neuropathic pain (8D62.1 Neuropathic pain), which will facilitate the collection of pertinent epidemiological data on treatments for neuropathic pain.

Table 11: *Regulatory approval of gabapentin for neuropathic pain by major national and regional regulatory bodies*

Registration authority	Indicated for neuropathic pain	Specifics of the indication
Food and Drug Administration (FDA), USA	Yes	Treatment of postherpetic neuralgia in adults
European Medicines Agency (EMA), European Union	Yes	Treatment of peripheral neuropathic pain such as painful diabetic neuropathy and post-herpetic neuralgia in adults
Therapeutic Goods Administration (TGA), Australia	Yes	Treatment of neuropathic pain
Pharmaceuticals and Medical Devices Agency (PMDA), Japan	No	
Health Canada, Canada	No	

Availability of pharmacopoeial standards (British Pharmacopoeia, International Pharmacopoeia, United States Pharmacopoeia, European Pharmacopeia).

Pharmacopoeial standards for gabapentin are included in the:

- United States Pharmacopoeia (USP)
- European Pharmacopoeia (PhEur)

Source files and citation information

Source files:

All R and RMarkdown scripts, Latex templates, and associated files used to generate this document are available at: WHO-EML-application-2016 GitHub repository

Cite this article as:

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Appendix 1

Organizations supporting the application

1. International Society of Physical and Rehabilitation Medicine (ISPRM)
2. World Federation of Societies of Anaesthesiology (WFSA)
3. World Medical Association (WMA)
4. National Chapters of the International Association for the Study of Pain
    - American Pain Society
    - Asociación Chilena para el Estudio del Dolor [Chile]
    - Asociacion Dominicana para el Estudio y Tratamiento del Dolor y Cuidados Paliativos [Dominican Republic]
    - Asociación Istmeña para el Estudio del Dolor [Panama]
    - Australian Pain Society
    - Bangladesh Society for Study of Pain
    - Belgian Pain Society
    - British Pain Society
    - Chinese Association for the Study of Pain
    - Croatian Pain Society
    - Dutch Pain Society
    - German Pain Society
    - Hong Kong Pain Society
    - Indian Society for Study of Pain
    - Iranian Pain Society
    - Irish Pain Society
    - Lebanese Society for the Study of Pain
    - Lithuanian Pain Society
    - Malaysian Association for the Study of Pain
    - New Zealand Pain Society
    - Österreichische Schmerzgesellschaft [Austria]
    - Pain Society of the Philippines
    - PainSA [South Africa]
    - Professional Health Association – Pain Section, Kosovo
    - Saudi Society of Pain Medicine
    - Serbian Pain Association of Pain Research and Treatment
    - Sociedad Española Del Dolor [Spain]
    - Society for the Study of Pain, Nigeria
    - Sri Lanka Association for the Study of Pain
    - Thai Association for the Study of Pain

ISPRM
INTERNATIONAL SOCIETY OF PHYSICAL AND REHABILITATION MEDICINE

ISPRM Office
Rue François Versonnex 7
1207 Geneva
Switzerland

18 November, 2016

To: WHO Expert Committee on Selection and Use of Essential Medicines

Re: Endorsement letter advocating gabapentin

To whom it may concern,

The **International Society of Physical and Rehabilitation Medicine** (ISPRM) strongly supports the inclusion of gabapentin for the management of neuropathic pain in the WHO Model List of Essential Medicines.

Currently, amitriptyline is the only medicine that the WHO Model List of Essential Medicines recommends as a first or second-line treatment in the management of neuropathic pain. Unfortunately, limiting treatment to amitriptyline reduces medical options when initial treatment fails or contraindications arise.

ISPRM believes it is important to include gabapentin on the WHO list because of its proven efficacy in managing neuropathic pain. Moreover, gabapentin can be used alone or in combination with amitriptyline; it is available off-patent worldwide; and it is a cost-effective treatment for many conditions.

Therefore, we urge the 21st Expert Committee on the Selection and Use of Essential Medicines to look favorably on the application by the International Association for the Study of Pain and the International Association for Hospice and Palliative Care that seeks inclusion of gabapentin for the treatment of neuropathic pain on the WHO Model List of Essential Medicines.

Sincerely yours,

Jorge Laíns
ISPRM President

ISPRM Office
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WFSA unites anaesthesiologists around the world to improve patient care and access to safe anaesthesia

07th November 2016

To Whom It May Concern:

The World Federation of Societies of Anaesthesiologists (WFSA) strongly supports the inclusion of gabapentin for the management of neuropathic pain in the WHO Model List of Essential Medicines.

The WFSA notes that neuropathic pain is poorly recognised throughout the world and acknowledges that education in this area is needed for both diagnosis and treatment.

Currently, amitriptyline is the only medicine that the WHO Model List of Essential Medicines recommends as a first or second-line treatment in the management of neuropathic pain. The WFSA believes it is important to include gabapentin as an additional agent to the WHO list because of its proven efficacy in managing neuropathic pain. Gabapentin can be used alone or in combination with amitriptyline; it is available off-patent worldwide; and it is a cost-effective treatment for many conditions causing neuropathic pain.

Therefore, we urge the 21st Expert Committee on the Selection and Use of Essential Medicines to look favourably on the application by the International Association for the Study of Pain and the International Association for Hospice and Palliative Care that seeks inclusion of gabapentin for the treatment of neuropathic pain on the WHO Model List of Essential Medicines.

Yours sincerely,

Gonzalo Barreiro
President WFSA

Roger Goucke
Chair, Pain Management Committee

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THE WORLD MEDICAL ASSOCIATION, INC.
L'ASSOCIATION MEDICALE MONDIALE, INC
ASOCIACION MEDICA MUNDIAL, INC

14 November 2016

To Whom It May Concern:

The World Medical Association (WMA) strongly supports the inclusion of gabapentin for the management of neuropathic pain in the WHO Model List of Essential Medicines.

Currently, amitriptyline is the only medicine that the WHO Model List of Essential Medicines recommends as a first or second-line treatment in the management of neuropathic pain. Unfortunately, limiting treatment to amitriptyline reduces medical options when initial treatment fails or contraindications arise.

It is important to include gabapentin on the WHO list because of its proven efficacy in managing neuropathic pain. Moreover, gabapentin can be used alone or in combination with amitriptyline; it is available off-patent worldwide; and it is a cost-effective treatment for many conditions. The inclusion of Gabapentin in WHO Essential Medicines List is no replacement of opioids, both being necessary for the treatment of pain in general.

Therefore, the WMA respectfully recommends to the 21st Expert Committee on the Selection and Use of Essential Medicines to look favourably on the application by the International Association for the Study of Pain and the International Association for Hospice and Palliative Care that seeks inclusion of gabapentin for the treatment of neuropathic pain on the WHO Model List of Essential Medicines.

Yours sincerely,

Dr. Otmar Kloiber
Secretary General

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International Association for the Study of Pain
IASP
Working together for pain relief

November 28, 2016

To Whom It May Concern:

The International Association for the Study of Pain and its affiliated chapters listed below strongly support the inclusion of gabapentin for the management of neuropathic pain in the WHO Model List of Essential Medicines.

Currently, amitriptyline is the only medicine that the WHO Model List of Essential Medicines recommends as a first or second-line treatment in the management of neuropathic pain. Unfortunately, limiting treatment to amitriptyline reduces medical options when initial treatment fails or contraindications arise.

IASP and each organization below believe it is important to include gabapentin on the WHO list because of its proven efficacy in managing neuropathic pain. Moreover, gabapentin can be used alone or in combination with amitriptyline; it is available off-patent worldwide; and it is a cost-effective treatment for many conditions.

IASP and the 30 affiliated chapters below champion pain relief worldwide, and represent pain researchers and clinicians across six continents and a full range of low-, middle-, and high-income economies. We urge the 21st Expert Committee on the Selection and Use of Essential Medicines to look favorably on the application by the International Association for the Study of Pain and the International Association for Hospice and Palliative Care that seeks inclusion of gabapentin for the treatment of neuropathic pain on the WHO Model List of Essential Medicines.

Sincerely,

Judith A. Turner, Ph.D.

Judith A. Turner, PhD
President

IASP is a tax-exempt, nonprofit organization.

IASP Chapters around the world in support of the adding gabapentin to the Essential Medicines List

American Pain Society
Asociación Chilena para el Estudio del Dolor (ACHED) [Chile]
Asociacion Dominicana para el Estudio y Tratamiento del Dolor y Cuidados Paliativos [Dominican Republic]
Asociación Istmeña para el Estudio del Dolor (AIPED) [Panama]
Australian Pain Society
Austrian Pain Society (Österreichische Schmerzgesellschaft ÖSG)
Bangladesh Society for Study of Pain (BSSP)
Belgian Pain Society (BPS)
British Pain Society
Chinese Association for the Study of Pain (CASP)
Croatian Pain Society
Dutch Pain Society
German Pain Society
Hong Kong Pain Society
Indian Society for Study of Pain
Iranian Pain Society
Irish Pain Society
Lebanese Society for the Study of Pain (LSSP)
Lithuanian Pain Society
Malaysian Association for the Study of Pain
New Zealand Pain Society
Pain Society of the Philippines
PainSA [South Africa]
Professional Health Association – Pain Section, Kosovo
Saudi Society of Pain Medicine
Serbian Pain Association of Pain Research and Treatment
Sociedad Española Del Dolor [Spain]
Society for the Study of Pain, Nigeria
Sri Lanka Association for the Study of Pain
Thai Association for the Study of Pain

Appendix 2

Description and bias assessment of studies included in GRADE assessment

Adapted from: Moore RA, Wiffen PJ, Derry S, Toelle T, Rice ASC. Gabapentin for chronic neuropathic pain and fibromyalgia in adults. *Cochrane Database of Systematic Reviews* **4**: CD007938, 2014. DOI: 10.1002/14651858.CD007938.pub3

BACKONJA 1998

Backonja M, 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 (21):1831–6. [PMID: 9846777]

Description	
Methods	Multicentre, randomised, double-blind, placebo-controlled, parallel-group, not enriched, LOCF Titration to maximum tolerated dose or 3600 mg daily over 4 weeks, then stable dose for 4 weeks (8 weeks in total)
Pain assessment	0-10 numerical pain rating scale (minimum baseline pain: 4/10)
Participants	Painful diabetic neuropathy. N = 165, mean age 53 years, 40% women. Pain duration > 3 months before treatment, initial mean pain score 6.4/10
Interventions	Gabapentin 3600 mg daily (max), n = 84 Placebo, n = 81 Medication for diabetes control remained stable during study. Paracetamol (max 3 g daily) allowed
Outcomes	PGIC much or moderately improved ≥ 50% reduction in pain (CTR) PGIC much improved (CTR) PGIC moderately or much improved (CTR) Adverse events Withdrawals
Notes	Oxford Quality Score: R = 2, DB = 2, W = 1, Total = 5 Registration/protocol: Parke Davis/Pfizer 945-306 (unpublished report no. RR430-00125)

Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	Not reported
Blinding? All outcomes	Yes	"supplied in identical capsules in blinded fashion". "All participants were supplied with an equal number of capsules"
Incomplete outcome data addressed?	Unclear	LOCF
Size Efficacy	Unclear	165
Study duration Efficacy	Yes	8 weeks
Outcomes reported	Yes	At least 50% reduction in pain
Adequate statistical power	Yes	Minimum sample size: 75 per arm (90% power to detect 30% difference between gabapentin and placebo)

DB: Double-blind; **LOCF:** Last observation carried forward; **PGIC:** Patients Global Impression of Change; **R:** Randomisation; **W:** Withdrawals and dropouts

BONE 2002

Bone M, Critchley P, Buggy DJ. Gabapentin in postamputation phantom limb pain: a randomized, double- blind, placebo-controlled, cross-over study. *Regional Anesthesia and Pain Medicine* 2002;**27**(5):481–6. [DOI: 10.1053/rapm.2002.35169]

Description		
Methods	Randomised, double-blind, placebo-controlled, cross-over, not enriched. No imputation method mentioned Titration to maximum tolerated dose or 2400 mg daily over 1 week, then stable dose for 5 weeks (6 weeks total); 1-week washout, then cross-over	
Pain assessment	0-100mm visual analogue scale (minimum baseline pain: 40/100)	
Participants	Established phantom limb pain ≥ 6 months, N = 19, mean age 56 years, 21% women. initial pain score 6.4/10 14 completed both treatment periods	
Interventions	Gabapentin 2400 mg daily (max) Placebo Paracetamol + codeine 500 mg/30mg (max 12 tablets daily) allowed as rescue medication. Stable, low doses of TCAs continued	
Outcomes	No dichotomous efficacy data Adverse events	
Notes	Oxford Quality Score: R = 2, DB = 2, W = 1, Total = 5 Registration/protocol: Not described	
Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	Not described - but probably OK - remote
Blinding? All outcomes	Yes	"identical, coded medication bottles containing identical tablets of gabapentin or placebo"
Incomplete outcome data addressed?	Unclear	No imputation mentioned
Size Efficacy	No	19 randomised
Study duration Efficacy	Unclear	6 weeks each period
Outcomes reported	No	No dichotomous data
Adequate statistical power	Yes	Minimum sample size: 16 (80% power to detect 20mm change on VAS)

DB: Double-blind; **R:** Randomisation; **W:** Withdrawals and dropouts

CTR 945-1008

Anonymous. Protocol A9451008. A 15 Week, randomized, double-blind, placebo-controlled, parallel-group, multi- center study of Neurontin (gabapentin) for efficacy and quality of life in patients with painful diabetic peripheral neuropathy. PhrmaWebSynopsis - Final 2 June 2005.

Description	
Methods	Multicentre, randomised, double-blind, placebo-controlled, parallel-group, no obvious enrichment, LOCF Titration from 300 mg/day to maximum tolerated dose or 3600 mg daily over 3 weeks, then stable dose for 12 weeks (15 weeks total)
Pain assessment	0-100mm visual analogue scale (minimum baseline pain: 40/100)
Participants	Painful diabetic neuropathy. N =389, mean age 58 years, “more men than women”. Pain duration > 3 months
Interventions	Gabapentin 3600 mg daily (max), n = 200 Placebo, n = 189
Outcomes	≥ 30% reduction in pain ≥ 50% reduction in pain Adverse events Withdrawals
Notes	Oxford Quality Score: R = 1, DB = 2, W = 1, Total = 4 Registration/protocol: Protocol A9451008

Risk of bias		
Item	**Authors’ judgement**	**Description**
Allocation concealment?	Unclear	Not described
Blinding? All outcomes	Yes	Matching placebo
Incomplete outcome data addressed?	Unclear	LOCF
Size Efficacy	Yes	389 randomised
Study duration Efficacy	Unclear	14 weeks
Outcomes reported	Yes	At least 50% reduction in pain
Adequate statistical power	Unclear	Not described

DB: Double-blind; **LOCF:** Last observation carried forward; **R:** Randomisation; **W:** Withdrawals and dropouts

GILRON 2005

Gilron I, Bailey JM, Tu D, Holden RR, Weaver DF, Houlden RL. Morphine, gabapentin, or their combination for neuropathic pain. *New England Journal of Medicine* 2005;**352**(13):1324–34. [PMID: 15800228]

Description	
Methods	Randomised, double-blind, placebo-controlled 4-period cross-over, no enrichment. No imputation method mentioned (but if half of scores missing, outcome considered missing) Titration to target doses or limit of tolerability over 3 weeks, then stable dose for 1 week, and tapered dose for 1 week (5 weeks in total); 3-day washout and cross-over to next treatment
Pain assessment	0-10 numerical pain rating scale (minimum baseline score: daily moderate pain)
Participants	PDN and PHN. N = 57, median age 62 years, 44% women. Pain ≥ moderate for 3 months, initial mean pain score 5.8/10
Interventions	Gabapentin 3200 mg daily (max) Morphine 120 mg daily (max) Gabapentin plus morphine 2400 mg/60 mg daily (max) Placebo (lorazepam) 1.6 mg Mean maximum tolerated doses: gabapentin alone 2207 ± 89 mg, morphine alone 45. 3 ± 3.9 mg, gabapentin + morphine 1705 ± 83 + 34.4 ± 2.6 mg
Outcomes	Pain relief for those completing a given treatment (5-point scale) Withdrawals
Notes	Oxford Quality Score: R = 2, DB = 2, W = 1, Total = 5 Registration/protocol: Not described

Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	"concealed allocation schedule" prepared remotely
Blinding? All outcomes	Yes	"identical appearing blue and grey capsules …. in accord with a double-dummy design"
Incomplete outcome data addressed?	Unclear	Imputation not mentioned
Size Efficacy	No	Although 57 randomised, data available 40-44 completing a given treatment
Study duration Efficacy	Unclear	5 weeks each period
Outcomes reported	Unclear	At least moderate pain relief
Adequate statistical power	Yes	Minimum sample size: 40 (80% power to detect 1-point change on NRS)

DB: Double-blind; **R:** Randomisation; **W:** Withdrawals and dropouts

GORDH 2008

Gordh TE, Stubhaug A, Jensen TS, Arner S, Biber B, Boivie J, et al. Gabapentin in traumatic nerve injury pain: a randomized, double-blind, placebo-controlled, cross- over, multi-center study. *Pain* 2008;**138**(2):255–66. [DOI: 10.1016/j.pain.2007.12.011]

Description	
Methods	Multicentre, randomised, double-blind, placebo-controlled, cross-over, not enriched. No imputation method mentioned Titration over 2 weeks from 300 mg to maximum pain relief at a tolerable dose or 2400 mg daily, then stable dose for 3 weeks (5 weeks total); 3-week washout, then cross-over
Pain assessment	0-100mm visual analogue scale (minimum baseline pain: 30/100)
Participants	Peripheral nerve injury with pain ≥ 6 months. N = 120, mean age 49 years, 53% women. Initial pain intensity 53/100 Efficacy analysis based on 98 who completed both treatment periods
Interventions	Gabapentin 2400 mg daily (max) Placebo Mean daily dose of gabapentin 2243 ± 402 mg Paracetamol ± codeine and dextropropoxyphene permitted as rescue medication Analgesics and NSAIDs used by ~50% during study
Outcomes	≥ 50% pain relief (weekly mean pain score) ≥ 30% pain relief Marked pain relief (5-point scale) Marked or moderate pain relief (5-point scale) Adverse events Withdrawals
Notes	Oxford Quality Score: R = 2, DB = 2, W = 1, Total = 5 Registration/protocol: Not described

Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	Central, remote allocation, "sealed code envelope"
Blinding? All outcomes	Yes	"capsules that were identical in appearance"
Incomplete outcome data addressed?	Unclear	Imputation not mentioned
Size Efficacy	Unclear	120 randomised
Study duration Efficacy	Unclear	5-week period
Outcomes reported	Yes	At least 50% reduction in pain
Adequate statistical power	Yes	Minimum sample size: 80 (80% power to detect 11mm change on VAS)

DB: Double-blind; **R:** Randomisation; **W:** Withdrawals and dropouts

GORSON 1999

Gorson KC, Schott C, Herman R, Ropper AH. Gabapentin in the treatment of painful diabetic neuropathy: a placebo controlled, double blind, crossover trial. *Journal of Neurology, Neurosurgery and Psychiatry* 1999;**66**:251–2. [PMID: 10071116]

Description	
Methods	Randomised, double-blind, placebo-controlled, cross-over, not enriched. No imputation method mentioned Titration over 3 days to 900 mg, then fixed dose for remainder of 6-week period; 3-week washout, then cross-over
Pain assessment	0-10 numerical pain rating scale (minimum baseline pain: daily moderate pain)
Participants	Painful diabetic neuropathy 1 to 5 years, pain ≥ moderate for over 3 months. N = 40, mean age 62 years, 23% women. Initial pain intensity not reported
Interventions	Gabapentin 900 mg, n = 19 (first phase) Placebo, n = 21 (first phase) Medication for diabetes control remained stable during study. Stable doses of NSAID or narcotics allowed
Outcomes	Pain relief at end of treatment (4-point global score) moderate or excellent Adverse events
Notes	Oxford Quality Score: R = 1, DB = 1, W = 0, Total = 3 Registration/protocol: Not described Other: No separate data for first period, small group sizes, non-standard global scale

Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	Not reported
Blinding? All outcomes	Unclear	Not reported
Incomplete outcome data addressed?	Unclear	Imputation not mentioned
Size Efficacy	No	40 randomised
Study duration Efficacy	Unclear	6-week period
Outcomes reported	Unclear	Moderate or excellent pain relief
Adequate statistical power	Yes	Minimum sample size: 40 (80% power to detect a 20% reduction in pain score)

DB: Double-blind; **NSAID:** Non-steroidal anti-inflammatory drug; **R:** Randomisation; **W:** Withdrawals and dropouts

HAHN 2004

Hahn K, Arendt G, Braun JS, von Giesen HJ, Husstedt IW, et al. German Neuro-AIDS Working Group. A placebo- controlled trial of gabapentin for painful HIV-associated sensory neuropathies. *Journal of Neurology* 2004;**251**(10): 1260–6. [DOI: 10.1007/s00415-004-0529-6]

Description	
Methods	Randomised, double-blind, placebo-controlled, parallel-group, not enriched. No imputation method mentioned Titration over 2 weeks to adequate pain relief or 2400 mg daily, then stable dose for 2 weeks (4 weeks in total)
Pain assessment	0-100mm visual analogue scale (minimum baseline pain: not described)
Participants	Painful HIV sensory neuropathy by standard definitions. N = 26, mean age 45 years, 23% women. Initial mean pain score 4.9/10 (lower limit of range 1.5)
Interventions	Gabapentin 2400 mg daily (max), n = 15 (10 participants took max dose) Placebo, n = 11
Outcomes	No dichotomous efficacy data Adverse events Withdrawals
Notes	Oxford Quality Score: R = 2, DB = 2, W = 1, Total = 5 Registration/protocol: Not described

Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	Remote allocation
Blinding? All outcomes	Yes	"identically appearing capsules"
Incomplete outcome data addressed?	Unclear	Imputation not mentioned
Size Efficacy	No	26 randomised
Study duration Efficacy	Unclear	4 weeks
Outcomes reported	No	No dichotomous data
Adequate statistical power	Unclear	Not described

DB: Double-blind; **R:** Randomisation; **W:** Withdrawals and dropouts

LEVENDOGLU 2004

Levendoglu F, Ogun CO, Ozerbil O, Ogun TC, Ugurlu H. Gabapentin is a first line drug for the treatment of neuropathic pain in spinal cord injury. *Spine* 2004;**29**(7): 743–51. [DOI: 10.1097/01.BRS.0000112068.16108.3A]

Description	
Methods	Randomised, double-blind, placebo-controlled, cross-over, not enriched. No imputation method mentioned Titration to limit of tolerability or maximum of 3600 mg over 4 weeks, then stable dose for remainder of 8-week period; 2-week washout then cross-over
Pain assessment	0-10 numerical pain rating scale (minimum baseline pain: 4/10)
Participants	Complete traumatic SCI at lumbar or thoracic level. N = 20, mean age 36 years, 35% women. Pain duration before treatment ≥ 6 months, initial average daily pain 9/10
Interventions	Gabapentin 3600 mg daily (max) Placebo Mean max tolerated dose of gabapentin 2850 ± 751 mg No concurrent analgesics allowed
Outcomes	Pain reduction (mean data only) Adverse events Withdrawals
Notes	Oxford Quality Score: R = 1, DB = 2, W = 1, Total = 4 Registration/protocol: Not described

Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	Not reported
Blinding? All outcomes	Yes	"identically appearing capsules"
Incomplete outcome data addressed?	Unclear	Imputation not mentioned
Size Efficacy	No	20 randomised
Study duration Efficacy	Yes	8-week period
Outcomes reported	No	No dichotomous data
Adequate statistical power	Yes	Minimum sample size: 17 (80% power to detect 3-point change on NRS)

DB: Double-blind; **LOCF:** Last observation carried forward; **PGIC:** Patients Global Impression of Change; **R:** Randomisation; **W:** Withdrawals and dropouts

RICE 2001

Rice AS, Maton S, Postherpetic Neuralgia Study Group. Gabapentin in postherpetic neuralgia: a randomised, double blind, placebo controlled study. *Pain* 2001;**94**(2):215–24. [DOI: 10.1016/S0304-3959(01)00407-9]

Description	
Methods	Multicentre, randomised, double-blind, placebo-controlled, parallel-group, partial enrichment, LOCF 4 day forced titration, then further titration over 2 weeks to target dose, and stable dose for 4 weeks (7 weeks in total). Participants unable to tolerate dosing regimen were withdrawn
Pain assessment	0-10 numerical pain rating scale (minimum baseline pain: 4/10)
Participants	Postherpetic neuralgia. N = 334, median age 75 years, 59% women. Pain > 3 months after healing of rash, initial average daily pain 6.5/10
Interventions	Gabapentin 1800 mg daily, n = 115 Gabapentin 2400 mg daily, n = 108 Placebo, n = 111
Outcomes	≥ 50% reduction in mean pain score PGIC much or very much improved PGIC much and very much improved (CTR) Adverse events Withdrawals
Notes	Oxford Quality Score: R = 2, DB = 2, W = 1, Total = 5 Registration/protocol: Parke-Davis 945-295 (unpublished report no. RR-430-00124 2000)

Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	List held securely and released only after study completion
Blinding? All outcomes	Yes	"identical-appearing capsules"
Incomplete outcome data addressed?	Unclear	LOCF
Size Efficacy	Yes	334 randomised
Study duration Efficacy	Unclear	7-week period
Outcomes reported	Yes	At least 50% reduction in pain
Adequate statistical power	Yes	Total sample size: 334 (95% power to detect 1-point change on NRS; *post-hoc*)

DB: Double-blind; **LOCF:** Last observation carried forward; **PGIC:** Patients Global Impression of Change; **R:** Randomisation; **W:** Withdrawals and dropouts

RINTALA 2007

Rintala DH, Holmes SA, Courtade D, Fiess RN, Tastard LV, Loubser PG. Comparison of the effectiveness of amitriptyline and gabapentin on chronic neuropathic pain in persons with spinal cord injury. *Archives of Physical Medicine and Rehabilitation* 2007;**88**(12):1547–60. [DOI: 10.1016/j.apmr.2007.07.038]

Description	
Methods	Randomised, double-blind, placebo-controlled, 3-way cross-over, not enriched. No imputation method mentioned Titration over 4 weeks to pain control, limit of tolerability, or maximum amitriptyline 150 mg daily, gabapentin 3600 mg daily, then stable dose for remainder of 8-week period; 1-week washout then cross-over Analysis for completers only
Pain assessment	0-100mm visual analogue scale (minimum baseline pain: 50/100)
Participants	SCI at any level and degree of completeness. N = 38, only 22 patients completed all three cross-overs. Mean age 43 years, 9% women. Pain duration before treatment > 6 months, initial pain intensity 5.6/10
Interventions	Amitriptyline 150 mg daily (max) Gabapentin 3600 mg daily (max) Placebo (diphenhydramine) 75 mg daily Oxycodone + paracetamol 5/325 mg (max 8 tablets daily) allowed for rescue medication
Outcomes	No dichotomous data for efficacy or harm Withdrawals
Notes	Oxford Quality Score: R = 2, DB = 2, W = 1, Total = 5 Registration/protocol: Not described

Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	Prepared, packaged and labelled by remote, commercial compounding pharmacy
Blinding? All outcomes	Yes	"identical capsules"
Incomplete outcome data addressed?	No	Completers only
Size Efficacy	No	38 randomised
Study duration Efficacy	Yes	8-week period
Outcomes reported	No	No dichotomous data
Adequate statistical power	No	Minimum sample size: 31 (80% power to detect an 18mm change on VAS)

DB: Double-blind; **R:** Randomisation; **W:** Withdrawals and dropouts

ROWBOTHAM 1998

Rowbotham M,Harden N,Stacey B,Bernstein P,Magnus-Miller L. Gabapentin for the treatment of postherpetic neuralgia: a randomized controlled trial. *JAMA* 1998;**280** (21):1837–42. [PMID: 9846778]

Description	
Methods	Multicentre, randomised, double-blind, placebo-controlled, parallel-group, no enrichment, LOCF 4-week titration to maximum tolerated dose, or 3600 mg then stable dose for 4 weeks (8 weeks in total)
Pain assessment	0-10 numerical pain rating scale (minimum baseline pain: 4/10)
Participants	Postherpetic neuralgia. N = 229, median age 73 years, 48% women. Pain > 3 months after healing of rash, initial average daily pain 6.4/10
Interventions	Gabapentin 3600 mg daily (max), n = 113. (83% had > 2400 mg daily) Placebo, n = 116
Outcomes	PGIC moderate or much improved PGIC CTR moderate and much improved No change in pain SF36 and QoL Adverse events Withdrawals
Notes	Oxford Quality Score: R = 1, DB = 2, W = 1, Total = 3 Registration/protocol: Parke-Davis 945-211 (unpublished report no. RR-995-00070 1998)

Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	"subject-specific bottles based on randomisation schedule"
Blinding? All outcomes	Yes	"identically appearing capsules"
Incomplete outcome data addressed?	Unclear	LOCF
Size Efficacy	Yes	229 randomised
Study duration Efficacy	Yes	8-week period
Outcomes reported	Yes	PGIC much improved (top level)
Adequate statistical power	Yes	Minimum sample size: 80 per arm (80% power to detect 1.5-point change in NRS)

DB: Double-blind; **LOCF:** Last observation carried forward; **PGIC:** Patients Global Impression of Change; **R:** Randomisation; **W:** Withdrawals and dropouts

SERPELL 2002

Serpell MG, Neuropathic pain study group. Gabapentin in neuropathic pain syndromes: a randomised, double- blind, placebo-controlled trial. *Pain* 2002;**99**(3):557–66. [DOI: 10.1016/S0304-3959(02)00255-5]

Description	
Methods	Multicentre, randomised, double-blind, placebo-controlled, parallel-group, partial enrichment. No imputation method mentioned. Patients withdrawing due to lack of efficacy were defined as non-responders (n = 6), but treatment of substantial AE withdrawals (n = 49) and all-cause withdrawals (n = 73) not reported Titration over 5 weeks from 900 mg daily until pain controlled, or to maximum of 2400 mg daily, then fixed dose (8 weeks in total)
Pain assessment	0-10 numerical pain rating scale (minimum baseline pain: 4/10)
Participants	Mixed neuropathic pain, most common conditions were CRPS (28%), PHN (14%). N = 305, median age 57 years, 53% women. Initial mean pain score 7.2/10 Excluded: individuals who had previously failed to respond to gabapentin at > 900 mg daily, or had experienced intolerable side effects at any dose
Interventions	Gabapentin 2400 mg daily (max), n = 153 Placebo, n = 152 101 took 2400 mg, 189 took 1800 mg, 27 took 900 mg Stable antidepressant therapy and NSAID/opioid therapy for other conditions allowed Paracetamol 500 mg/codeine 30 mg or paracetamol 500 mg (max 8 tablets daily) allowed as rescue medication
Outcomes	> 50% reduction in pain PGIC much or very much improved PGIC much improved and very much improved (CTR) Adverse events Withdrawals
Notes	Oxford Quality Score: R = 2, DB = 2, W = 1, Total = 5 Registration/protocol: Parke Davis/Pfizer 945-430-306

Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	Randomisation list centrally held - remote allocation
Blinding? All outcomes	Yes	"identical capsules"
Incomplete outcome data addressed?	Unclear	Imputation not mentioned
Size Efficacy	Yes	305 randomised
Study duration Efficacy	Yes	8-week period
Outcomes reported	Yes	At least 50% reduction in pain
Adequate statistical power	Unclear	Not described

AE: Adverse events; **DB:** Double-blind; **PGIC:** Patients Global Impression of Change; **R:** Randomisation; **W:** Withdrawals and dropouts

SIMPSON 2001

Simpson DA. Gabapentin and venlafaxine for the treatment of painful diabetic neuropathy. *Journal of Clinical Neuromuscular Disease* 2001;**3**(2):53–62. [PMID: 19078655]

Description	
Methods	Randomised, double-blind, placebo-controlled, parallel-group, not obviously enriched (part 1 of study only) Titration over 4 weeks to maximum tolerated dose, then stable dose for 4 weeks (8 weeks in total)
Pain assessment	0-10 numerical pain rating scale (minimum pain score: 4/10)
Participants	Painful diabetic neuropathy. N = 60, mean age 50 years, 40% female. Pain duration > 3 months before treatment, initial pain score 6.5/10
Interventions	Gabapentin 3600 mg daily (max), n = 30 Placebo, n = 30
Outcomes	PGIC moderate or much improved Adverse events Withdrawals
Notes	Oxford Quality Score: R = 1, DB = 1, W = 1, Total = 3 Registration/protocol: Not described

Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	Not reported
Blinding? All outcomes	Unclear	Not reported
Incomplete outcome data addressed? Efficacy	Unclear	Imputation not mentioned
Size Efficacy	Unclear	60 randomised
Study duration Efficacy	Yes	8-week period
Outcomes reported	Unclear	Moderate or much improved
Adequate statistical power	Unclear	Not described

DB: Double-blind; **PGIC:** Patients Global Impression of Change; **R:** Randomisation; **W:** Withdrawals and dropouts

SMITH 2005

Smith DG, Ehde DM, Hanley MA, Campbell KM, Jensen MP, Hoffman AJ, et al. Efficacy of gabapentin in treating chronic phantom limb and residual limb pain. *Journalof Rehabilitation Research and Development* 2005;**42**(5): 645–54. [DOI: 10.1682/JRRD.2005.05.0082]

Description	
Methods	Randomised, double-blind, placebo-controlled, cross-over, no enrichment. No imputation method mentioned Titration in 300 mg increments every 2 to 3 days until pain intensity of0 or uncomfortable side effects, or maximum 3600 mg daily, then stable dose for remainder of 6-week treatment period, followed by titration off medication in week 7; 5-week washout, then cross-over
Pain assessment	0-10 numerical pain rating scale (minimum baseline pain: 3/10)
Participants	Phantom limb pain and residual limb pain. N = 24, mean age 52 years, 25% women. Time since amputation > 6 months, initial pain intensity 4.4/10
Interventions	Gabapentin 3600 mg daily (max), (19/24 took max dose) Placebo
Outcomes	Meaningful decrease in pain (5-point scale)
Notes	Oxford Quality Score: R = 2, DB = 2, W = 0, Total = 4 Registration/protocol: Not described

Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	Not described
Blinding? All outcomes	Yes	"capsules that were identical in appearance"
Incomplete outcome data addressed? Efficacy	Unclear	Imputation not mentioned
Size Efficacy	No	24 randomised
Study duration Efficacy	Unclear	6-week period
Outcomes reported	Unclear	Meaningful decrease in pain
Adequate statistical power	Unclear	No described

DB: Double-blind; **R:** Randomisation; **W:** Withdrawals and dropouts

Appendix 3

Summary of outcomes of studies included in GRADE assessment

Adapted from: Moore RA, Wiffen PJ, Derry S, Toelle T, Rice ASC. Gabapentin for chronic neuropathic pain and fibromyalgia in adults. *Cochrane Database of Systematic Reviews* **4**: CD007938, 2014. DOI: 10.1002/14651858.CD007938.pub3

BACKONJA 1998

Backonja M, 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 (21):1831–6. [PMID: 9846777]

Withdrawals	Efficacy	Adverse events (general)	Adverse events (specific)
All-cause withdrawal Gabapentin 14/84 Placebo 16/81 *AE withdrawal* Gabapentin 7/84 Placebo 5/81 *LoE withdrawal* Gabapentin 1/84 Placebo 5/81	*Difference in end-point mean pain score (placebo - gabapentin):* *-1.2 (95% CI: -1.9 to -0.6)* *PGIC much or moderately improved* Gabapentin 47/84 Placebo 25/81 *At least 50% reduction in pain (CTR)* Gabapentin 39/84 Placebo 16/81 *PGIC much improved (CTR)* Gabapentin 33/84 Placebo 12/81 *PGIC moderately or much improved (CTR)* Gabapentin 47/84 Placebo 25/81	*At least one AE* Gabapentin 70/84 Placebo 54/81 *Serious AE* Gabapentin 3/84 Placebo 2/81 *Deaths* Gabapentin 0/84 Placebo 0/81	*Dizziness* Gabapentin 20/84 Placebo 4/81 *Somnolence* Gabapentin 19/84 Placebo 5/81

AE: Adverse event; **LoE:** Lack of effect; **PGIC:** Patient Global Impression of Change

BONE 2002

Bone M, Critchley P, Buggy DJ. Gabapentin in postamputation phantom limb pain: a randomized, double- blind, placebo-controlled, cross-over study. *Regional Anesthesia and Pain Medicine* 2002;**27**(5):481–6. [DOI: 10.1053/rapm.2002.35169]

Withdrawals	Efficacy	Adverse events (general)	Adverse events (specific)
No data on where withdrawals occurred	No dichotomous data Significant benefit for gabapentin by week 6 for pain. *Change in average weekly pain score between baseline and end-point (gabapentin vs placebo)*: -3.2 (SD: 2.1) vs -1.6 (SD: 0.7)	No data	*Somnolence* Gabapentin: 7/19 Placebo: 2/19 *Dizziness* Gabapentin: 2/19 Placebo: 1/19

CTR 945-1008

Anonymous. Protocol A9451008. A 15 Week, randomized, double-blind, placebo-controlled, parallel-group, multi- center study of Neurontin (gabapentin) for efficacy and quality of life in patients with painful diabetic peripheral neuropathy. PhrmaWebSynopsis - Final 2 June 2005.

Withdrawals	Efficacy	Adverse events (general)	Adverse events (specific)
*All-cause withdrawa*l Gabapentin 64/200 Placebo 54/189 *AE withdrawal* Gabapentin 27/200 Placebo 18/189 *LoE withdrawal* Gabapentin 1/200 Placebo 4/189	*At least 30% reduction in pain* Gabapentin 113/200 Placebo 77/189 *At least 50% reduction in pain* Gabapentin 77/200 Placebo 46/189	*At least one AE* Gabapentin: 159/200 Placebo: 126/189 *Serious AE* Gabapentin: 15/200 Placebo: 15/189 *Deaths* Gabapentin: 1/200 Placebo: 1/189	*Somnolence* Gabapentin: 31/200 Placebo: 8/189 *Dizziness* Gabapentin: 38/200 Placebo: 15/189 *Asthenia* Gabapentin: 22/200 Placebo: 8/189 *Peripheral oedema* Gabapentin: 33/200 Placebo: 7/189

AE: Adverse event; **LoE:** Lack of effect

GILRON 2005
Gilron I, Bailey JM, Tu D, Holden RR, Weaver DF, Houlden RL. Morphine, gabapentin, or their combination for neuropathic pain. *New England Journal of Medicine* 2005;**352**(13):1324–34. [PMID: 15800228]

Withdrawals	Efficacy	Adverse events (general)	Adverse events (specific)
16 withdrawals during treatment	*At least moderate pain relief (5-point scale) for those completing a given treatment* Gabapentin: 27/44 Morphine: 35/44 Gabapentin + morphine: 32/41 Placebo: 13/42 *Change in average weekly pain score between baseline and end-point (gapapentin vs morphine vs morphine + gabapentin vs placebo):* -1.6 vs -2.0 vs -2.7 vs -1.2	Not interpretable	Not interpretable

GORDH 2008

Gordh TE, Stubhaug A, Jensen TS, Arner S, Biber B, Boivie J, et al. Gabapentin in traumatic nerve injury pain: a randomized, double-blind, placebo-controlled, cross- over, multi-center study. *Pain* 2008;**138**(2):255–66. [DOI: 10.1016/j.pain.2007.12.011]

Withdrawals	Efficacy	Adverse events (general)	Adverse events (specific)
All-cause withdrawal Gabapentin: 11/120 Placebo: 11/120 *AE withdrawal* Gabapentin: 7/120 Placebo: 3/120 *LoE withdrawal* Gabapentin: 1/120 Placebo: 2/120	*Marked pain relief* Gabapentin: 18/98 Placebo: 5/98 *Marked or moderate pain relief* Gabapentin: 31/98 Placebo: 14/98 *No pain relief* Gabapentin: 54/98 Placebo: 70/98 *At least 50% pain relief* Gabapentin: 13/98 Placebo: 9/98 *At least 30% pain relief* Gabapentin: 29/98 Placebo: 19/98 Benefits from gabapentin over placebo for sleep and some aspects of quality of life *Change in average weekly pain score between baseline and end-point (gabapentin vs placebo):* -7.2 (SD: 17.8) vs -6.9 (SD: 15.5) (study period 1) and -5.1 (SD: 11.6) vs -0.5 (SD: 9.7) (study period 2)	*Serious AE* Gabapentin: 5/120 Placebo: 1/120	*Dizziness* Gabapentin: 39/120 Placebo: 9/120

AE: Adverse event; **LoE:** Lack of effect

GORSON 1999

Gorson KC, Schott C, Herman R, Ropper AH. Gabapentin in the treatment of painful diabetic neuropathy: a placebo controlled, double blind, crossover trial. *Journal of Neurology, Neurosurgery and Psychiatry* 1999;**66**:251–2. [PMID: 10071116]

Efficacy	Adverse events (general)
Moderate or excellent pain relief Gabapentin: 17/40 Placebo: 9/40 *Difference in change in pain score between gabapentin and placebo:* 0.4 (95% CI: 0.1 to 0.5)	*At least one AE* Gabapentin: 12/40 Placebo: 4/40 *Serious AE* Gabapentin: 0/40 Placebo: 0/40 *Deaths (inferred*) Gabapentin: 0/40 Placebo: 0/40

AE: Adverse event; **LoE:** Lack of effect

HAHN 2004

Hahn K, Arendt G, Braun JS, von Giesen HJ, Husstedt IW, et al. German Neuro-AIDS Working Group. A placebo- controlled trial of gabapentin for painful HIV-associated sensory neuropathies. *Journal of Neurology* 2004;**251**(10): 1260–6. [DOI: 10.1007/s00415-004-0529-6]

Withdrawals	Efficacy	Adverse events (general)	Adverse events (specific)
All-cause withdrawal Gabapentin: 1/15 Placebo: 1/11 *AE withdrawal* Gabapentin: 1/15 Placebo: 0/11	Improvement in pain and sleep interference with gabapentin and placebo, with sustained difference in sleep but not pain. *Difference in median weekly pain score between baseline and end-point (gabapentin vs placebo):* -2.6 vs -1.4	No serious AE or deaths reported	*Somnolence* Gabapentin: 12/15 Placebo: 2/11 *Dizziness* Gabapentin: 9/15 Placebo: 5/11 *Disturbed gait* Gabapentin: 7/15 Placebo: 3/11

AE: Adverse event

LEVENDOGLU 2004

Levendoglu F, Ogun CO, Ozerbil O, Ogun TC, Ugurlu H. Gabapentin is a first line drug for the treatment of neuropathic pain in spinal cord injury. *Spine* 2004;**29**(7): 743–51. [DOI: 10.1097/01.BRS.0000112068.16108.3A]

Withdrawals	Efficacy	Adverse events (general)	Adverse events (specific)
All completed	*Average fall in pain* Gabapentin: 62% Placebo: 13% Mean scores without standard deviations. No dichotomous results. *Percent change in pain score between baseline and end-point (gabapentin vs placebo):* 62% vs 12%	*All-cause AE* Gabapentin: 13/20 Placebo: 5/20	*Sedation* Gabapentin: 3/20 Placebo: 0/20 *Oedema* Gabapentin: 3/20 Placebo: 0/20

AE: Adverse event

RICE 2001

Rice AS, Maton S, Postherpetic Neuralgia Study Group. Gabapentin in postherpetic neuralgia: a randomised, double blind, placebo controlled study. *Pain* 2001;**94**(2):215–24. [DOI: 10.1016/S0304-3959(01)00407-9]

Withdrawals	Efficacy	Adverse events (general)	Adverse events (specific)
All-cause 22 Gaba 1800mg: 22 Gaba 2400mg: 23 Placebo: 17 *AE withdrawal* Gaba 1800mg: 15 Gaba 2400mg: 19 Placebo: 7 *LoE withdrawal* Gaba 1800mg: 4 Gaba 2400mg: 1 Placebo: 4	*At least 50% reduction in mean pain score* Gaba 1800: 37/115 Gaba 2400: 37/108 Placebo: 16/111 *PGIC very much or much improved* Gaba 1800: 44/115 Gaba 2400: 42/108 Placebo: 24/111 *PGIC very much improved (CTR)* Gaba 1800: 18/115 Gaba 2400: 12/108 Placebo: 7/111 *PGIC much improved (CTR)* Gaba 1800: 26/115 Gaba 2400: 30/108 Placebo: 17/111 *Change in average weekly pain score between baseline and end-point (gabapentin 2400 mg vs gabapentin 1800 mg vs placebo):* -2.3 vs -2.2 vs -1.1	*At least one AE* Gaba 1800: 81/115 Gaba 2400: 81/108 Placebo: 55/111 *Serious AE* Gaba 1800: 3/115 Gaba 2400: 1/108 Placebo: 1/111 *Death* Gaba 1800: 0/115 Gaba 2400: 1/108 Placebo: 0/111	*Somnolence* Gaba 1800: 20/115 Gaba 2400: 22/108 Placebo: 7/111 *Dizziness* Gaba 1800: 36/115 Gaba 2400: 36/108 Placebo: 11/111 *Asthenia* Gaba 1800: 7/115 Gaba 2400: 6/108 Placebo: 4/111 *Peripheral oedema* Gaba 1800: 6/115 Gaba 2400: 12/108 Placebo: 0/111

AE: Adverse event; **LoE:** Lack of effect; **PGIC:** Patient Global Impression of Change

RINTALA 2007

Rintala DH, Holmes SA, Courtade D, Fiess RN, Tastard LV, Loubser PG. Comparison of the effectiveness of amitriptyline and gabapentin on chronic neuropathic pain in persons with spinal cord injury. *Archives of Physical Medicine and Rehabilitation* 2007;**88**(12):1547–60. [DOI: 10.1016/j.apmr.2007.07.038]

Withdrawals	Efficacy	Adverse events (general)	Adverse events (specific)
16/38 withdrew	No dichotomous data. The paper claims statistical superiority of amitriptyline over gabapentin using paired t-tests for 22 patients completing all 3 phases. It also claims no benefit of gabapentin over placebo. *Average pain rating during the 8th week of each study arm (gabapentin vs amitriptyline vs placebo, baseline: 5.6):* 4.9 vs 3.5 vs 5.1	No dichotomous data	No dichotomous data

ROWBOTHAM 1998

Rowbotham M,Harden N,Stacey B,Bernstein P,Magnus-Miller L. Gabapentin for the treatment of postherpetic neuralgia: a randomized controlled trial. *JAMA* 1998;**280** (21):1837–42. [PMID: 9846778]

Withdrawals	Efficacy	Adverse events (general)	Adverse events (specific)
All-cause Gabapentin: 24 Placebo: 21 *AE withdrawal* Gabapentin: 21 Placebo: 14 *LoE withdrawal* Gabapentin: 0 Placebo: 2	*PGIC moderate or much improved* Gabapentin: 47/113 Placebo: 14/116 *PGIC CTR much improved* Gabapentin: 21/113 Placebo: 6/116 *PGIC CTR moderately improved* Gabapentin: 26/113 Placebo: 8/116 *No change in pain* Gabapentin: 23% Placebo: 60% *No change/worse in pain* Gabapentin: 26% Placebo: 68%	*At least one AE* Gabapentin: 84/113 Placebo: 60/116 *Minor AE (treatment related)* Gabapentin: 62/113 Placebo: 32/116 *Serious AE (treatment related)* Gabapentin: 0/113 (10/113 CTR) Placebo: 0/116 (5/116 CTR) *Death:* Gabapentin: 0/113 Placebo: 1/116	*Somnolence* Gabapentin: 31/113 Placebo: 6/116 *Dizziness* Gabapentin: 27/113 Placebo: 6/116 *Ataxia* Gabapentin: 8/113 Placebo: 0/116 *Peripheral oedema* Gabapentin: 11/113 Placebo: 4/116

AE: Adverse event; **LoE:** Lack of effect; **PGIC:** Patient Global Impression of Change

SERPELL 2002

Serpell MG, Neuropathic pain study group. Gabapentin in neuropathic pain syndromes: a randomised, double- blind, placebo-controlled trial. *Pain* 2002;**99**(3):557–66. [DOI: 10.1016/S0304-3959(02)00255-5]

Withdrawals	Efficacy	Adverse events (general)	Adverse events (specific)
All-cause withdrawals Gabapentin: 32/153 Placebo: 41/152 *AE withdrawals* Gabapentin: 24/153 Placebo: 25/152 *LoE withdrawals* Gabapentin: 1/153 Placebo: 5/152	*At least 50% reduction in pain* Gabapentin: 32/153 Placebo: 22/152 *PGIC very much or much improved* Gabapentin: 48/153 Placebo: 22/152 *PGIC very much improved CTR* Gabapentin: 18/153 Placebo: 9/152 *PGIC much improved CTR* Gabapentin: 30/153 Placebo: 13/152 *Change in average weekly pain score between baseline and end-point (gapapentin vs placebo):* -1.5 vs -1.0	*At least one AE* Gabapentin: 117/153 Placebo: 103/152 *Serious AE* Gabapentin: 4/153 Placebo: 4/152 *Deaths* Gabapentin: 0/153 Placebo: 2/152	*Somnolence* Gabapentin: 22/153 Placebo: 8/152 *Dizziness* Gabapentin: 37/153 Placebo: 12/152

AE: Adverse event; **LoE:** Lack of effect; **PGIC:** Patient Global Impression of Change

SIMPSON 2001
Simpson DA. Gabapentin and venlafaxine for the treatment of painful diabetic neuropathy. *Journal of Clinical Neuromuscular Disease* 2001;**3**(2):53–62. [PMID: 19078655]

Withdrawals	Efficacy	Adverse events (general)	Adverse events (specific)
All-cause withdrawal Gabapentin: 3/30 Placebo: 3/30 *AE withdrawal* Gabapentin: 2/30 Placebo: 2/30 *LoE withdrawal* Gabapentin: 1/30 Placebo: 1/30	*PGIC moderate or much improved* Gabapentin: 15/30 Placebo: 7/30 *Mean change in pain score compared to baseline (gabapentin vs placebo):* -2.4 vs 0.4	No deaths reported, and no serious adverse events reported	*Somnolence* Gabapentin: 6/27 Placebo: 1/27 *Dizziness* Gabapentin: 6/27 Placebo: 1/28

AE: Adverse event; **LoE:** Lack of effect

SMITH 2005

Smith DG, Ehde DM, Hanley MA, Campbell KM, Jensen MP, Hoffman AJ, et al. Efficacy of gabapentin in treating chronic phantom limb and residual limb pain. *Journalof Rehabilitation Research and Development* 2005;**42**(5): 645–54. [DOI: 10.1682/JRRD.2005.05.0082]

Withdrawals	Efficacy	Adverse events (general)	Adverse events (specific)
No apparent withdrawals	*"Meaningful decrease in pain"* Gabapentin: 13/24 Placebo: 5/24 *Change in average weekly pain score between baseline and end-point gabapentin vs placebo):* -0.9 vs -0.5 (phantom limb pain) -1.2 vs -0.7 (stump pain)	No data	No data

Appendix 4

Finnerup NB, Attal N, Haroutounian S, McNicol E, Baron R, Dworkin RH, Gilron I, Haanpää M, Hansson P, Jensen TS, Kamerman PR, Lund K, Moore A, Raja SN, Rice AS, Rowbotham M, Sena E, Siddall P, Smith BH, Wallace M

Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis

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Supplementary data

All supplementary information for the systematic review and meta-analysis is available for download.

Access online

Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis

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Summary

Background New drug treatments, clinical trials, and standards of quality for assessment of evidence justify an update of evidence-based recommendations for the pharmacological treatment of neuropathic pain. Using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE), we revised the Special Interest Group on Neuropathic Pain (NeuPSIG) recommendations for the pharmacotherapy of neuropathic pain based on the results of a systematic review and meta-analysis.

Methods Between April, 2013, and January, 2014, NeuPSIG of the International Association for the Study of Pain did a systematic review and meta-analysis of randomised, double-blind studies of oral and topical pharmacotherapy for neuropathic pain, including studies published in peer-reviewed journals since January, 1966, and unpublished trials retrieved from ClinicalTrials.gov and websites of pharmaceutical companies. We used number needed to treat (NNT) for 50% pain relief as a primary measure and assessed publication bias; NNT was calculated with the fixed-effects Mantel-Haenszel method.

Findings 229 studies were included in the meta-analysis. Analysis of publication bias suggested a 10% overstatement of treatment effects. Studies published in peer-reviewed journals reported greater effects than did unpublished studies (r^2 9·3%, p=0·009). Trial outcomes were generally modest: in particular, combined NNTs were 6·4 (95% CI 5·2–8·4) for serotonin-noradrenaline reuptake inhibitors, mainly including duloxetine (nine of 14 studies); 7·7 (6·5–9·4) for pregabalin; 7·2 (5·9–9·21) for gabapentin, including gabapentin extended release and enacarbil; and 10·6 (7·4–19·0) for capsaicin high-concentration patches. NNTs were lower for tricyclic antidepressants, strong opioids, tramadol, and botulinum toxin A, and undetermined for lidocaine patches. Based on GRADE, final quality of evidence was moderate or high for all treatments apart from lidocaine patches; tolerability and safety, and values and preferences were higher for topical drugs; and cost was lower for tricyclic antidepressants and tramadol. These findings permitted a strong recommendation for use and proposal as first-line treatment in neuropathic pain for tricyclic antidepressants, serotonin-noradrenaline reuptake inhibitors, pregabalin, and gabapentin; a weak recommendation for use and proposal as second line for lidocaine patches, capsaicin high-concentration patches, and tramadol; and a weak recommendation for use and proposal as third line for strong opioids and botulinum toxin A. Topical agents and botulinum toxin A are recommended for peripheral neuropathic pain only.

Interpretation Our results support a revision of the NeuPSIG recommendations for the pharmacotherapy of neuropathic pain. Inadequate response to drug treatments constitutes a substantial unmet need in patients with neuropathic pain. Modest efficacy, large placebo responses, heterogeneous diagnostic criteria, and poor phenotypic profiling probably account for moderate trial outcomes and should be taken into account in future studies.

Funding NeuPSIG of the International Association for the Study of Pain.

Introduction

Neuropathic pain, caused by a lesion or disease affecting the somatosensory nervous system,[1] has a substantial effect on quality of life and is associated with a high economic burden for the individual and society.[2–4] It is now regarded as a distinct clinical entity despite a large variety of causes.[5]

Epidemiological surveys have shown that many patients with neuropathic pain do not receive appropriate treatment.[2,6,7] The reasons might be low diagnostic accuracy and ineffective drugs, and perhaps also insufficient knowledge about effective drugs and their appropriate use in clinical practice.[8] Evidence-based recommendations for the pharmacotherapy of neuropathic pain are therefore essential.

Over the past 10 years, a few recommendations have been proposed for the pharmacotherapy of neuropathic pain[9–11] or specific neuropathic pain disorders, particularly painful diabetic neuropathies and post-herpetic neuralgia.[12–14] Meanwhile, new pharmacological therapies have been developed and high-quality clinical trials have been done. Previously undisclosed and unpublished large trials can now be identified online (ClinicalTrials.gov and pharmaceutical industry websites), which, together with an analysis of publication bias, might reduce the risk of bias in reporting data. Furthermore,

there were some discrepancies in previous recommendations due to inconsistencies in methods used to assess the quality of evidence.[13,15,16] To address these inconsistencies, the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) was introduced in 2000[17,18] and received widespread international acceptance. Together, these reasons justify an update of the evidence-based recommendations for the pharmacotherapy of neuropathic pain.

We did a systematic review and meta-analysis of randomised controlled trials of all drug treatments for neuropathic pain published since 1966 and of unpublished trials with available results, and assessed publication bias. We used GRADE to rate the quality of evidence and the strength of recommendations.[17,18] On the basis of the updated review and meta-analysis, we revised the recommendations of the Special Interest Group on Neuropathic Pain (NeuPSIG) of the International Association for the Study of Pain for the systemic and topical pharmacological treatment of neuropathic pain.[19] Non-pharmacological management strategies such as neurostimulation techniques were beyond the scope of this work.[20]

Methods

Search strategy and selection criteria

We followed the 23-item Appraisal of Guidelines for Research and Evaluation (AGREE II) for developing and reporting recommendations.[21] For details of the working group, criteria for eligibility of studies for the analysis, search methods, reporting, and statistical analysis, see the appendix.

The systematic review of the literature complied with the PRISMA statement.[22] We used a standardised review and data extraction protocol (unpublished, appendix). The full reports of randomised, controlled, double-blind studies published in peer-reviewed journals between January, 1966, and April, 2013, were identified with searches of PubMed, Medline, the Cochrane Central Register of Controlled Trials, and Embase. Additional papers were identified from published reviews and the reference lists of selected papers. Studies reporting results were searched in all primary registries in the WHO Registry Network and in registries approved by the International Committee of Medical Journal Editors in April, 2013 (appendix). Only ClinicalTrials.gov had relevant data. An additional search up to Jan 31, 2014, retrieved papers from PubMed and the ClinicalTrials.gov website. Data from a search in May, 2009, of the Pharmaceutical Research and Manufacturers of America (PhRMA) clinical study results website were also included.[23]

The target population was patients of any age with neuropathic pain according to the International Association for the Study of Pain definition (ie, pain caused by a lesion or disease of the somatosensory nervous system):[1] post-herpetic neuralgia, diabetic and non-diabetic painful polyneuropathy, post-amputation pain, post-traumatic or post-surgical neuropathic pain including plexus avulsion and complex regional pain syndrome type 2 (which was generally subsumed into post-traumatic or post-surgical neuropathic pain), central post-stroke pain, spinal cord injury pain, and multiple-sclerosis-associated pain. Neuropathic pain pertaining to different causes was also included. Neuropathic pain associated with nociceptive components (eg, neuropathic cancer-related pain and radiculopathy) was included if the primary outcome of the study was related to neuropathic pain. Disorders such as complex regional pain syndrome type 1, low back pain without radicular pain, fibromyalgia, and atypical facial pain were not included because they do not meet the current definition of neuropathic pain.[1] Trigeminal neuralgia was assessed separately because the response to drug treatment was generally distinct from other neuropathic pain.[10,24]

The interventions were systemic or topical treatments (oral, sublingual, oropharyngeal, intranasal, topical, subcutaneous, intradermal, and smoking) with at least 3 weeks of treatment. Single-administration treatments with long-term efficacy (high-concentration capsaicin patches and botulinum toxin) were included if there was a minimum follow-up of 3 weeks. Studies in which intramuscular, intravenous, or neuroaxial routes of administration were used and those of pre-emptive analgesia were excluded (for details, see Dworkin and colleagues[20]).

We included randomised, double-blind, placebo-controlled studies with parallel group or crossover study designs that had at least ten patients per group. We separately summarised enriched-enrolment, randomised withdrawal trials. We excluded studies published only as abstracts and included double-blind, active comparator trials of drugs generally proposed as first-line or second-line treatments.[23] The study outcome (positive or negative) was based on the effect on the primary outcome measure—eg, neuropathic pain intensity. We excluded studies in which the primary outcome included a composite score of pain and paraesthesia or paraesthesia only.

Five investigators (SH, EM, KL, NBF, and NA) assessed studies for methodological quality by using the five-point Oxford Quality Scale (appendix).[25] A minimum score of 2 of 5 (randomised and double-blind study) was required for inclusion.[25] We also assessed the serious risk of bias relating to absence of allocation concealment, incomplete accounting of outcome events, selective outcome reporting, stopping early for benefit, use of invalidated outcome measures, and carryover effects in crossover trials.

Evidence summary and reporting

The GRADE classification was used to assess recommendations based on the results from a group of randomised controlled trials of the same drug or drug class when relevant (eg, tricyclic antidepressants),[17,18] with final quality of evidence rated as strong or weak for the

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For more on the **Special Interest Group on Neuropathic Pain of the International Association for the Study of Pain** see http://www.neupsig.org

See Online for appendix

treatment, strong or weak against the treatment, or inconclusive (the last category was added because of the large number of inconsistent results in randomised controlled trials). We did not do a new health economic analysis of costs,[16] but estimated three levels of drug costs in various countries in relation to the average price of oral drugs for each country using price data for the daily dose as defined by WHO (appendix). The mean of these percentages for the countries was calculated, and the cost was rated as low if it was less than 67%, moderate if 67–300%, and high if more than 300% of the mean across all drugs. The final recommendations were agreed on by consensus of the authors.

Statistical analysis

Number needed to treat (NNT) for 50% pain intensity reduction (or 30% pain reduction or at least moderate pain relief) was the primary effect measure, and the number needed to harm (NNH) was calculated as the number of patients who needed to be treated for one patient to drop out because of adverse effects. The 95% CIs for NNT and NNH were calculated as the reciprocal values of the 95% CIs for the absolute risk difference by use of the normal approximation. In dose-finding studies, data from subgroups treated with low doses (eg, pregabalin 150 mg) were not included in the meta-analysis. Difference in pain intensity was a secondary outcome. Serious and common (>10% incidence) adverse events were recorded on the data extraction form (appendix).

We used funnel plots,[26] Egger's regression,[27] and Duval and Tweedie's non-parametric trim-and-fill approach[28] to assess publication bias (appendix). Additionally, we estimated the susceptibility to bias for individual drug classes.[29,30] The extent to which the variability (heterogeneity) in treatment effects is explained by publication in a peer-reviewed journal was assessed with meta-regression. Heterogeneity in trials was presented as a L'Abbé plot[31] and as the I^2 statistic.

Role of the funding source

NA, NBF, PRK, RB, ASCR, MH, SNR, and BHS are members of the NeuPSIG management committee and had a role in study design, data gathering, data analysis, data interpretation, and the writing of the report. The corresponding author and all co-authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Figure 1 shows the results of the database and registry search. 191 published reports and 21 unpublished studies were included in the quantitative synthesis. Study characteristics are summarised in the appendix. Additionally, five published and 12 unpublished studies were retrieved between April, 2013, and January, 2014. Thus, a total of 229 reports or studies were included (see appendix for details of the references).

In studies eligible for inclusion in the meta-analysis, the following drugs were investigated: tricyclic antidepressants, serotonin-noradrenaline reuptake inhibitor antidepressants, other antidepressants, pregabalin, gabapentin or gabapentin extended release and enacarbil, other antiepileptics, tramadol, opioids, cannabinoids, lidocaine 5% patch, capsaicin high-concentration patch and cream, botulinum toxin A, NMDA antagonists, mexiletine, miscellaneous topical treatments, newer systemic drugs, and combination therapies. 127 (55%) of 229 trials were done in patients with diabetic painful polyneuropathy or post-herpetic neuralgia. NNT and NNH could be calculated in 176 (77%) of 229 published placebo-controlled trials.

The Oxford Quality Scale (Jadad) scores for individual trials are presented in the appendix. The mean score was 4·1 (SD 0·87, range 2–5). It was lower for older studies of tricyclic antidepressants and capsaicin (3–4) and higher for more recent studies of pregabalin, gabapentin, serotonin-noradrenaline reuptake inhibitors, opioids, and capsaicin high-concentration patches (>4). Detailed descriptions of the limitations of individual studies are available from the corresponding authors on request.

Figures 2 and 3 show the NNT for individual studies for drugs with strong recommendation for use (see

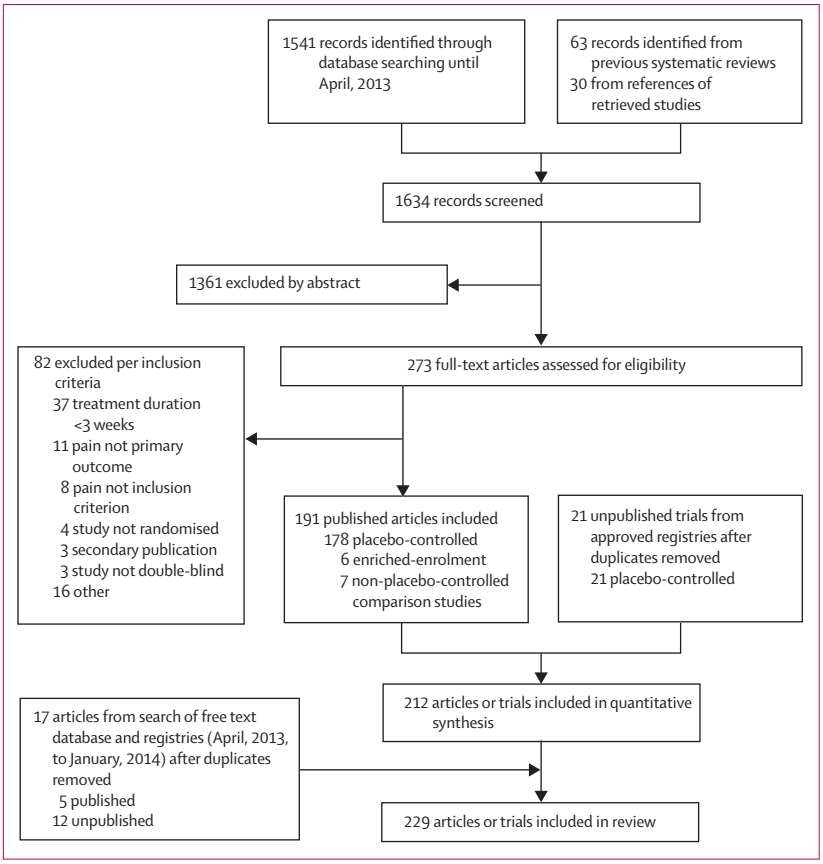

Figure 1: **Flow chart of study selection**

appendix for other drugs) and the appendix shows the heterogeneity and the L'Abbé plot. Heterogeneity, particularly that which was not easily explained by differences in drug dose, diagnosis, and size of placebo response, was included in the GRADE recommendation.

165 published or unpublished trials with dichotomous data were analysed for publication bias. The funnel plot showed asymmetry, which was confirmed by use of Egger's regression test (figure 4A and B). The trim-and-fill method suggested 34 theoretical missing studies (figure 4C) and we adjusted our effect size from an odds ratio of 1·8 (95% CI 1·7–1·9) to 1·6 (1·5–1·7). This suggests about a 10% overstatement of treatment effects. Table 1 provides a summary of the analysis of

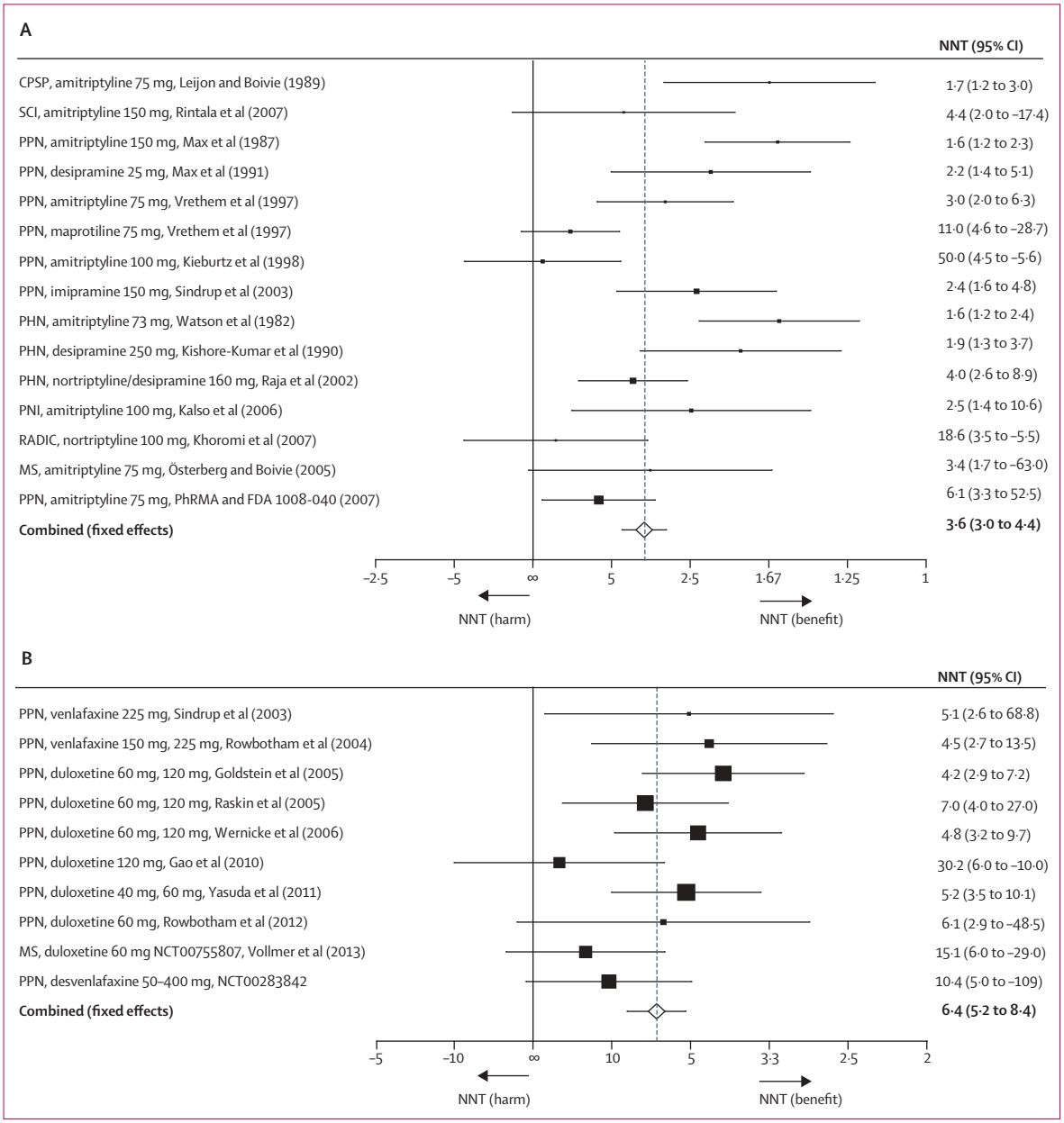

Figure 2: **Forest plot of data for tricyclic antidepressants (A) and serotonin-noradrenaline reuptake inhibitors (B) included in the meta-analysis**
NNTs with 95% CI are shown for each trial and for the overall estimate (fixed effects, Mantel-Haenszel) for first-line drugs. The size of the square represents the Mantel-Haenszel weight that the study exerts in the meta-analysis. The solid line indicates the NNT of infinity, corresponding to an absolute risk difference of zero (no effect). A positive NNT indicates benefit of the drug over placebo and a negative NNT indicates that pain intensity is higher during drug treatment than during placebo treatment (harm). The dotted line represents the overall estimate. References for the studies are provided in the appendix. NNT=number needed to treat. CPSP=central post-stroke pain. SCI=spinal cord injury pain. PPN=painful polyneuropathy. FDA=US Food and Drug Administration. PHN=post-herpetic neuralgia. PNI=peripheral nerve injury. RADIC=painful radiculopathy. MS=multiple sclerosis. PhRMA= Pharmaceutical Research and Manufacturers of America.

the susceptibility to publication bias in individual drug classes. Only the estimated effect size of capsaicin 8% patches showed susceptibility to change to a clinical non-significant effect if studies with no effect were published. Using meta-regression, we identified that for studies published in peer-reviewed journals the

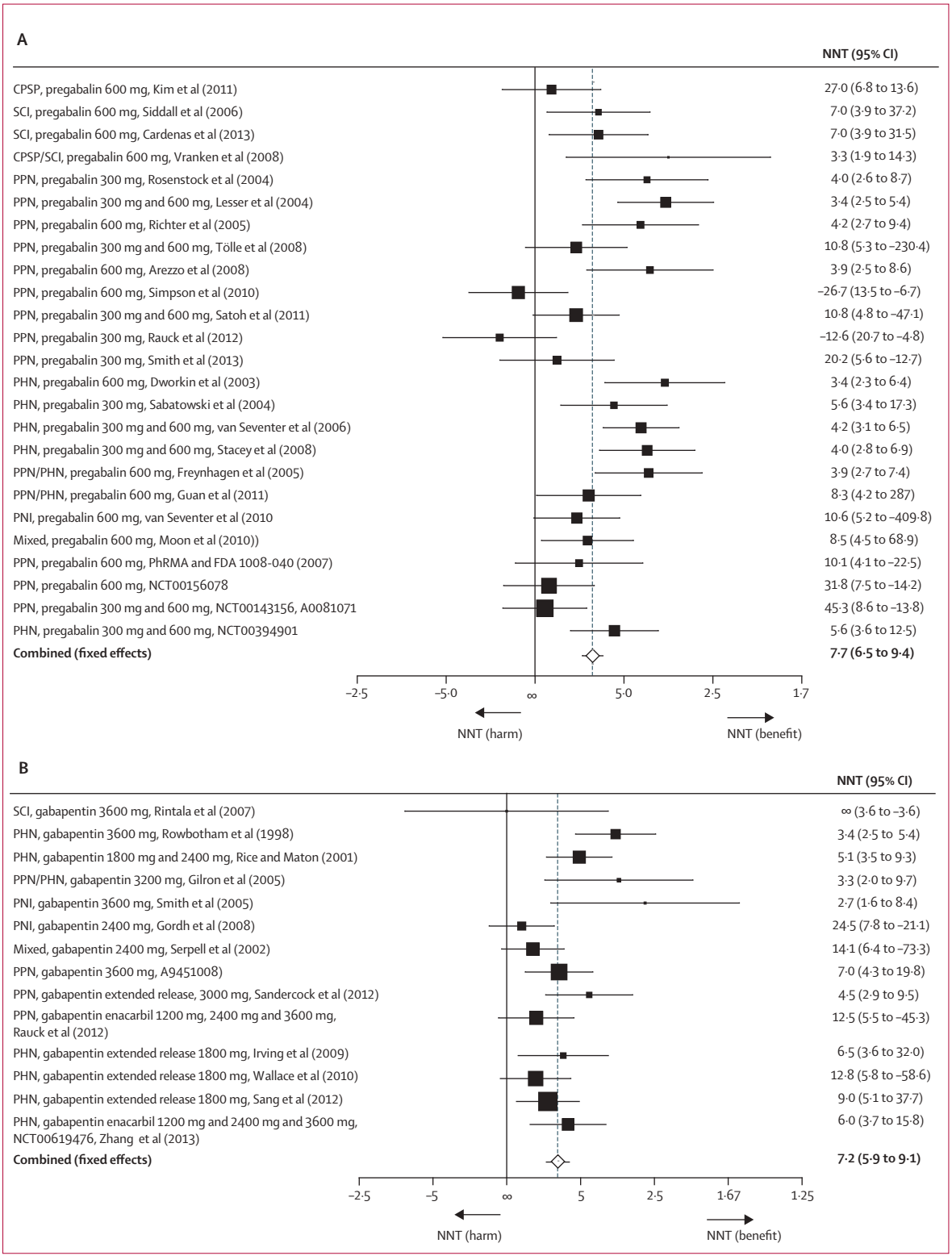

***Figure 3*: Forest plot of data for pregabalin (A) and gabapentin including extended release and enacarbil (B) included in the meta-analysis**

NNTs with 95% CI are shown for each trial and for the overall estimate (fixed effects, Mantel-Haenszel) for first-line drugs. The size of the square represents the Mantel-Haenszel weight that the study exerts in the meta-analysis. The solid line indicates the NNT of infinity, corresponding to an absolute risk difference of zero (no effect). A positive NNT indicates benefit of the drug over placebo and a negative NNT indicates that pain intensity is higher during drug treatment than during placebo treatment (harm). The dotted line represents the overall estimate. References for the studies are provided in the appendix. NNT=number needed to treat. CPSP=central post-stroke pain. SCI=spinal cord injury pain. PPN=painful polyneuropathy. FDA=US Food and Drug Administration. PHN=post-herpetic neuralgia. PNI=peripheral nerve injury. PhRMA= Pharmaceutical Research and Manufacturers of America.

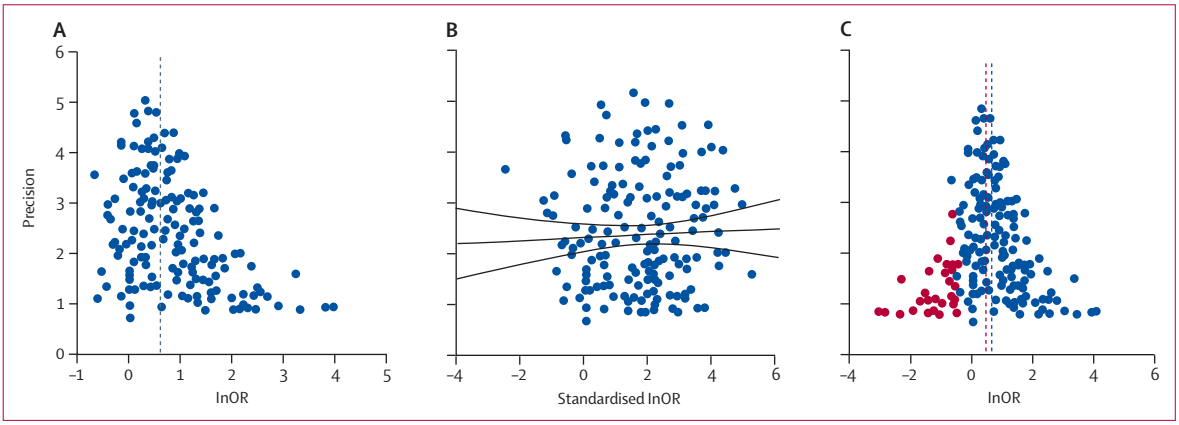

Figure 4: **Evidence of publication (reporting) bias**
(A) Funnel plot showing the precision (inverse of SE) against the effect size; in the absence of bias the points should resemble a symmetrical inverted funnel. (B) Egger's regression showing the precision plotted against the standardised effect size; the 95% CIs of the regression line do not include the origin, suggesting funnel plot asymmetry. (C) Funnel plot showing the additional missing studies imputed by trim and fill in red; the red vertical line indicates the possible summary if the theoretical missing studies were to be included. InOR=natural log of the odds ratio.

reported treatment effects were greater (2·2, 1·5–3·0, n=153; adjusted r^2 9·3%, p=0·009) than were those for studies identified through online repositories (1·4, 1·0–1·9, n=17).

The results of individual and combined NNT and NNH for placebo-controlled studies are presented in the appendix, along with other studies, quality of evidence, and risk differences calculated with fixed-effect and random-effects models. Generally, there was no evidence of different efficacies for most drugs in distinct neuropathic pain disorders (figures 2, 3; appendix). Few studies lasted longer than 12 weeks, with the longest lasting 24 weeks.

In 18 placebo-controlled trials (20 comparisons with placebo, of which seven comparisons had active placebos; 12 trials assessed amitriptyline [25–150 mg/day]), 16 comparisons were positive. The final quality of evidence was moderate (appendix). There was no evidence of a dose-response effect. Combined NNT for 15 studies was 3·6 (95% CI 3·0–4·4) and NNH was 13·4 (9·3–24·4).

We identified 14 studies of serotonin-noradrenaline reuptake inhibitors with available results: nine with duloxetine (20–120 mg, seven positive), four with venlafaxine (doses 150–225 mg/day, two positive, and two negative with low doses), one with desvenlafaxine (negative; appendix). The final quality of evidence was high. Combined NNT was 6·4 (5·2–8·4) and NNH was 11·8 (9·5–15·2).

18 of 25 placebo-controlled randomised trials of pregabalin (150–600 mg/day) were positive, with high final quality of evidence (appendix). There was a dose-response gradient (higher response with 600 mg daily than with 300 mg daily; data not shown). Two trials of HIV-related painful polyneuropathy with high placebo responses were negative (34% and 43% had 50% pain relief with placebo). Combined NNT was 7·7 (95% CI 6·5–9·4) and NNH was 13·9 (11·6–17·4).

	Comparisons*	Participants†	Active pain relief	Placebo	Number needed to treat (95% CI)	Susceptibility to bias‡
Tricyclic antidepressants	15	948	217/473	85/475	3·6 (3·0–4·4)	1973
Serotonin-noradrenaline reuptake inhibitors	10	2541	676/1559	278/982	6·4 (5·2–8·4)	1826
Pregabalin	25	5940	1359/3530	578/2410	7·7 (6·5–9·4)	2534
Gabapentin§	14	3503	719/2073	291/1430	7·2 (5·9–9·1)	1879
Tramadol	6	741	176/380	96/361	4·7 (3·6–6·7)	982
Strong opioids	7	838	211/426	108/412	4·3 (3·4–5·8)	1326
Capsaicin 8%	6	2073	466/1299	212/774	10·6 (7·4–18·8)	70¶
Botulinum toxin A	4	137	42/70	4/67	1·9 (1·5–2·4)	678

Data are number, unless otherwise indicated. *Number of comparisons with placebo in published trials and unpublished trials included in the meta-analysis; results from registries were included if they reported numbers of responders. †Total number of patients treated with active treatment and placebo; patients were counted twice if the study had a crossover design. ‡Number of patients needed to be treated in a new study showing no effect to make the number needed to treat (NNT) greater than 11, which is the cutoff for clinical relevance; susceptibility to publication bias implies that a new study with fewer than 400 participants with no effect might increase the NNT to greater than 11. §Including gabapentin extended release and enacarbil. ¶Susceptible to publication bias.

Table 1: **Analysis of susceptibility to bias in published and unpublished trials**

We identified 14 randomised controlled trials of gabapentin (900–3600 mg/day; nine positive) and six of gabapentin extended release or gabapentin enacarbil (1200–3600 mg/day; four positive). Combined NNT was 6·3 (95% CI 5·0–8·3) for gabapentin and 8·3 (6·2–13·0) for gabapentin extended release or enacarbil. There was no evidence of a dose-response effect. Safety was good (NNH 25·6, 15·3–78·6, for gabapentin and 31·9, 17·1–230·0, for gabapentin extended release or enacarbil).

Most studies with other antiepileptic drugs were negative. Topiramate, zonisamide, and oxcarbazepine or carbamazepine had the poorest safety profiles, with a combined NNH of 6·3 (95% CI 5·1–8·0), 2·0 (1·3–4·6), and 5·5 (4·3–7·9), respectively.

Tramadol is a weak opioid agonist and a serotonin-noradrenaline reuptake inhibitor. All seven studies of tramadol (mainly tramadol extended release up to 400 mg/day) were positive, with moderate final quality of evidence (appendix). Combined NNT was 4·7 (95% CI 3·6–6·7), with the highest NNT (6·4) in the largest study (appendix). Combined NNH was 12·6 (8·4–25·3).

Tapentadol is a μ opioid agonist with noradrenaline reuptake inhibition. We identified one negative study and one positive enrichment study of tapentadol extended release; the study of the extended release formulation had potential bias (probable unmasking of the patients enrolled in the double-blind period) and high NNT (10·2, 95% CI 5·3–185·5) in 67% of the patients responding to the open phase.

We identified 13 trials of strong opioids, in which oxycodone (10–120 mg/day) and morphine (90–240 mg/day) were used mainly in peripheral neuropathic pain. The final quality of evidence was moderate. Ten trials were positive: combined NNT was 4·3 (95% CI 3·4–5·8) and NNH was 11·7 (8·4–19·3). Maximum effectiveness seemed to be associated with 180 mg morphine or equivalent (no additional benefit for higher doses; appendix).

Nabiximols (Sativex) is an oromucosally delivered spray prepared from extracts of the plant cannabis sativa with several active constituents (mainly standardised 27 mg/mL Δ-9-tetrahydrocannabinol and 25 mg/mL cannabidiol). We identified nine trials of nabiximols in neuropathic pain, of which only two were positive. One of these two studies of pain associated with multiple sclerosis was positive, whereas the other larger study had a negative primary outcome.

Based on our inclusion criteria (trials of at least 3 weeks), we identified only one small negative study of 5% lidocaine patches in post-surgical neuropathic pain and two enriched-enrolment studies in post-herpetic neuralgia. The smaller study was positive; the larger study was negative in the intention-to-treat population, but positive in the per-protocol population. However, studies of shorter duration were positive, and safety and tolerability were good in all cases.[23]

The results of five of seven studies (in patients with post-herpetic neuralgia or HIV-related painful polyneuropathy) showed sustained efficacy of a single application of high-concentration capsaicin patch (8%, better results for 60 min application in post-herpetic neuralgia and 30 min in HIV neuropathy) compared with a low-concentration patch (0·04%, to minimise the risk of unmasking related to the burning sensation of capsaicin).

	Total daily dose and dose regimen	Recommendations
Strong recommendations for use		
Gapabentin	1200–3600 mg, in three divided doses	First line
Gabapentin extended release or enacarbil	1200–3600 mg, in two divided doses	First line
Pregabalin	300–600 mg, in two divided doses	First line
Serotonin-noradrenaline reuptake inhibitors duloxetine or venlafaxine*	60–120 mg, once a day (duloxetine); 150–225 mg, once a day (venlafaxine extended release)	First line
Tricyclic antidepressants	25–150 mg, once a day or in two divided doses	First line†
Weak recommendations for use		
Capsaicin 8% patches	One to four patches to the painful area for 30-60 min every 3 months	Second line (peripheral neuropathic pain)‡
Lidocaine patches	One to three patches to the region of pain once a day for up to 12 h	Second line (peripheral neuropathic pain)
Tramadol	200–400 mg, in two (tramadol extended release) or three divided doses	Second line
Botulinum toxin A (subcutaneously)	50–200 units to the painful area every 3 months	Third line; specialist use (peripheral neuropathic pain)
Strong opioids	Individual titration	Third line§

GRADE=Grading of Recommendations Assessment, Development, and Evaluation (see appendix for details about the GRADE classification). *Duloxetine is the most studied, and therefore recommended, of the serotonin-noradrenaline reuptake inhibitors. †Tricyclic antidepressants generally have similar efficacy (appendix); tertiary amine tricyclic antidepressants (amitriptyline, imipramine, and clomipramine) are not recommended at doses greater than 75 mg/day in adults aged 65 years and older because of major anticholinergic and sedative side-effects and potential risk of falls;[33] an increased risk of sudden cardiac death has been reported with tricyclic antidepressants at doses greater than 100 mg daily.[34] ‡The long-term safety of repeated applications of high-concentration capsaicin patches in patients has not been clearly established, particularly with respect to degeneration of epidermal nerve fibres, which might be a cause for concern in progressive neuropathy. §Sustained release oxycodone and morphine have been the most studied opioids (maximum doses of 120 mg/day and 240 mg/day, respectively, in clinical trials; appendix); long-term opioid use might be associated with abuse, particularly at high doses, cognitive impairment, and endocrine and immunological changes.[35-37]

Table 2: **Drugs or drug classes with strong or weak recommendations for use based on the GRADE classification**

Panel: **Drugs or drug classes with inconclusive recommendations for use or recommendations against use based on the GRADE classification**

Inconclusive recommendations

- Combination therapy
- Capsaicin cream
- Carbamazepine
- Clonidine topical
- Lacosamide
- Lamotrigine
- NMDA antagonists
- Oxcarbazepine
- SSRI antidepressants
- Tapentadol
- Topiramate
- Zonisamide

Weak recommendations against use

- Cannabinoids
- Valproate

Strong recommendations against use

- Levetiracetam
- Mexiletine

GRADE=Grading of Recommendations Assessment, Development, and Evaluation (see appendix for details about the GRADE classification).

The final quality of evidence was high. Combined NNT was 10·6 (95% CI 7·4–18·8). Results for the secondary outcomes were inconsistent (data not shown).

Six randomised controlled trials to assess the efficacy of a single administration of botulinum toxin A (50–200 units, subcutaneously, in the region of pain) in peripheral neuropathic pain were identified. The smaller studies had a positive primary outcome (NNT 1·9, 95% CI 1·5–2·4, for four studies) with a low placebo effect, but one large, unpublished study was negative. Safety was generally good (appendix).

Results for other drugs (selective serotonin reuptake inhibitor antidepressants, capsaicin cream, NMDA antagonists, Δ-9-tetrahydrocannabinol, mexiletine, and newer topical or oral drugs) are reported in the appendix. There were no randomised controlled trials with conventional non-opioid analgesics (non-steroidal anti-inflammatory drugs or acetaminophen).

Of seven randomised controlled trials of various combination therapies in neuropathic pain (appendix), the results of two showed that gabapentin combined with morphine or nortriptyline was superior to drugs given as monotherapies (and placebo in one study) at reduced doses, with no more side-effects. However, the results of the largest study (not placebo controlled) showed no difference in efficacy or side-effects between pregabalin combined with duloxetine at moderate doses (300 mg/day and 60 mg/day, respectively) and pregabalin and duloxetine monotherapies at high doses (600 mg/day and 120 mg/day, respectively) in patients unresponsive to monotherapy at moderate doses.

We identified seven comparative randomised controlled trials without placebo (appendix). Neither individual studies nor their statistical combination showed significant differences in efficacy or safety between drugs. Despite small sample sizes and unknown assay sensitivity because of the absence of a placebo, results suggested similar efficacy for first-line and most second-line recommended treatments.

There was generally no evidence of efficacy for particular drugs in specific disorders. Therefore, these recommendations apply to neuropathic pain in general. However, they might not be applicable to trigeminal neuralgia, for which we could extract only one study complying with our inclusion criteria. We therefore recommend referring to previous specific guidelines for this disorder.[10,24] Few studies included cancer-related neuropathic pain; the recommendations for the use of opioids might be different in certain cancer populations. Similarly, these recommendations do not apply to acute pain or acute pain exacerbation. Treatment of neuropathic pain in children is neglected.[32] None of the studies assessed paediatric neuropathic pain and therefore the current guidelines only apply to adults.

Details of the GRADE recommendations and practical use are provided in table 2, the panel, table 3, and the appendix. A few relevant trials have been reported since our meta-analysis, but none affected the recommendations (appendix). Based mainly on moderate or high quality of evidence and efficacy in most trials, tricyclic antidepressants, serotonin-noradrenaline reuptake inhibitor antidepressants (particularly duloxetine), pregabalin, gabapentin, gabapentin extended release and enacarbil have strong GRADE recommendations for use in neuropathic pain and are proposed as first-line treatments, with caution recommended for several tricyclic antidepressants at high doses (table 2). Tramadol, lidocaine patches, and high-concentration capsaicin patches have weak GRADE recommendations for use and are proposed as generally second line because of lower tolerability or safety (tramadol), and low effect sizes but high values or preferences and tolerability or safety (topical agents). Topical treatments are recommended for peripheral neuropathic pain with presumed local pain

	First-line drugs			Second-line drugs			Third-line drugs	
	Serotonin-noradrenaline reuptake inhibitors duloxetine and venlafaxine	Tricyclic antidepressants	Pregabalin, gabapentin, gabapentin extended release or enacarbil	Tramadol	Capsaicin 8% patches	Lidocaine patches	Strong opioids	Botulinum toxin A
Quality of evidence	High	Moderate	High	Moderate	High	Low	Moderate	Moderate
Balance between desirable and undesirable effects								
Effect size	Moderate	Moderate	Moderate	Moderate	Low	Unknown	Moderate	Moderate
Tolerability and safety*	Moderate	Low-moderate	Moderate-high	Low-moderate	Moderate-high	High	Low-moderate	High
Values and preferences	Low-moderate	Low-moderate	Low-moderate	Low-moderate	High	High	Low-moderate	High
Cost and resource allocation	Low-moderate	Low	Low-moderate	Low	Moderate-high	Moderate-high	Low-moderate	Moderate-high
Strength of recommendation	Strong	Strong	Strong	Weak	Weak	Weak	Weak	Weak
Neuropathic pain conditions	All	All	All	All	Peripheral	Peripheral	All	Peripheral

GRADE=Grading of Recommendations Assessment, Development, and Evaluation (see appendix for details about the GRADE classification). *Common side-effects: antidepressants: somnolence, constipation, dry mouth (particularly with tricyclic antidepressants), and nausea (particularly duloxetine); pregabalin or gabapentin: somnolence, dizziness, and weight gain; opioids (including tramadol): constipation, nausea, vomiting, tiredness, somnolence, dizziness, dry mouth, and itch; lidocaine patches: local irritation; capsaicin patches: local pain, oedema, and erythema; botulinum toxin A: local pain; see the appendix for further information about safety issues.

Table 3: **Summary of GRADE recommendations**

generator, such as post-herpetic neuralgia, post-traumatic painful neuropathies, and painful polyneuropathies. In some circumstances—eg, when there are concerns because of side-effects or safety of first-line treatments, particularly in frail and elderly patients—lidocaine patches might be a first-line option.

Strong opioids (particularly oxycodone and morphine) and botulinum toxin A (specialist use for peripheral neuropathic pain with presumed local pain generator) have weak GRADE recommendations for use and are recommended as third line mainly because of safety concerns (opioids) or weak quality of evidence (botulinum toxin A). Prescription of strong opioids should be strictly monitored, particularly for patients requiring high doses (including tracking the dose in morphine equivalence, use of risk assessment methods and treatment agreements).[38,39]

The GRADE recommendations for tapentadol, other antiepileptics, capsaicin cream, topical clonidine, selective serotonin reuptake inhibitor antidepressants, NMDA antagonists, and combination therapy[40–42] are inconclusive mainly because of discrepant findings. However, the combination of pregabalin or gabapentin and duloxetine or tricyclic antidepressants might be an alternative option to increasing doses of monotherapy for patients unresponsive to moderate doses of monotherapy (see appendix for details).

Cannabinoids and valproate have weak recommendations against their use in neuropathic pain and levetiracetam and mexiletine have strong recommendations against their use because of generally negative trials or safety concerns, or both (see appendix for details).

	NeuPSIG recommendation for future trials in neuropathic pain
Patient population (appendix)	
All randomised controlled trials were in adults	Do more studies in the paediatric population
Absence of validated diagnostic criteria and algorithms for neuropathic pain	Use NeuPSIG diagnostic criteria for probable or definite neuropathic pain and validated screening tools to confirm diagnosis*
Classification of patients is generally based on the cause of the pain	Classification should be based on sensory phenotypes rather than merely on the cause of the pain†
Characteristics of the trials (appendix)	
Trial duration is 12 weeks or less in 81% of the trials	Consider longer trial duration
High placebo response, particularly in recent trials	Exclude patients with low pain intensity and high variability of pain at baseline[44]

NeuPSIG=Special Interest Group on Neuropathic Pain. *Criteria for neuropathic pain diagnosis were not available before the development of the screening methods and of diagnostic algorithms for neuropathic pain (2008);[49,50] less than 10% of clinical trials conducted over the past decade have used screening methods or diagnostic algorithms for neuropathic pain (detailed descriptions of the individual studies are available on request). †Results of recent clinical trials[51,52] and post-hoc analyses of recent clinical trials[53] that could not be included in the present meta-analysis lend support to this recommendation; the results of some trials suggested that drugs such as oxcarbazepine or topical clonidine might be significantly more effective in subgroups of patients with preserved nociceptive function compared with those without this phenotype,[54,49] but these individual trials need to be replicated and do not change the current level of recommendation for these drug treatments.

Table 4: **Limitations of clinical trials in neuropathic pain included in the present systematic review and meta-analysis, and NeuPSIG recommendations for implementation of future clinical trials in neuropathic pain**

Discussion

In accordance with previous reports,[23] results of our meta-analysis show that the efficacy of systemic drug treatments is generally not dependent on the cause of the underlying disorder (appendix). Side-effects might, however, to some degree depend on the cause—eg, drugs with CNS-related side-effects might be tolerated less well in patients with CNS lesions.[43] Pain due to HIV-related painful polyneuropathy and radiculopathy seems more refractory than other types of pain in our meta-analysis. This difference might be due to large placebo responses in HIV-related neuropathy trials,[44] a distinct clinical phenotype in subgroups of patients with radiculopathy,[45] or psychological or psychosocial comorbidities, often neglected in large trials. Topical agents have no known relevance for use in central pain, and this is clearly stated in our recommendations.

The strengths of this systematic review and meta-analysis include the analysis of publication bias[29] and unpublished trials. Publication bias can occur if studies with positive results are published whereas those with no data or negative results are not.[29] It might lead to a major overestimation of efficacy in therapeutic studies.[46] Our results show that the effect sizes estimated from studies published in peer-reviewed journals were higher than those estimated from studies available in open databases. This finding emphasises the need to search these databases in systematic reviews. Analysis of further publication bias (eg, studies that are unpublished or show no results in open trial registries) suggested a small overstatement of overall efficacy of drug treatments (by about 10%), although available methods to assess publication bias have limitations.[47] Here, we found that high-concentration capsaicin patches were the most susceptible to publication bias—ie, a new study with fewer than 400 participants with no effect can increase the NNT to an unacceptable level. This finding lends support to the robustness of a meta-analysis that includes unpublished trials and suggests that effect sizes were overestimated in previous meta-analyses of pharmacotherapy for neuropathic pain.

Results of quantitative data for individual drugs, showing NNT for 50% pain relief ranging from about 4 to 10 for most positive trials, emphasise the modest overall study outcomes in neuropathic pain. Inadequate response to drug therapy constitutes a substantial unmet need in patients with neuropathic pain and might have important consequences in terms of psychological or social adjustment.[48] However, our results might also indicate insufficient assay sensitivity in clinical trials of neuropathic pain (table 4).[55] One major issue is the placebo response, which seems to have increased in recent trials of neuropathic pain and can lead to an underestimation of drug effects.[56] Placebo response was higher in HIV-related neuropathies,[44] and in patients with low or variable pain scores at inclusion.[54] Conversely, it seems to be lower in post-herpetic neuralgia.[44] Another issue is the

heterogeneous diagnostic criteria for neuropathic pain in several trials (detailed descriptions of the individual studies are available on request). The use of diagnostic algorithms[49] and screening methods[50] should contribute to a reduction in diagnostic heterogeneity (table 4). Additionally, a largely debated issue is the heterogeneity of patients' phenotypes in clinical trials, which might indicate various underlying mechanisms.[57–59] The results of some recent trials or post-hoc analyses of recent trials suggest that some drugs might be differentially effective in patients classified according to their sensory phenotypes.[51–53]

Like previous NeuPSIG recommendations,[19] the current recommendations are determined by drug treatments rather than by the cause of pain. Our updated therapeutic algorithm for neuropathic pain based on GRADE differs in several ways from previous therapeutic recommendations. The previous recommendations generally proposed tricyclic antidepressants, pregabalin, gabapentin, and lidocaine patches as first line for neuropathic pain.[9–13,15–16,19,60] We now also recommend gabapentin extended release or enacarbil, and duloxetine as first line based on strong GRADE recommendations for use. We no longer propose lidocaine patches as first line because of weak quality of evidence. However, because of the excellent safety profile, high values and preferences, and initial positive short-term studies, we propose lidocaine as a second-line treatment for peripheral neuropathic pain. Strong opioids are now recommended as third line, contrasting with several previous recommendations in which they were generally thought of as first or second line.[19,60] This stems mainly from the consideration of potential risk of abuse, particularly with high doses,[35] and concerns about a recent increase in prescription-opioid-associated overdose mortality, diversion, misuse, and other opioid-related morbidity particularly in the USA, Canada, and the UK.[61–63] High-concentration capsaicin patches and cannabinoids are considered for the first time in therapeutic recommendations for neuropathic pain. Capsaicin patches are proposed as second line for peripheral neuropathic pain because of high quality of evidence, but small effect size, training requirement, and potential safety concerns on sensation with long-term use.[64] We provide a weak recommendation against the use of cannabinoids in neuropathic pain, mainly because of negative results, potential misuse, diversion, and long-term mental health risks of cannabis particularly in susceptible individuals.[65–70]

One important issue when proposing recommendations is the extent to which they are applied by practitioners and the question of whether the use of recommendations can contribute to improvements in practice. Few studies have investigated the real-life effect of evidence-based recommendations on physicians' practices. It has recently been reported that the drug treatment of post-herpetic neuralgia by primary care physicians was roughly consistent with the US recommendations issued some years before.[6] By contrast, a recent large study of general practitioners' adherence to current French recommendations noted a paucity of appropriate recall of first-line drugs.[8] It will be important to facilitate the dissemination of the present recommendations and subsequently to assess their real-life implementation in various countries.[7]

Contributors

NA, NBF, PRK, RB, ASCR, MH, SNR, and BHS are members of the NeuPSIG management committee. NA, NBF, SH, KL, and EM did the search and extracted data. NBF performed the meta-analysis. ES did the analysis of publication bias. NA and NBF drafted the report and the tables. PH, MR, PS, and MW were external advisers who reviewed the NeuPSIG recommendations before publication. All authors contributed to the guidelines in formulating the recommendations, and revising and editing the final text. All authors contributed to the final version of the report.

Declaration of interests

NA has served on advisory boards or speakers panels for Astellas Pharma, Adir Servier, Eli Lilly, Grünenthal, Johnson & Johnson, Sanofi Pasteur Merieux, and Pfizer, and has been an investigator in studies sponsored by Astellas, Grünenthal, and AstraZeneca. RB has received grant or research support from Pfizer, Genzyme, Grünenthal, German Federal Ministry of Education and Research, German Research Network on Neuropathic Pain, NoPain System Biology, and German Research Foundation; he has received speaker's honoraria from Pfizer, Genzyme, Grünenthal, Mundipharma, Sanofi Pasteur, Medtronic, Eisai, Eli Lilly, Boehringer Ingelheim, Astellas, Desitin, Teva Pharma, Bayer-Schering, and Merck Sharp & Dohme, and has served as a consultant for Pfizer, Genzyme, Grünenthal, Mundipharma, Allergan, Sanofi Pasteur, Medtronic, Eisai, Eli Lilly, Boehringer Ingelheim, Astellas, Novartis, Bristol-Myers Squibb, Biogenidec, AstraZeneca, Merck, and Abbvie. RHD has received research grants from the US Food and Drug Administration and US National Institutes of Health, and compensation for activities involving clinical trial research methods from Acorda, Adynxx, Allergan, Analgesic Solutions, Anika, Astellas, AstraZeneca, Avanir, Axsome, Bayer, Biogen, Bioness, Bristol-Myers Squibb, Cardiome, Centrexion, Charleston, Chromocell, Collegium, Concert, Daiichi Sankyo, Depomed, Depuy, Eli Lilly, Epicept, Flexion, Genzyme, Glenmark, Inhibitex, Johnson & Johnson, Lpath, Medicinova, Merck, Metys, MMS Holdings, Nektar, Neura, NeurogesX, Olatec, Ono, Periphagen, Pfizer, Phillips, Phosphagenics, Prolong, Q-Med, QRxPharma, Regenesis, Relmada, Sanofi-Aventis, Salix, Smith & Nephew, Sorrento, Spinifex, Takeda, Taris, Teva, Theravance, and Xenon. NBF has received speaker's honoraria from Pfizer, Grünenthal, and Norpharma, a research grant from Grünenthal, and consultancy fees from Astellas. MH has received honoraria from Eli Lilly, Janssen-Cilag, Merck Sharp & Dohme, Mundipharma, Orion, and Sanofi-Aventis for lectures, honoraria from Pfizer, Allergan, and Astellas for lectures and consulting, and honoraria from Abbvie for consulting. TSJ has received grants or honoraria, as a speaker and advisory board participant, from Pfizer, Grünenthal, Astellas, Orion, and Sanofi Pasteur. PRK has served on an advisory board for Reckitt Benckizer and has received speaker's honoraria from Pfizer. KL has received travel grants from Pfizer and Astellas. EM received grants from the Richard Saltonstall Charitable Foundation, USA, during the study. AM has received speaker's honoraria from Pfizer, speaker's honoraria and consultancy fees from Eli Lilly and Grünenthal, and a research grant from Grünenthal. SNR has served on advisory boards of Purdue Pharma, QRxPharma, Salix Pharmaceuticals, and Shionogi. ASCR has share options in Spinifex Pharmaceuticals; he undertakes consulting for Imperial College Consultants, and has received fees from Spinifex Pharmaceuticals, Astellas, Servier, Allergan, Asahi Kasei, and Medivir. Through Europain, ASCR's laboratory has received funding for research studentships from Pfizer and Astellas; other recent or current grant or studentship funding for ASCR's laboratory is from the Wellcome Trust (London Pain Consortium), Dunhill Medical Trust, National Centre for the Replacement Refinement & Reduction of Animals in Research, Westminster Medical School Research Trust, International Association for the Study of Pain, National Institute of Academic Anaesthesia, Derek Butler Trust, Medical Research Council Industrial, Biotechnology and Biological Sciences Research Council, and Pfizer-Christian-Albrechts

University of Kiel (Neuropain). ASCR is a member of the England and Wales Joint Committee on Vaccination and Immunisation (varicella subgroup). MR reports personal fees, stock options, or stock ownership from Afferent Pharmaceuticals, Centrexion, Xenoport, Nektar Therapeutics, ViroBay, Chromocell, Adynxx, Lilly, Zalicus, and Biogen IDEC outside the submitted work. PS has a patent for a system and method for detecting pain and its components using magnetic resonance spectroscopy (US patent 08755862). BHS has consulted for Pfizer and Napp, and received unconditional educational grants from Pfizer to support epidemiological research. MW reports personal fees from Boston Scientific, Jazz Pharmaceutical, Spinal Modulations, Depomed, and Inergetics. RB, NBF, KL, TSJ, and ASCR are members of the Innovative Medicines Initiative Europain collaboration, the industry members of which are AstraZeneca, Pfizer, Esteve, UCB-Pharma, Sanofi-Aventis, Grünenthal, Eli Lilly, Boehringer Ingelheim, Astellas, Abbott, and Lundbeck. The other authors declare no competing interests. No author was paid to write this report by a pharmaceutical company or other agency.

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Appendix 5

Kamerman PR, Wadley AL, Davis KD, Hietaharju A, Jain P, Kopf A, Meyer AC, Raja SN, Rice AS, Smith BH, Treede RD, Wiffen PJ

World Health Organization essential medicines lists: where are the drugs to treat neuropathic pain?

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Supplementary data

All supplementary information, including data and analysis scripts, are available in a public GitHub repository.

Access online

Topical Review

PAIN®

World Health Organization essential medicines lists: where are the drugs to treat neuropathic pain?

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1. Introduction

Neuropathic pain has been deemed a priority health issue[5] and is the topic of the 2014 to 2015 Global Year Against Neuropathic Pain campaign of the International Association for the Study of Pain (http://www.iasp-pain.org/GlobalYear/NeuropathicPain). Between 6% and 10% of adults are affected by chronic pain with neuropathic features,[6,24,26] and this prevalence is significantly greater among individuals with specific conditions. For example, neuropathic pain is a common comorbidity in infectious diseases such as HIV, leprosy, and herpes zoster, and in noninfectious conditions such as diabetes mellitus, stroke, multiple sclerosis, and traumatic limb and spinal cord injury.[7,13,15,18,20] The pain is associated with significant decreases in quality of life and socioeconomic well-being, even more so than nonneuropathic chronic pain.[9,19,21] Developing and emerging countries share the greatest burden of conditions that are associated with the development of neuropathic pain[5,10] and can ill afford the negative consequences of this pain.

There are medicines with proven efficacy in the treatment of neuropathic pain.[11,12] Nevertheless, the pain can be difficult to treat, with significant interindividual variation in efficacy within and between drug classes, independent of the underlying peripheral or central nervous system lesion or disease.[2,4] Effective management of neuropathic pain within a population therefore requires access to a small, but crucial, group of drug classes with proven efficacy.

The World Health Organization's (WHO) model list of essential medicines (http://www.who.int/selection_medicines/list/en/) presents medicines deemed necessary to meet priority health needs, and local implementation of essential medicines policies is associated with improved quality use of medicines.[14,17] However, none of the analgesic medicines included in the WHO model list is recommended as first-line treatments for neuropathic pain.[11] Thus, the WHO model list is not a good framework from which national policies on managing neuropathic pain can be structured, but countries do adapt the model list according to local needs and resources.[17] To estimate the nominal availability of medicines recommended for the treatment of neuropathic pain in developing and emerging countries, we assessed national essential medicines lists (NEMLs) for the inclusion of recommended treatments. We also assessed whether the coverage of recommended drugs classes on these NEMLs was dependent on countries' economic status.

2. Methods

2.1. National essential medicines list selection

We confined our analysis to the 117 NEMLs accessible through the WHO Web site (http://www.who.int/selection_medicines/country_lists/en/). Updated editions of the 117 NEMLs were sought on public, crawler-based search engines using country names, and titles of the downloaded documents as search terms; 14 newer editions were identified.

2.2. Data extraction

Each NEML was independently reviewed by 2 authors. The NEMLs were assessed for drugs recently recommended as first or second-line treatments for neuropathic pain after a meta-analysis and grading of the evidence.[11] Drug classes and drugs assessed included the following: (1) tricyclic antidepressants (TCA)—amitriptyline, nortriptyline, clomipramine, desipramine, and imipramine; (2) serotonin and noradrenaline reuptake inhibitors—duloxetine and venlafaxine; (3) anticonvulsants—gabapentin and pregabalin; (4) opioids—tramadol; and (5) topical agents—capsaicin and lidocaine. Drugs were recorded as being listed if they appeared anywhere on an NEML, irrespective of therapeutic class classification or treatment indications. Lidocaine was only recorded as being listed if it was specified as a topical formulation and at a concentration of at least 5%, or was a eutectic mix of 2.5% lidocaine: 2.5% prilocaine. Capsaicin was only recorded as being listed if the concentration was specified to be at least 8%.

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Information was also extracted on the strong opioids morphine, methadone, and oxycodone, which are listed in the WHO model list and are recommended as second or third-line therapy for neuropathic pain.[3,11] Anticonvulsants that are listed on the WHO model list, but for which the data on their efficacy in treating neuropathic pain are inconclusive (carbamazepine and oxcarbazepine) or against their use (sodium valproate), were also assessed.[11]

2.3. Data analysis

Only countries and territories classified as developing or emerging by the International Monetary Fund (IMF) were included in the analysis, which resulted in the exclusion of NEMLs from Sweden, Malta, Slovenia, and Slovakia.[16] The NEML of the Democratic People's Republic of Korea also was excluded because the list was generated by the WHO, and not by the country itself. The NEMLs of the remaining 112 countries were then categorised according to the World Bank system of low, lower-middle, higher-middle, and high income.[22] Data from 8 countries (Bahrain, Barbados, Chile, Croatia, Oman, Poland, Trinidad and Tobago, Uruguay), which are classified as developing or emerging by the IMF, but as high income by the World Bank, were included in the analyses. Basic descriptive statistics were generated on whether the selected drugs were listed, and the number of recommended first-line drug classes included on each NEML. The χ^2 test for trend was used to assess whether country income category predicted which of the drugs assessed were listed, and the number of first and second-line drug classes listed. The Holm method was used to correct P values for multiple comparisons.

3. Results

3.1. Coverage of developing and emerging countries

The 112 documents analysed covered 24/34 (71%) developing or emerging countries and territories classified as low income by The World Bank, 40/50 (80%) countries classified as lower-middle income, 37/55 (67%) countries classified as higher-middle income, and 8/38 (21%) developing or emerging countries and territories classified as high income.[22] Thirty-nine countries were in Africa, 23 in the Americas, 30 in Asia (including the Middle East), 8 in Europe, and 12 in Oceania. The median NEML publication date was 2009 (range, 2002 to 2014). Additional information on the 112 NEMLs is provided in Supplemental Digital Content 1, available online at http://links.lww.com/PAIN/A51.

3.2. Listing of individual drugs

Table 1 summarizes the listing of individual drugs. Tricyclic antidepressants were almost universally listed, with amitriptyline being the most commonly listed agent. Only the NEMLs of Angola, Bulgaria, and Cambodia did not list any of the assessed TCAs. There was a positive association between country income and listing of imipramine (corrected $P = 0.037$), but not of the other TCAs. Serotonin and noradrenaline reuptake inhibitors duloxetine and venlafaxine were infrequently listed, and no association was detected between drug listing and country income. The majority of NEMLs did not include an $\alpha2\delta$ calcium channel antagonist, but when they did, it was more likely to be gabapentin than pregabalin, and the NEML was more likely to be from an upper-middle income or high-income country than a country from a lower-income category (corrected $P = 0.005$).

Approximately half the NEMLs listed tramadol, and no association was detected between the income category and drug listing. Only one-fifth of the countries' lists included topical lidocaine (no association between income and drug listing was detected), and none of the NEMLs included high-dose capsaicin.

Morphine and the anticonvulsants carbamazepine and sodium valproate were almost universally listed (Supplemental Digital Content 2 for countries that did not list morphine, available online at http://links.lww.com/PAIN/A52), and no associations between income and drug listings were detected. There were low rates of inclusion for other strong opioids, oxycodone and methadone, and the anticonvulsant oxcarbazepine. Inclusion of methadone and oxcarbazepine was positively associated with the country's income status (corrected $P < 0.05$ for both drugs).

Very few NEMLs indicated that the assessed drugs were for the treatment of neuropathic pain, with amitriptyline (9% of NEMLs) and carbamazepine (14% of NEMLs) receiving the most indications for treating neuropathic pain (Supplemental Digital Content 3, available online at http://links.lww.com/PAIN/A53).

3.3. Listing of drug classes

Figure 1 shows the percentage of NEMLs that included 0, 1, 2, or 3 drug classes recommended for the treatment of neuropathic pain. Approximately two-thirds of countries had only 1 class of first-line agent (typically TCAs), and approximately half had only 1 second-line agent (typically tramadol), included on their NEMLs. Two countries (Angola and Cambodia) had no first-line treatment classes listed, and almost 40% of countries had no second-line therapies listed. There was an association between the income category and number of drug classes listed for first (corrected $P < 0.001$) and second-line (corrected $P < 0.001$) therapies. No low-income countries had all 3 first-line drug classes listed, compared with half of all high-income countries. Only 1 low-income country (Tanzania) had 2 first-line classes listed (TCA and $\alpha2\delta$ calcium channel antagonists), compared with one-quarter of high-income countries.

4. Discussion

Our analysis shows gross deficiencies in the scope of drugs recommended for the treatment of neuropathic pain on the NEMLs of developing and emerging countries. The poor selection of recommended treatments means that should a patient fail to respond to initial therapy (number needed to treat for 50% pain relief is typically $\geq$4 for neuropathic pain[11]), have significant side effects, or have contraindications to a drug's use, there are no or limited alternative therapies available. Furthermore, even when recommended drugs are listed, the drugs generally are not indicated, or are inappropriately indicated, for the treatment of neuropathic pain.

Management of pain is a priority issue that has been codified in the WHO model list since 1977.[30,32] Indeed, the WHO[31] recently urged member states to ensure, "the availability of essential medicines for the management of symptoms, including pain," and "(the) education and training of healthcare professionals, in order to ensure adequate responses to palliative care needs." Yet for neuropathic pain, the WHO model list fails on both accounts, being deficient in drugs with proven efficacy in treating neuropathic pain, and it provides no guidance on appropriate medications to use for treating neuropathic pain. These deficiencies are echoed in the NEMLs of developing and emerging countries. Although the WHO model list informs the development of NEMLs, countries tailor their lists according to local needs. For example, tramadol was included on approximately half the NEMLs we assessed, but it is not on the WHO model list. Thus, the dearth of recommended medications for

Table 1

Drug listings on the national essential medicines lists of 112 developing countries.

	Overall listing, n (%)	Listing by World Bank income category, n (% countries within a category)				
		Low (n = 24)	Lower middle (n = 40)	Upper middle (n = 37)	High (n = 8)	Other* (n = 3)
First-line medications						
TCA						
Amitriptyline	105 (94)	23 (96)	38 (95)	33 (89)	8 (100)	3 (100)
Clomipramine	53 (47)	11 (46)	21 (52)	16 (43)	5 (62)	0 (0)
Desipramine	2 (2)	0 (0)	1 (2)	1 (3)	0 (0)	0 (0)
Imipramine†	46 (41)	3 (12)	17 (42)	20 (54)	6 (75)	0 (0)
Nortriptyline	10 (9)	1 (4)	2 (5)	6 (16)	1 (12)	0 (0)
SNRI						
Duloxetine	5 (5)	0 (0)	3 (8)	1 (3)	1 (12)	0 (0)
Venlafaxine	19 (17)	0 (0)	7 (18)	8 (22)	4 (50)	0 (0)
$\alpha 2\delta$ antagonist						
Gabapentin†	33 (30)	1 (4)	10 (25)	16 (43)	6 (75)	0 (0)
Pregabalin	11 (10)	0 (0)	3 (8)	6 (16)	1 (12)	1 (33)
Second-line medications						
Opioid						
Tramadol	61 (55)	8 (33)	19 (48)	26 (70)	7 (88)	1 (33)
Topical						
8% capsaicin	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
5% lidocaine	22 (20)	3 (12)	6 (15)	9 (24)	3 (38)	1 (33)
Strong opioid medications						
Methadone†	34 (30)	4 (17)	8 (20)	16 (43)	6 (75)	0 (0)
Morphine	106 (95)	22 (92)	40 (100)	33 (89)	8 (100)	3 (100)
Oxycodone	15 (13)	0 (0)	4 (10)	9 (24)	2 (25)	0 (0)
Other anticonvulsant medications						
Carbamazepine	109 (97)	22 (92)	40 (100)	36 (97)	8 (100)	3 (100)
Oxcarbazepine†	15 (13)	0 (0)	3 (8)	8 (22)	4 (50)	0 (0)
Sodium valproate	107 (95)	22 (92)	40 (100)	35 (95)	7 (88)	3 (100)

* Countries not included on the World Bank income list: Cook Islands, Nauru, Niue.

† $P < 0.05$ for χ^2 test for trend (listing vs income category).

$\alpha 2\delta$ antagonist, $\alpha 2\delta$ calcium channel antagonists; SNRI, serotonin and noradrenaline reuptake inhibitors; TCA, tricyclic antidepressants.

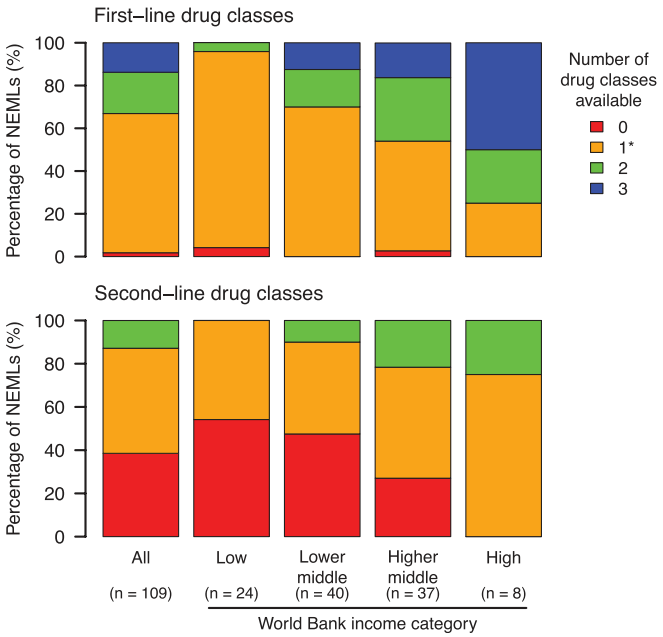

Figure 1. Percentage of national essential medicine lists (NEMLs) that included 0, 1, 2, or 3 drug classes recommended for the treatment of neuropathic pain. Data are shown grouped according to World Bank income category and for all countries (n = 109, data from the Cook Islands, Nauru, and Niue were not included because the World Bank does not index them). The top panel shows drug-classes recommended as first-line treatment, and the bottom panel shows second-line drug classes. First-line drug classes include: tricyclic antidepressants, serotonin and norepinephrine reuptake inhibitors, and a2d calcium channel antagonists. Second-line drug classes include: opioids (tramadol) and topical agents (5% lidocaine). There was a positive association between income category and the number of first-line and second-line drug classes listed on NEMLs (corrected $P < 0.001$). *The tricyclic antidepressant amitriptyline was the only first-line drug listed on the NEMLs of 32% of low income countries, 36% of lower-middle income countries, 28% of higher-middle income countries and 4% of high income countries.

treating neuropathic pain reflects deficiencies at the international and national level.

4.1 Limitations

Our assessment was limited to 112 developing or emerging countries, and the median publication date of the NEML assessed was 2009. Nevertheless, we believe that our assessment provides an accurate appraisal of the current situation. First, our sample included the majority of countries classified as low, lower-middle, and higher-middle income. Second, no medications relevant to treatment of neuropathic pain have been added to the WHO model list in over a decade.[27,28] Finally, since 2009, only approximately 5% of countries have transitioned to a higher World Bank income category.

Indeed, NEMLs only indicate nominal drug availability, whereas actual drug availability tends to be low in developing countries because of poor policy implementation, lack of infrastructure and logistical support, drug cost, availability of reimbursement, and knowledge of health care professionals.[23,25,29] Low availability of oral formulations of drugs such as the opioids also may limit the use of these medications to the clinic setting; although our analysis indicates that most of the opioids are nominally available in oral and parenteral formulations (Supplemental Digital Content 4, available online at http://links.lww.com/PAIN/A54). Furthermore, most of the medications to treat neuropathic pain are included on NEMLs as treatments for depression or epilepsy. Stigma toward these conditions by communities and health care providers may be an important barrier to inclusion on NEMLs and their use by health care providers and patients.[1,8] Thus, even when a drug is physically available, a combination of attitudes, health care professional knowledge, and prescription policies could mean that a drug is not prescribed. We therefore believe that our analysis probably overestimates the actual availability of neuropathic pain medications in these countries.

4.2. Recommendations

As a first step in improving the management of neuropathic pain, we believe that there is a strong enough therapeutic need and a sufficient evidence base to warrant applying for inclusion of additional recommended treatments for neuropathic pain in the 19th edition of the WHO model NEML. Indeed, the need to expand the scope of essential medicines lists is one of the subjects of a commission on essential medicine policies recently established by The Lancet (http://www.bu.edu/lancet-commission-essential-medicines-policies/). To facilitate the appropriate use of new and existing medications on the WHO model list, the medicines should be listed under a neuropathic pain subsection of the "pain and palliative care" section of the model list. In addition, we also motivate for research into the actual cost and availability of these medications in rural and urban settings, and to identify the knowledge, attitudes, beliefs, and training needs of prescribers that are required to improve access to care for neuropathic pain treatments worldwide.

Conflict of interest statement

A. Hietaharju received honoraria or consultancy fees from AbbVie, Glaxo Smith Kline, Lilly, Mundipharma, Pfizer, and Sanofi in the past 36 months. P. R. Kamerman declared consultancy fees from Reckitt Benckiser, lecture fees from Pfizer and Novartis, and travel support from Janssen. A. Kopf received consultancy fees from Grunenthal and Mundipharma, lecture fees from Grunenthal, Janssen, Pfizer, and Mundipharma, developed educational material for Grunenthal, and was on the advisory board of Astellas. A. C. Meyer declared receiving research support from the US National Institutes of Health, World Federation of Neurology, a drug donation from Valeant Pharmaceuticals, and travel support from Abbott Pharmaceuticals. A. S. C. Rice undertakes consulting for Imperial College Consultants, and in the past 36 months received fees from Spinifex Pharmaceuticals, Astellas, Servier, Abide, Relmada, Allergan, Asahi Kasei, and Medivir. ASCR's laboratory received research funding from Pfizer and Astellas. S. N. Raja received research funding from Medtronic and was a member of an advisory board for Mistsibushi Tanabe and QRx Pharma. B. H. Smith declared receiving occasional lecture and consultancy fees in the past 36 months, on behalf of his institution, from Pfizer, Napp, and Grunenthal. R. D. Treede received research support or honoraria from AbbVie, Allergan, Astellas, AWD, Bauerfeind, Boehringer Ingelheim, Bundesministerium für Bildung und Forschung, Deutsche Forschungsgemeinschaft, European Union, Glaxo Smith Kline, Grünenthal, Kade, Lily, Merz, Mundipharma, Nycomed, Pfizer, Sanofi, StarMedTec, Schwarz, US National Institutes of Health. The other authors have no conflicts of interest to declare.

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Appendices. Supplemental Digital Content

Supplemental Digital Content associated with this article can be found online at http://links.lww.com/PAIN/A51, http://links.lww.com/PAIN/A52, http://links.lww.com/PAIN/A53, http://links.lww.com/PAIN/A54.

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Appendix 6

NEURONTIN

Full prescribing information

Food and Drug Administration (FDA)

United States of America

Updated: September 2015; **Reference ID:** 3818812

Access online

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use NEURONTIN safely and effectively. See full prescribing information for NEURONTIN.

NEURONTIN® (gabapentin) capsules, for oral use
NEURONTIN® (gabapentin) tablets, for oral use
NEURONTIN® (gabapentin) oral solution
Initial U.S. Approval: 1993

----------RECENT MAJOR CHANGES----------
- Warnings and Precautions: Anaphylaxis and Angioedema: discontinue NEURONTIN and evaluate patient immediately (5.2) 9/2015

---------- INDICATIONS AND USAGE----------
NEURONTIN is indicated for:
- Postherpetic neuralgia in adults (1)
- Adjunctive therapy in the treatment of partial onset seizures, with and without secondary generalization, in adults and pediatric patients 3 years and older with epilepsy (1)

----------DOSAGE AND ADMINISTRATION----------
- Postherpetic Neuralgia (2.1)
  - Dose can be titrated up as needed to a dose of 1800 mg/day
  - Day 1: Single 300 mg dose
  - Day 2: 600 mg/day (i.e., 300 mg two times a day)
  - Day 3: 900 mg/day (i.e., 300 mg three times a day)
- Epilepsy with Partial Onset Seizures (2.2)
  - Patients 12 years of age and older: starting dose is 300 mg three times daily; may be titrated up to 600 mg three times daily
  - Patients 3 to 11 years of age: starting dose range is 10 to 15 mg/kg/day, given in three divided doses; recommended dose in patients 3 to 4 years of age is 40 mg/kg/day, given in three divided doses; the recommended dose in patients 5 to 11 years of age is 25 to 35 mg/kg/day, given in three divided doses. The recommended dose is reached by upward titration over a period of approximately 3 days
- Dose should be adjusted in patients with reduced renal function (2.3, 2.4)

---------- DOSAGE FORMS AND STRENGTHS----------
- Capsules: 100 mg, 300 mg, and 400 mg (3)
- Tablets: 600 mg, and 800 mg (3)
- Oral Solution: 250 mg/5mL (3)

---------- CONTRAINDICATIONS ----------
- Known hypersensitivity to gabapentin or its ingredients (4)

---------- WARNINGS AND PRECAUTIONS ----------
- Drug Reaction with Eosinophilia and Systemic Symptoms (Multiorgan hypersensitivity): discontinue NEURONTIN if an alternative etiology cannot be established (5.1)
- Anaphylaxis and Angioedema: discontinue NEURONTIN and evaluate patient immediately (5.2)
- Driving impairment: warn patients not to drive until they have gained sufficient experience with NEURONTIN to assess whether it will impair their ability to drive (5.3)
- Somnolence/Sedation and Dizziness: NEURONTIN may impair the patient's ability to operate complex machinery (5.4)
- Increased seizure frequency may occur in patients with seizure disorders if NEURONTIN is abruptly discontinued (5.5)
- Suicidal Behavior and Ideation*:* monitor for suicidal thoughts and behavior (5.6)
- Neuropsychiatric Adverse Reactions in Children 3-12 Years of Age: monitor for such events (5.7)

---------- ADVERSE REACTIONS ----------
Most common adverse reactions (incidence ≥8% and at least twice that for placebo) were:
- Postherpetic neuralgia: dizziness, somnolence, and peripheral edema (6.1)
- Epilepsy in patients >12 years of age: somnolence, dizziness, ataxia, fatigue, and nystagmus (6.1)
- Epilepsy in patients 3 to 12 years of age: viral infection, fever, nausea and/or vomiting, somnolence, and hostility (6.1)

----------DRUG INTERACTIONS----------
- Morphine increases gabapentin concentrations; dose adjustment may be needed (5.4, 7.2)

To report SUSPECTED ADVERSE REACTIONS, contact Pfizer, Inc. at 1-800-438-1985 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

----------USE IN SPECIFIC POPULATIONS----------
- Pregnancy: based on animal data, may cause fetal harm. (8.1)
- Pediatric Use: effectiveness as adjunctive therapy in treatment of partial seizures in pediatric patients below the age of 3 years has not been established (8.4)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 9/2015

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

NEURONTIN® is indicated for:

- Management of postherpetic neuralgia in adults
- Adjunctive therapy in the treatment of partial onset seizures, with and without secondary generalization, in adults and pediatric patients 3 years and older with epilepsy

2 DOSAGE AND ADMINISTRATION

2.1 Dosage for Postherpetic Neuralgia

In adults with postherpetic neuralgia, NEURONTIN may be initiated on Day 1 as a single 300 mg dose, on Day 2 as 600 mg/day (300 mg two times a day), and on Day 3 as 900 mg/day (300 mg three times a day). The dose can subsequently be titrated up as needed for pain relief to a dose of 1800 mg/day (600 mg three times a day). In clinical studies, efficacy was demonstrated over a range of doses from 1800 mg/day to 3600 mg/day with comparable effects across the dose range; however, in these clinical studies, the additional benefit of using doses greater than 1800 mg/day was not demonstrated.

2.2 Dosage for Epilepsy with Partial Onset Seizures

Patients 12 years of age and above

The starting dose is 300 mg three times a day. The recommended maintenance dose of NEURONTIN is 300 mg to 600 mg three times a day. Dosages up to 2400 mg/day have been well tolerated in long-term clinical studies. Doses of 3600 mg/day have also been administered to a small number of patients for a relatively short duration, and have been well tolerated. Administer NEURONTIN three times a day using 300 mg or 400 mg capsules, or 600 mg or 800 mg tablets. The maximum time between doses should not exceed 12 hours.

Pediatric Patients Age 3 to 11 years

The starting dose range is 10 mg/kg/day to 15 mg/kg/day, given in three divided doses, and the recommended maintenance dose reached by upward titration over a period of approximately 3 days. The recommended maintenance dose of NEURONTIN in patients 3 to 4 years of age is 40 mg/kg/day, given in three divided doses. The recommended maintenance dose of NEURONTIN in patients 5 to 11 years of age is 25 mg/kg/day to 35 mg/kg/day, given in three divided doses. NEURONTIN may be administered as the oral solution, capsule, or tablet, or using combinations of these formulations. Dosages up to 50 mg/kg/day have been well tolerated in a long-term clinical study. The maximum time interval between doses should not exceed 12 hours.

2.3 Dosage Adjustment in Patients with Renal Impairment

Dosage adjustment in patients 12 years of age and older with renal impairment or undergoing hemodialysis is recommended, as follows (see dosing recommendations above for effective doses in each indication):

TABLE 1. NEURONTIN Dosage Based on Renal Function

Renal Function Creatinine Clearance (mL/min)	Total Daily Dose Range (mg/day)	Dose Regimen (mg)				
≥ 60	900 to 3600	300 TID	400 TID	600 TID	800 TID	1200 TID
>30 to 59	400 to 1400	200 BID	300 BID	400 BID	500 BID	700 BID
>15 to 29	200 to 700	200 QD	300 QD	400 QD	500 QD	700 QD
15[a]	100 to 300	100 QD	125 QD	150 QD	200 QD	300 QD
		Post-Hemodialysis Supplemental Dose (mg)[b]				
Hemodialysis		125[b]	150[b]	200[b]	250[b]	350[b]

TID = Three times a day; BID = Two times a day; QD = Single daily dose

[a] For patients with creatinine clearance <15 mL/min, reduce daily dose in proportion to creatinine clearance (e.g., patients with a creatinine clearance of 7.5 mL/min should receive one-half the daily dose that patients with a creatinine clearance of 15 mL/min receive).

[b] Patients on hemodialysis should receive maintenance doses based on estimates of creatinine clearance as indicated in the upper portion of the table and a supplemental post-hemodialysis dose administered after each 4 hours of hemodialysis as indicated in the lower portion of the table.

Creatinine clearance (CLCr) is difficult to measure in outpatients. In patients with stable renal function, creatinine clearance can be reasonably well estimated using the equation of Cockcroft and Gault:

$$\text{CLCr} = \frac{\left[140 - \text{age (years)}\right] \times \text{weight (kg)}}{72 \times \text{serum creatinine (mg/dL)}} \quad (\times\ 0.85 \text{ for female patients})$$

The use of NEURONTIN in patients less than 12 years of age with compromised renal function has not been studied.

2.4 Dosage in Elderly

Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and dose should be adjusted based on creatinine clearance values in these patients.

2.5 Administration Information

Administer NEURONTIN orally with or without food.

NEURONTIN capsules should be swallowed whole with water.

Inform patients that, should they divide the scored 600 mg or 800 mg NEURONTIN tablet in order to administer a half-tablet, they should take the unused half-tablet as the next dose. Half-tablets not used within 28 days of dividing the scored tablet should be discarded.

If the NEURONTIN dose is reduced, discontinued, or substituted with an alternative medication, this should be done gradually over a minimum of 1 week (a longer period may be needed at the discretion of the prescriber).

3 DOSAGE FORMS AND STRENGTHS

Capsules:

- 100 mg: white hard gelatin capsules printed with "PD" on the body and "Neurontin/100 mg" on the cap
- 300 mg: yellow hard gelatin capsules printed with "PD" on the body and "Neurontin/300 mg" on the cap
- 400 mg: orange hard gelatin capsules printed with "PD" on the body and "Neurontin/400 mg" on the cap

Tablets:

- 600 mg: white elliptical film-coated scored tablets debossed with "NT" and "16" on one side
- 800 mg: white elliptical film-coated scored tablets debossed with "NT" and "26" on one side

Oral solution: 250 mg per 5 mL (50 mg per mL), clear colorless to slightly yellow solution

4 CONTRAINDICATIONS

NEURONTIN is contraindicated in patients who have demonstrated hypersensitivity to the drug or its ingredients.

5 WARNINGS AND PRECAUTIONS

5.1 Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)/Multiorgan Hypersensitivity

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), also known as multiorgan hypersensitivity, has occurred with NEURONTIN. Some of these reactions have been fatal or life-threatening. DRESS typically, although not exclusively, presents with fever, rash, and/or lymphadenopathy, in association with other organ system involvement, such as hepatitis,

nephritis, hematological abnormalities, myocarditis, or myositis sometimes resembling an acute viral infection. Eosinophilia is often present. This disorder is variable in its expression, and other organ systems not noted here may be involved.

It is important to note that early manifestations of hypersensitivity, such as fever or lymphadenopathy, may be present even though rash is not evident. If such signs or symptoms are present, the patient should be evaluated immediately. NEURONTIN should be discontinued if an alternative etiology for the signs or symptoms cannot be established.

5.2 Anaphylaxis and Angioedema

NEURONTIN can cause anaphylaxis and angioedema after the first dose or at any time during treatment. Signs and symptoms in reported cases have included difficulty breathing, swelling of the lips, throat, and tongue, and hypotension requiring emergency treatment. Patients should be instructed to discontinue NEURONTIN and seek immediate medical care should they experience signs or symptoms of anaphylaxis or angioedema.

5.3 Effects on Driving and Operating Heavy Machinery

Patients taking NEURONTIN should not drive until they have gained sufficient experience to assess whether NEURONTIN impairs their ability to drive. Driving performance studies conducted with a prodrug of gabapentin (gabapentin enacarbil tablet, extended release) indicate that gabapentin may cause significant driving impairment. Prescribers and patients should be aware that patients' ability to assess their own driving competence, as well as their ability to assess the degree of somnolence caused by NEURONTIN, can be imperfect. The duration of driving impairment after starting therapy with NEURONTIN is unknown. Whether the impairment is related to somnolence *[see Warnings and Precautions (5.4)]* or other effects of NEURONTIN is unknown.

Moreover, because NEURONTIN causes somnolence and dizziness *[see Warnings and Precautions (5.4)]*, patients should be advised not to operate complex machinery until they have gained sufficient experience on NEURONTIN to assess whether NEURONTIN impairs their ability to perform such tasks.

5.4 Somnolence/Sedation and Dizziness

During the controlled epilepsy trials in patients older than 12 years of age receiving doses of NEURONTIN up to 1800 mg daily, somnolence, dizziness, and ataxia were reported at a greater rate in patients receiving NEURONTIN compared to placebo: i.e., 19% in drug versus 9% in placebo for somnolence, 17% in drug versus 7% in placebo for dizziness, and 13% in drug versus 6% in placebo for ataxia. In these trials somnolence, ataxia and fatigue were common adverse reactions leading to discontinuation of NEURONTIN in patients older than 12 years of age, with 1.2%, 0.8% and 0.6% discontinuing for these events, respectively.

During the controlled trials in patients with post-herpetic neuralgia, somnolence and dizziness were reported at a greater rate compared to placebo in patients receiving NEURONTIN, in

dosages up to 3600 mg per day: i.e., 21% in NEURONTIN-treated patients versus 5% in placebo-treated patients for somnolence and 28% in NEURONTIN-treated patients versus 8% in placebo-treated patients for dizziness. Dizziness and somnolence were among the most common adverse reactions leading to discontinuation of NEURONTIN.

Patients should be carefully observed for signs of central nervous system (CNS) depression, such as somnolence and sedation, when NEURONTIN is used with other drugs with sedative properties because of potential synergy. In addition, patients who require concomitant treatment with morphine may experience increases in gabapentin concentrations and may require dose adjustment [*see Drug Interactions (7.2)*].

5.5 Withdrawal Precipitated Seizure, Status Epilepticus

Antiepileptic drugs should not be abruptly discontinued because of the possibility of increasing seizure frequency.

In the placebo-controlled epilepsy studies in patients >12 years of age, the incidence of status epilepticus in patients receiving NEURONTIN was 0.6% (3 of 543) vs. 0.5% in patients receiving placebo (2 of 378). Among the 2074 patients >12 years of age treated with NEURONTIN across all epilepsy studies (controlled and uncontrolled), 31 (1.5%) had status epilepticus. Of these, 14 patients had no prior history of status epilepticus either before treatment or while on other medications. Because adequate historical data are not available, it is impossible to say whether or not treatment with NEURONTIN is associated with a higher or lower rate of status epilepticus than would be expected to occur in a similar population not treated with NEURONTIN.

5.6 Suicidal Behavior and Ideation

Antiepileptic drugs (AEDs), including NEURONTIN, increase the risk of suicidal thoughts or behavior in patients taking these drugs for any indication. Patients treated with any AED for any indication should be monitored for the emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior.

Pooled analyses of 199 placebo-controlled clinical trials (mono- and adjunctive therapy) of 11 different AEDs showed that patients randomized to one of the AEDs had approximately twice the risk (adjusted Relative Risk 1.8, 95% CI:1.2, 2.7) of suicidal thinking or behavior compared to patients randomized to placebo. In these trials, which had a median treatment duration of 12 weeks, the estimated incidence rate of suicidal behavior or ideation among 27,863 AED-treated patients was 0.43%, compared to 0.24% among 16,029 placebo-treated patients, representing an increase of approximately one case of suicidal thinking or behavior for every 530 patients treated. There were four suicides in drug-treated patients in the trials and none in placebo-treated patients, but the number is too small to allow any conclusion about drug effect on suicide.

The increased risk of suicidal thoughts or behavior with AEDs was observed as early as one week after starting drug treatment with AEDs and persisted for the duration of treatment

assessed. Because most trials included in the analysis did not extend beyond 24 weeks, the risk of suicidal thoughts or behavior beyond 24 weeks could not be assessed.

The risk of suicidal thoughts or behavior was generally consistent among drugs in the data analyzed. The finding of increased risk with AEDs of varying mechanisms of action and across a range of indications suggests that the risk applies to all AEDs used for any indication. The risk did not vary substantially by age (5-100 years) in the clinical trials analyzed. Table 2 shows absolute and relative risk by indication for all evaluated AEDs.

TABLE 2 Risk by Indication for Antiepileptic Drugs in the Pooled Analysis

Indication	Placebo Patients with Events Per 1000 Patients	Drug Patients with Events Per 1000 Patients	Relative Risk: Incidence of Events in Drug Patients/Incidence in Placebo Patients	Risk Difference: Additional Drug Patients with Events Per 1000 Patients
Epilepsy	1.0	3.4	3.5	2.4
Psychiatric	5.7	8.5	1.5	2.9
Other	1.0	1.8	1.9	0.9
Total	2.4	4.3	1.8	1.9

The relative risk for suicidal thoughts or behavior was higher in clinical trials for epilepsy than in clinical trials for psychiatric or other conditions, but the absolute risk differences were similar for the epilepsy and psychiatric indications.

Anyone considering prescribing NEURONTIN or any other AED must balance the risk of suicidal thoughts or behavior with the risk of untreated illness. Epilepsy and many other illnesses for which AEDs are prescribed are themselves associated with morbidity and mortality and an increased risk of suicidal thoughts and behavior. Should suicidal thoughts and behavior emerge during treatment, the prescriber needs to consider whether the emergence of these symptoms in any given patient may be related to the illness being treated.

Patients, their caregivers, and families should be informed that AEDs increase the risk of suicidal thoughts and behavior and should be advised of the need to be alert for the emergence or worsening of the signs and symptoms of depression, any unusual changes in mood or behavior, or the emergence of suicidal thoughts, behavior, or thoughts about self-harm. Behaviors of concern should be reported immediately to healthcare providers.

5.7 Neuropsychiatric Adverse Reactions (Pediatric Patients 3-12 Years of Age)

Gabapentin use in pediatric patients with epilepsy 3-12 years of age is associated with the occurrence of central nervous system related adverse reactions. The most significant of these can be classified into the following categories: 1) emotional lability (primarily behavioral problems), 2) hostility, including aggressive behaviors, 3) thought disorder, including concentration problems and change in school performance, and 4) hyperkinesia (primarily restlessness and hyperactivity). Among the gabapentin-treated patients, most of the reactions were mild to moderate in intensity.

In controlled clinical epilepsy trials in pediatric patients 3–12 years of age, the incidence of these adverse reactions was: emotional lability 6% (gabapentin-treated patients) vs. 1.3% (placebo-treated patients); hostility 5.2% vs. 1.3%; hyperkinesia 4.7% vs. 2.9%; and thought disorder 1.7% vs. 0%. One of these reactions, a report of hostility, was considered serious. Discontinuation of gabapentin treatment occurred in 1.3% of patients reporting emotional lability and hyperkinesia and 0.9% of gabapentin-treated patients reporting hostility and thought disorder. One placebo-treated patient (0.4%) withdrew due to emotional lability.

5.8 Tumorigenic Potential

In an oral carcinogenicity study, gabapentin increased the incidence of pancreatic acinar cell tumors in rats *[see Nonclinical Toxicology (13.1)]*. The clinical significance of this finding is unknown. Clinical experience during gabapentin's premarketing development provides no direct means to assess its potential for inducing tumors in humans.

In clinical studies in adjunctive therapy in epilepsy comprising 2085 patient-years of exposure in patients >12 years of age, new tumors were reported in 10 patients (2 breast, 3 brain, 2 lung, 1 adrenal, 1 non-Hodgkin's lymphoma, 1 endometrial carcinoma *in situ*), and preexisting tumors worsened in 11 patients (9 brain, 1 breast, 1 prostate) during or up to 2 years following discontinuation of NEURONTIN. Without knowledge of the background incidence and recurrence in a similar population not treated with NEURONTIN, it is impossible to know whether the incidence seen in this cohort is or is not affected by treatment.

5.9 Sudden and Unexplained Death in Patients with Epilepsy

During the course of premarketing development of NEURONTIN, 8 sudden and unexplained deaths were recorded among a cohort of 2203 epilepsy patients treated (2103 patient-years of exposure) with NEURONTIN.

Some of these could represent seizure-related deaths in which the seizure was not observed, e.g., at night. This represents an incidence of 0.0038 deaths per patient-year. Although this rate exceeds that expected in a healthy population matched for age and sex, it is within the range of estimates for the incidence of sudden unexplained deaths in patients with epilepsy not receiving NEURONTIN (ranging from 0.0005 for the general population of epileptics to 0.003 for a clinical trial population similar to that in the NEURONTIN program, to 0.005 for patients with refractory epilepsy). Consequently, whether these figures are reassuring or raise further concern depends on comparability of the populations reported upon to the NEURONTIN cohort and the accuracy of the estimates provided.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed in greater detail in other sections:

- Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)/Multiorgan Hypersensitivity *[see Warnings and Precautions (5.1)]*
- Anaphylaxis and Angioedema *[see Warnings and Precautions (5.2)]*

- Somnolence/Sedation and Dizziness *[see Warnings and Precautions (5.4)]*
- Withdrawal Precipitated Seizure, Status Epilepticus *[see Warnings and Precautions (5.5)]*
- Suicidal Behavior and Ideation *[see Warnings and Precautions (5.6)]*
- Neuropsychiatric Adverse Reactions (Pediatric Patients 3-12 Years of Age) *[see Warnings and Precautions (5.7)]*
- Sudden and Unexplained Death in Patients with Epilepsy [*see Warnings and Precautions (5.9)*]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Postherpetic Neuralgia

The most common adverse reactions associated with the use of NEURONTIN in adults, not seen at an equivalent frequency among placebo-treated patients, were dizziness, somnolence, and peripheral edema.

In the 2 controlled trials in postherpetic neuralgia, 16% of the 336 patients who received NEURONTIN and 9% of the 227 patients who received placebo discontinued treatment because of an adverse reaction. The adverse reactions that most frequently led to withdrawal in NEURONTIN-treated patients were dizziness, somnolence, and nausea.

Table 3 lists adverse reactions that occurred in at least 1% of NEURONTIN-treated patients with postherpetic neuralgia participating in placebo-controlled trials and that were numerically more frequent in the NEURONTIN group than in the placebo group.

TABLE 3. Adverse Reactions in Pooled Placebo-Controlled Trials in Postherpetic Neuralgia

	NEURONTIN N=336 %	Placebo N=227 %
Body as a Whole		
Asthenia	6	5
Infection	5	4
Accidental injury	3	1
Digestive System		
Diarrhea	6	3
Dry mouth	5	1
Constipation	4	2
Nausea	4	3
Vomiting	3	2
Metabolic and Nutritional Disorders		
Peripheral edema	8	2
Weight gain	2	0
Hyperglycemia	1	0
Nervous System		
Dizziness	28	8
Somnolence	21	5
Ataxia	3	0
Abnormal thinking	3	0
Abnormal gait	2	0
Incoordination	2	0
Respiratory System		
Pharyngitis	1	0
Special Senses		
Amblyopia[a]	3	1
Conjunctivitis	1	0
Diplopia	1	0
Otitis media	1	0

[a] Reported as blurred vision

Other reactions in more than 1% of patients but equally or more frequent in the placebo group included pain, tremor, neuralgia, back pain, dyspepsia, dyspnea, and flu syndrome.

There were no clinically important differences between men and women in the types and incidence of adverse reactions. Because there were few patients whose race was reported as other than white, there are insufficient data to support a statement regarding the distribution of adverse reactions by race.

Epilepsy with Partial Onset Seizures (Adjunctive Therapy)

The most common adverse reactions with NEURONTIN in combination with other antiepileptic drugs in patients >12 years of age, not seen at an equivalent frequency among placebo-treated patients, were somnolence, dizziness, ataxia, fatigue, and nystagmus.

The most common adverse reactions with NEURONTIN in combination with other antiepileptic drugs in pediatric patients 3 to 12 years of age, not seen at an equal frequency among placebo-treated patients, were viral infection, fever, nausea and/or vomiting, somnolence, and hostility *[see Warnings and Precautions (5.5)]*.

Approximately 7% of the 2074 patients >12 years of age and approximately 7% of the 449 pediatric patients 3 to 12 years of age who received NEURONTIN in premarketing clinical trials discontinued treatment because of an adverse reaction. The adverse reactions most commonly associated with withdrawal in patients >12 years of age were somnolence (1.2%), ataxia (0.8%), fatigue (0.6%), nausea and/or vomiting (0.6%), and dizziness (0.6%). The adverse reactions most commonly associated with withdrawal in pediatric patients were emotional lability (1.6%), hostility (1.3%), and hyperkinesia (1.1%).

Table 4 lists adverse reactions that occurred in at least 1% of NEURONTIN-treated patients >12 years of age with epilepsy participating in placebo-controlled trials and were numerically more common in the NEURONTIN group. In these studies, either NEURONTIN or placebo was added to the patient's current antiepileptic drug therapy.

TABLE 4. Adverse Reactions in Pooled Placebo-Controlled Add-On Trials In Epilepsy Patients >12 years of age

	NEURONTIN[a] N=543 %	Placebo[a] N=378 %
Body As A Whole		
Fatigue	11	5
Increased Weight	3	2
Back Pain	2	1
Peripheral Edema	2	1
Cardiovascular		
Vasodilatation	1	0
Digestive System		
Dyspepsia	2	1
Dry Mouth or Throat	2	1
Constipation	2	1
Dental Abnormalities	2	0

TABLE 4. Adverse Reactions in Pooled Placebo-Controlled Add-On Trials In Epilepsy Patients >12 years of age

	NEURONTIN[a] N=543 %	Placebo[a] N=378 %
Nervous System		
Somnolence	19	9
Dizziness	17	7
Ataxia	13	6
Nystagmus	8	4
Tremor	7	3
Dysarthria	2	1
Amnesia	2	0
Depression	2	1
Abnormal thinking	2	1
Abnormal coordination	1	0
Respiratory System		
Pharyngitis	3	2
Coughing	2	1
Skin and Appendages		
Abrasion	1	0
Urogenital System		
Impotence	2	1
Special Senses		
Diplopia	6	2
Amblyopia[b]	4	1

[a] Plus background antiepileptic drug therapy
[b] Amblyopia was often described as blurred vision.

Among the adverse reactions occurring at an incidence of at least 10% in NEURONTIN-treated patients, somnolence and ataxia appeared to exhibit a positive dose-response relationship.

The overall incidence of adverse reactions and the types of adverse reactions seen were similar among men and women treated with NEURONTIN. The incidence of adverse reactions increased slightly with increasing age in patients treated with either NEURONTIN or placebo. Because only 3% of patients (28/921) in placebo-controlled studies were identified as nonwhite (black or other), there are insufficient data to support a statement regarding the distribution of adverse reactions by race.

Table 5 lists adverse reactions that occurred in at least 2% of NEURONTIN-treated patients, age 3 to 12 years of age with epilepsy participating in placebo-controlled trials, and which were numerically more common in the NEURONTIN group.

TABLE 5. Adverse Reactions in a Placebo-Controlled Add-On Trial in Pediatric Epilepsy Patients Age 3 to 12 Years

	NEURONTIN[a] N=119 %	Placebo[a] N=128 %
Body As A Whole		
Viral Infection	11	3
Fever	10	3
Increased Weight	3	1
Fatigue	3	2
Digestive System		
Nausea and/or Vomiting	8	7
Nervous System		
Somnolence	8	5
Hostility	8	2
Emotional Lability	4	2
Dizziness	3	2
Hyperkinesia	3	1
Respiratory System		
Bronchitis	3	1
Respiratory Infection	3	1

[a] Plus background antiepileptic drug therapy

Other reactions in more than 2% of pediatric patients 3 to 12 years of age but equally or more frequent in the placebo group included: pharyngitis, upper respiratory infection, headache, rhinitis, convulsions, diarrhea, anorexia, coughing, and otitis media.

6.2 Postmarketing Experience

The following adverse reactions have been identified during postmarketing use of NEURONTIN. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Hepatobiliary disorders: jaundice
Investigations: elevated creatine kinase, elevated liver function tests
Metabolism and nutrition disorders: hyponatremia
Musculoskeletal and connective tissue disorder: rhabdomyolysis
Nervous system disorders: movement disorder
Reproductive system and breast disorders: breast enlargement, changes in libido, ejaculation disorders and anorgasmia
Skin and subcutaneous tissue disorders: angioedema *[see Warnings and Precautions (5.2)]*, erythema multiforme, Stevens-Johnson syndrome.

Adverse reactions following the abrupt discontinuation of gabapentin have also been reported. The most frequently reported reactions were anxiety, insomnia, nausea, pain, and sweating.

7 DRUG INTERACTIONS

7.1 Other Antiepileptic Drugs

Gabapentin is not appreciably metabolized nor does it interfere with the metabolism of commonly coadministered antiepileptic drugs *[see Clinical Pharmacology (12.3)]*.

7.2 Opioids

Hydrocodone

Coadministration of NEURONTIN with hydrocodone decreases hydrocodone exposure *[see Clinical Pharmacology (12.3)]*. The potential for alteration in hydrocodone exposure and effect should be considered when NEURONTIN is started or discontinued in a patient taking hydrocodone.

Morphine

When gabapentin is administered with morphine, patients should be observed for signs of central nervous system (CNS) depression, such as somnolence, sedation and respiratory depression *[see Clinical Pharmacology (12.3)]*.

7.3 Maalox® (aluminum hydroxide, magnesium hydroxide)

The mean bioavailability of gabapentin was reduced by about 20% with concomitant use of an antacid (Maalox®) containing magnesium and aluminum hydroxides. It is recommended that gabapentin be taken at least 2 hours following Maalox administration *[see Clinical Pharmacology (12.3)]*.

7.4 Drug/Laboratory Test Interactions

Because false positive readings were reported with the Ames N-Multistix SG® dipstick test for urinary protein when gabapentin was added to other antiepileptic drugs, the more specific sulfosalicylic acid precipitation procedure is recommended to determine the presence of urine protein.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C: There are no adequate and well-controlled studies in pregnant women. In nonclinical studies in mice, rats, and rabbits, gabapentin was developmentally toxic when administered to pregnant animals at doses similar to or lower than those used clinically. NEURONTIN should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

When pregnant mice received oral doses of gabapentin (500, 1000, or 3000 mg/kg/day) during the period of organogenesis, embryo-fetal toxicity (increased incidences of skeletal variations) was observed at the two highest doses. The no-effect dose for embryo-fetal developmental toxicity in mice was 500 mg/kg/day or approximately ½ of the maximum recommended human dose (MRHD) of 3600 mg/kg on a body surface area (mg/m^2) basis.

In studies in which rats received oral doses of gabapentin (500 to 2000 mg/kg/day), during pregnancy, adverse effect on offspring development (increased incidences of hydroureter and/or hydronephrosis) were observed at all doses. The lowest effect dose for developmental toxicity in rats is approximately equal to the MRHD on a mg/m^2 basis.

When pregnant rabbits were treated with gabapentin during the period of organogenesis, an increase in embryo-fetal mortality was observed at all doses tested (60, 300, or 1500 mg/kg). The lowest effect dose for embryo-fetal developmental toxicity in rabbits is less than the MRHD on a mg/m^2 basis.

In a published study, gabapentin (400 mg/kg/day) was administered by intraperitoneal injection to neonatal mice during the first postnatal week, a period of synaptogenesis in rodents (corresponding to the last trimester of pregnancy in humans). Gabapentin caused a marked decrease in neuronal synapse formation in brains of intact mice and abnormal neuronal synapse formation in a mouse model of synaptic repair. Gabapentin has been shown *in vitro* to interfere with activity of the α2δ subunit of voltage-activated calcium channels, a receptor involved in neuronal synaptogenesis. The clinical significance of these findings is unknown.

To provide information regarding the effects of *in utero* exposure to NEURONTIN, physicians are advised to recommend that pregnant patients taking NEURONTIN enroll in the North American Antiepileptic Drug (NAAED) Pregnancy Registry. This can be done by calling the toll free number 1-888-233-2334, and must be done by patients themselves. Information on the registry can also be found at the website http://www.aedpregnancyregistry.org/.

8.3 Nursing Mothers

Gabapentin is secreted into human milk following oral administration. A nursed infant could be exposed to a maximum dose of approximately 1 mg/kg/day of gabapentin. Because the effect on the nursing infant is unknown, NEURONTIN should be used in women who are nursing only if the benefits clearly outweigh the risks.

8.4 Pediatric Use

Safety and effectiveness of NEURONTIN in the management of postherpetic neuralgia in pediatric patients have not been established.

Effectiveness as adjunctive therapy in the treatment of partial seizures in pediatric patients below the age of 3 years has not been established *[see Clinical Studies (14.2)]*.

8.5 Geriatric Use

The total number of patients treated with NEURONTIN in controlled clinical trials in patients with postherpetic neuralgia was 336, of which 102 (30%) were 65 to 74 years of age, and 168 (50%) were 75 years of age and older. There was a larger treatment effect in patients 75 years of age and older compared with younger patients who received the same dosage. Since gabapentin is almost exclusively eliminated by renal excretion, the larger treatment effect observed in patients ≥75 years may be a consequence of increased gabapentin exposure for a given dose that results from an age-related decrease in renal function. However, other factors cannot be excluded. The types and incidence of adverse reactions were similar across age groups except for peripheral edema and ataxia, which tended to increase in incidence with age.

Clinical studies of NEURONTIN in epilepsy did not include sufficient numbers of subjects aged 65 and over to determine whether they responded differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and dose should be adjusted based on creatinine clearance values in these patients *[see Dosage and Administration (2.4), Adverse Reactions (6), and Clinical Pharmacology (12.3)]*.

8.6 Renal Impairment

Dosage adjustment in adult patients with compromised renal function is necessary *[see Dosage and Administration (2.3) and Clinical Pharmacology (12.3)]*. Pediatric patients with renal insufficiency have not been studied.

Dosage adjustment in patients undergoing hemodialysis is necessary *[see Dosage and Administration (2.3) and Clinical Pharmacology (12.3)]*.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

Gabapentin is not a scheduled drug.

9.2 Abuse

Gabapentin does not exhibit affinity for benzodiazepine, opiate (mu, delta or kappa), or cannabinoid 1 receptor sites. A small number of postmarketing cases report gabapentin misuse and abuse. These individuals were taking higher than recommended doses of gabapentin for unapproved uses. Most of the individuals described in these reports had a history of poly-substance abuse or used gabapentin to relieve symptoms of withdrawal from other substances.

When prescribing gabapentin carefully evaluate patients for a history of drug abuse and observe them for signs and symptoms of gabapentin misuse or abuse (e.g., development of tolerance, self-dose escalation, and drug-seeking behavior).

9.3 Dependence

There are rare postmarketing reports of individuals experiencing withdrawal symptoms shortly after discontinuing higher than recommended doses of gabapentin used to treat illnesses for which the drug is not approved. Such symptoms included agitation, disorientation and confusion after suddenly discontinuing gabapentin that resolved after restarting gabapentin. Most of these individuals had a history of poly-substance abuse or used gabapentin to relieve symptoms of withdrawal from other substances. The dependence and abuse potential of gabapentin has not been evaluated in human studies.

10 OVERDOSAGE

A lethal dose of gabapentin was not identified in mice and rats receiving single oral doses as high as 8000 mg/kg. Signs of acute toxicity in animals included ataxia, labored breathing, ptosis, sedation, hypoactivity, or excitation.

Acute oral overdoses of NEURONTIN up to 49 grams have been reported. In these cases, double vision, slurred speech, drowsiness, lethargy, and diarrhea were observed. All patients recovered with supportive care. Coma, resolving with dialysis, has been reported in patients with chronic renal failure who were treated with NEURONTIN.

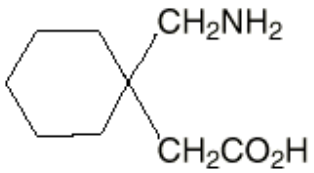
Gabapentin can be removed by hemodialysis. Although hemodialysis has not been performed in the few overdose cases reported, it may be indicated by the patient's clinical state or in patients with significant renal impairment.

If overexposure occurs, call your poison control center at 1-800-222-1222.

11 DESCRIPTION

The active ingredient in NEURONTIN capsules, tablets, and oral solution is gabapentin,which has the chemical name 1-(aminomethyl)cyclohexaneacetic acid.

The molecular formula of gabapentin is $C_9H_{17}NO_2$ and the molecular weight is 171.24. The structural formula of gabapentin is:



Gabapentin is a white to off-white crystalline solid with a pK_{a1} of 3.7 and a pK_{a2} of 10.7. It is freely soluble in water and both basic and acidic aqueous solutions. The log of the partition coefficient (n-octanol/0.05M phosphate buffer) at pH 7.4 is –1.25.

Each Neurontin capsule contains 100 mg, 300 mg, or 400 mg of gabapentin and the following inactive ingredients: lactose, cornstarch, talc, gelatin, titanium dioxide, FD&C Blue No. 2, yellow iron oxide (300 mg and 400 mg only), and red iron oxide (400 mg only).

Each Neurontin tablet contains 600 mg or 800 mg of gabapentin and the following inactive ingredients: poloxamer 407, copovidone, cornstarch, magnesium stearate, hydroxypropyl cellulose, talc, and candelilla wax

Neurontin oral solution contains 250 mg of gabapentin per 5 mL (50 mg per mL) and the following inactive ingredients: glycerin, xylitol, purified water, and artificial cool strawberry anise flavor.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The precise mechanisms by which gabapentin produces its analgesic and antiepileptic actions are unknown. Gabapentin is structurally related to the neurotransmitter gamma-aminobutyric acid (GABA) but has no effect on GABA binding, uptake, or degradation. *In vitro* studies have shown that gabapentin binds with high-affinity to the α2δ subunit of voltage-activated calcium channels; however, the relationship of this binding to the therapeutic effects of gabapentin is unknown.

12.3 Pharmacokinetics

All pharmacological actions following gabapentin administration are due to the activity of the parent compound; gabapentin is not appreciably metabolized in humans.

Oral Bioavailability

Gabapentin bioavailability is not dose proportional; i.e., as dose is increased, bioavailability decreases. Bioavailability of gabapentin is approximately 60%, 47%, 34%, 33%, and 27% following 900, 1200, 2400, 3600, and 4800 mg/day given in 3 divided doses, respectively. Food has only a slight effect on the rate and extent of absorption of gabapentin (14% increase in AUC and C_{max}).

Distribution

Less than 3% of gabapentin circulates bound to plasma protein. The apparent volume of distribution of gabapentin after 150 mg intravenous administration is 58±6 L (mean ±SD). In patients with epilepsy, steady-state predose (C_{min}) concentrations of gabapentin in cerebrospinal fluid were approximately 20% of the corresponding plasma concentrations.

Elimination

Gabapentin is eliminated from the systemic circulation by renal excretion as unchanged drug. Gabapentin is not appreciably metabolized in humans.

Gabapentin elimination half-life is 5 to 7 hours and is unaltered by dose or following multiple dosing. Gabapentin elimination rate constant, plasma clearance, and renal clearance are directly proportional to creatinine clearance. In elderly patients, and in patients with impaired renal function, gabapentin plasma clearance is reduced. Gabapentin can be removed from plasma by hemodialysis.

Specific Populations

Age

The effect of age was studied in subjects 20-80 years of age. Apparent oral clearance (CL/F) of gabapentin decreased as age increased, from about 225 mL/min in those under 30 years of age to about 125 mL/min in those over 70 years of age. Renal clearance (CLr) and CLr adjusted for body surface area also declined with age; however, the decline in the renal clearance of gabapentin with age can largely be explained by the decline in renal function. *[see Dosage and Administration (2.4) and Use in Specific Populations (8.5)]*.

Gender

Although no formal study has been conducted to compare the pharmacokinetics of gabapentin in men and women, it appears that the pharmacokinetic parameters for males and females are similar and there are no significant gender differences.

Race

Pharmacokinetic differences due to race have not been studied. Because gabapentin is primarily renally excreted and there are no important racial differences in creatinine clearance, pharmacokinetic differences due to race are not expected.

Pediatric

Gabapentin pharmacokinetics were determined in 48 pediatric subjects between the ages of 1 month and 12 years following a dose of approximately 10 mg/kg. Peak plasma concentrations were similar across the entire age group and occurred 2 to 3 hours postdose. In general, pediatric subjects between 1 month and <5 years of age achieved approximately 30% lower exposure (AUC) than that observed in those 5 years of age and older. Accordingly, oral clearance normalized per body weight was higher in the younger children. Apparent oral clearance of gabapentin was directly proportional to creatinine clearance. Gabapentin elimination half-life averaged 4.7 hours and was similar across the age groups studied.

A population pharmacokinetic analysis was performed in 253 pediatric subjects between 1 month and 13 years of age. Patients received 10 to 65 mg/kg/day given three times a day. Apparent oral clearance (CL/F) was directly proportional to creatinine clearance and this relationship was similar following a single dose and at steady state. Higher oral clearance values were observed in children <5 years of age compared to those observed in children 5 years of age and older, when normalized per body weight. The clearance was highly variable in infants <1 year of age. The normalized CL/F values observed in pediatric patients 5 years of age and older were consistent with values observed in adults after a single dose. The oral volume of distribution normalized per body weight was constant across the age range.

These pharmacokinetic data indicate that the effective daily dose in pediatric patients with epilepsy ages 3 and 4 years should be 40 mg/kg/day to achieve average plasma concentrations similar to those achieved in patients 5 years of age and older receiving gabapentin at 30 mg/kg/day *[see Dosage and Administration (2.1)]*.

Adult Patients with Renal Impairment

Subjects (N=60) with renal impairment (mean creatinine clearance ranging from 13-114 mL/min) were administered single 400 mg oral doses of gabapentin. The mean gabapentin half-life ranged from about 6.5 hours (patients with creatinine clearance >60 mL/min) to 52 hours (creatinine clearance <30 mL/min) and gabapentin renal clearance from about 90 mL/min (>60 mL/min group) to about 10 mL/min (<30 mL/min). Mean plasma clearance (CL/F) decreased from approximately 190 mL/min to 20 mL/min *[see Dosage and Administration (2.3) and Use in Specific Populations (8.6)]*. Pediatric patients with renal insufficiency have not been studied.

Hemodialysis

In a study in anuric adult subjects (N=11), the apparent elimination half-life of gabapentin on nondialysis days was about 132 hours; during dialysis the apparent half-life of gabapentin was reduced to 3.8 hours. Hemodialysis thus has a significant effect on gabapentin elimination in anuric subjects *[see Dosage and Administration (2.3) and Use in Specific Populations (8.6)]*.

Hepatic Disease

Because gabapentin is not metabolized, no study was performed in patients with hepatic impairment.

Drug Interactions

- In Vitro Studies

  In vitro studies were conducted to investigate the potential of gabapentin to inhibit the major cytochrome P450 enzymes (CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4) that mediate drug and xenobiotic metabolism using isoform selective marker substrates and human liver microsomal preparations. Only at the highest

concentration tested (171 mcg/mL; 1 mM) was a slight degree of inhibition (14%-30%) of isoform CYP2A6 observed. No inhibition of any of the other isoforms tested was observed at gabapentin concentrations up to 171 mcg/mL (approximately 15 times the C_{max} at 3600 mg/day).

- In Vivo Studies

  The drug interaction data described in this section were obtained from studies involving healthy adults and adult patients with epilepsy.

  Phenytoin

  In a single (400 mg) and multiple dose (400 mg three times a day) study of NEURONTIN in epileptic patients (N=8) maintained on phenytoin monotherapy for at least 2 months, gabapentin had no effect on the steady-state trough plasma concentrations of phenytoin and phenytoin had no effect on gabapentin pharmacokinetics.

  Carbamazepine

  Steady-state trough plasma carbamazepine and carbamazepine 10, 11 epoxide concentrations were not affected by concomitant gabapentin (400 mg three times a day; N=12) administration. Likewise, gabapentin pharmacokinetics were unaltered by carbamazepine administration.

  Valproic Acid

  The mean steady-state trough serum valproic acid concentrations prior to and during concomitant gabapentin administration (400 mg three times a day; N=17) were not different and neither were gabapentin pharmacokinetic parameters affected by valproic acid.

  Phenobarbital

  Estimates of steady-state pharmacokinetic parameters for phenobarbital or gabapentin (300 mg three times a day; N=12) are identical whether the drugs are administered alone or together.

  Naproxen

  Coadministration (N=18) of naproxen sodium capsules (250 mg) with NEURONTIN (125 mg) appears to increase the amount of gabapentin absorbed by 12% to 15%. Gabapentin had no effect on naproxen pharmacokinetic parameters. These doses are lower than the therapeutic doses for both drugs. The magnitude of interaction within the recommended dose ranges of either drug is not known.

  Hydrocodone

Coadministration of NEURONTIN (125 to 500 mg; N=48) decreases hydrocodone (10 mg; N=50) C_{max} and AUC values in a dose-dependent manner relative to administration of hydrocodone alone; C_{max} and AUC values are 3% to 4% lower, respectively, after administration of 125 mg NEURONTIN and 21% to 22% lower, respectively, after administration of 500 mg NEURONTIN. The mechanism for this interaction is unknown. Hydrocodone increases gabapentin AUC values by 14%. The magnitude of interaction at other doses is not known.

Morphine

A literature article reported that when a 60 mg controlled-release morphine capsule was administered 2 hours prior to a 600 mg NEURONTIN capsule (N=12), mean gabapentin AUC increased by 44% compared to gabapentin administered without morphine. Morphine pharmacokinetic parameter values were not affected by administration of NEURONTIN 2 hours after morphine. The magnitude of interaction at other doses is not known.

Cimetidine

In the presence of cimetidine at 300 mg QID (N=12), the mean apparent oral clearance of gabapentin fell by 14% and creatinine clearance fell by 10%. Thus, cimetidine appeared to alter the renal excretion of both gabapentin and creatinine, an endogenous marker of renal function. This small decrease in excretion of gabapentin by cimetidine is not expected to be of clinical importance. The effect of gabapentin on cimetidine was not evaluated.

Oral Contraceptive

Based on AUC and half-life, multiple-dose pharmacokinetic profiles of norethindrone and ethinyl estradiol following administration of tablets containing 2.5 mg of norethindrone acetate and 50 mcg of ethinyl estradiol were similar with and without coadministration of gabapentin (400 mg three times a day; N=13). The C_{max} of norethindrone was 13% higher when it was coadministered with gabapentin; this interaction is not expected to be of clinical importance.

Antacid (Maalox®) (aluminum hydroxide, magnesium hydroxide)

Antacid (Maalox®) containing magnesium and aluminum hydroxides reduced the mean bioavailability of gabapentin (N=16) by about 20%. This decrease in bioavailability was about 10% when gabapentin was administered 2 hours after Maalox.

Probenecid

Probenecid is a blocker of renal tubular secretion. Gabapentin pharmacokinetic parameters without and with probenecid were comparable. This indicates that gabapentin does not undergo renal tubular secretion by the pathway that is blocked by probenecid.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Gabapentin was administered orally to mice and rats in 2-year carcinogenicity studies. No evidence of drug-related carcinogenicity was observed in mice treated at doses up to 2000 mg/kg/day. At 2000 mg/kg, the plasma gabapentin exposure (AUC) in mice is approximately 2 times that in humans at the MRHD of 3600 mg/day. In rats, increases in the incidence of pancreatic acinar cell adenoma and carcinoma were found in male rats receiving the highest dose (2000 mg/kg), but not at doses of 250 or 1000 mg/kg/day. At 1000 mg/kg, the plasma gabapentin exposure (AUC) in rats is approximately 5 times that in humans at the MRHD.

Studies designed to investigate the mechanism of gabapentin-induced pancreatic carcinogenesis in rats indicate that gabapentin stimulates DNA synthesis in rat pancreatic acinar cells *in vitro* and, thus, may be acting as a tumor promoter by enhancing mitogenic activity. It is not known whether gabapentin has the ability to increase cell proliferation in other cell types or in other species, including humans.

Gabapentin did not demonstrate mutagenic or genotoxic potential in three *in vitro* and four *in vivo* assays. It was negative in the Ames test and the *in vitro* HGPRT forward mutation assay in Chinese hamster lung cells; it did not produce significant increases in chromosomal aberrations in the *in vitro* Chinese hamster lung cell assay; it was negative in the *in vivo* chromosomal aberration assay and in the *in vivo* micronucleus test in Chinese hamster bone marrow; it was negative in the *in vivo* mouse micronucleus assay; and it did not induce unscheduled DNA synthesis in hepatocytes from rats given gabapentin.

No adverse effects on fertility or reproduction were observed in rats at doses up to 2000 mg/kg. At 2000 mg/kg, the plasma gabapentin exposure (AUC) in rats is approximately 8 times that in humans at the MRHD.

14 CLINICAL STUDIES

14.1 Postherpetic Neuralgia

NEURONTIN was evaluated for the management of postherpetic neuralgia (PHN) in two randomized, double-blind, placebo-controlled, multicenter studies. The intent-to-treat (ITT) population consisted of a total of 563 patients with pain for more than 3 months after healing of the herpes zoster skin rash (Table 6).

TABLE 6. Controlled PHN Studies: Duration, Dosages, and Number of Patients

Study	Study Duration	Gabapentin (mg/day)[a] Target Dose	Patients Receiving Gabapentin	Patients Receiving Placebo
1	8 weeks	3600	113	116

2	7 weeks	1800, 2400	223	111
		Total	336	227

[a]Given in 3 divided doses (TID)

Each study included a 7- or 8-week double-blind phase (3 or 4 weeks of titration and 4 weeks of fixed dose). Patients initiated treatment with titration to a maximum of 900 mg/day gabapentin over 3 days. Dosages were then to be titrated in 600 to 1200 mg/day increments at 3- to 7-day intervals to the target dose over 3 to 4 weeks. Patients recorded their pain in a daily diary using an 11-point numeric pain rating scale ranging from 0 (no pain) to 10 (worst possible pain). A mean pain score during baseline of at least 4 was required for randomization. Analyses were conducted using the ITT population (all randomized patients who received at least one dose of study medication).

Both studies demonstrated efficacy compared to placebo at all doses tested.

The reduction in weekly mean pain scores was seen by Week 1 in both studies, and were maintained to the end of treatment. Comparable treatment effects were observed in all active treatment arms. Pharmacokinetic/pharmacodynamic modeling provided confirmatory evidence of efficacy across all doses. Figures 1 and 2 show pain intensity scores over time for Studies 1 and 2.

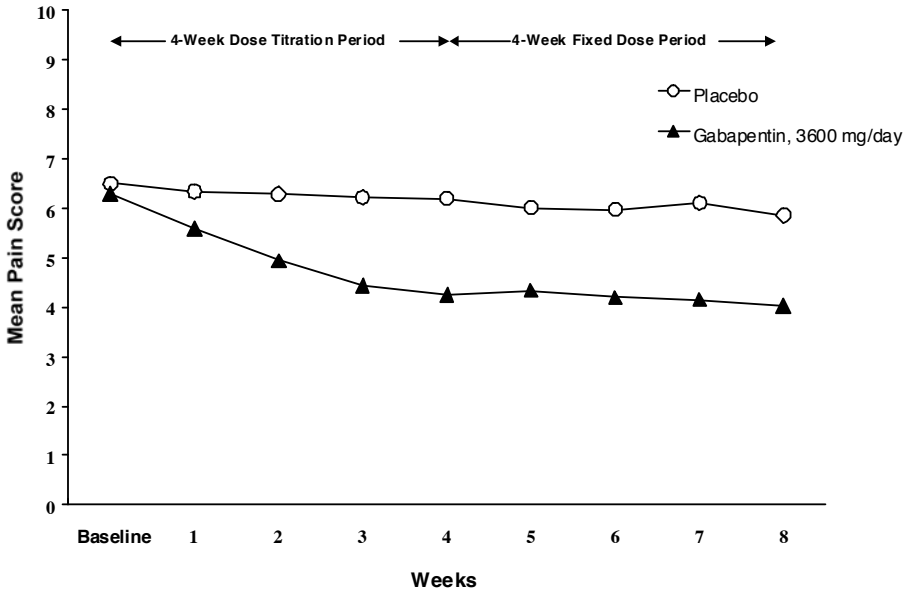


Figure 1. Weekly Mean Pain Scores (Observed Cases in ITT Population): Study 1

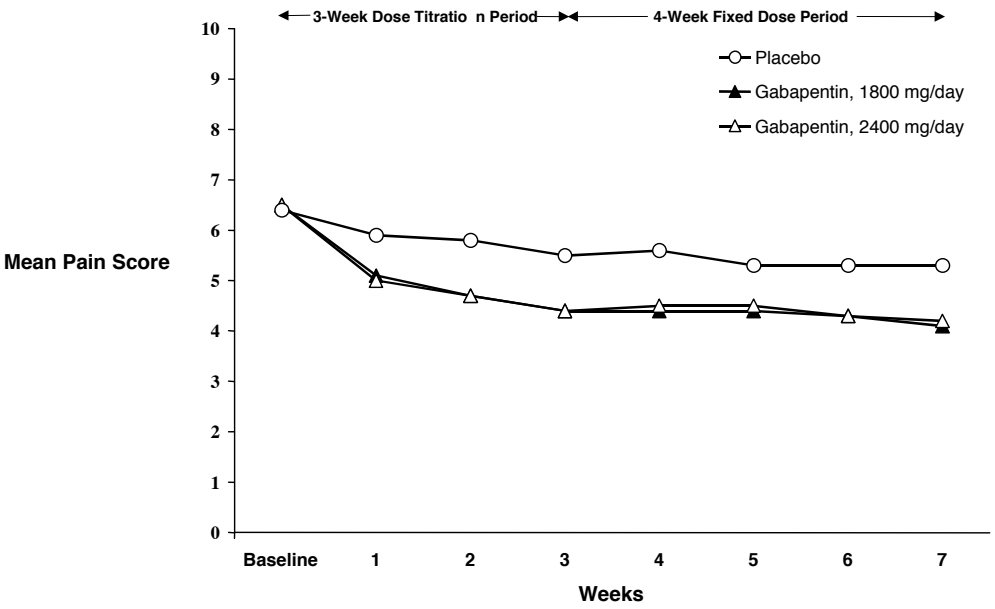


Figure 2. Weekly Mean Pain Scores (Observed Cases in ITT Population): Study 2

The proportion of responders (those patients reporting at least 50% improvement in endpoint pain score compared with baseline) was calculated for each study (Figure 3).

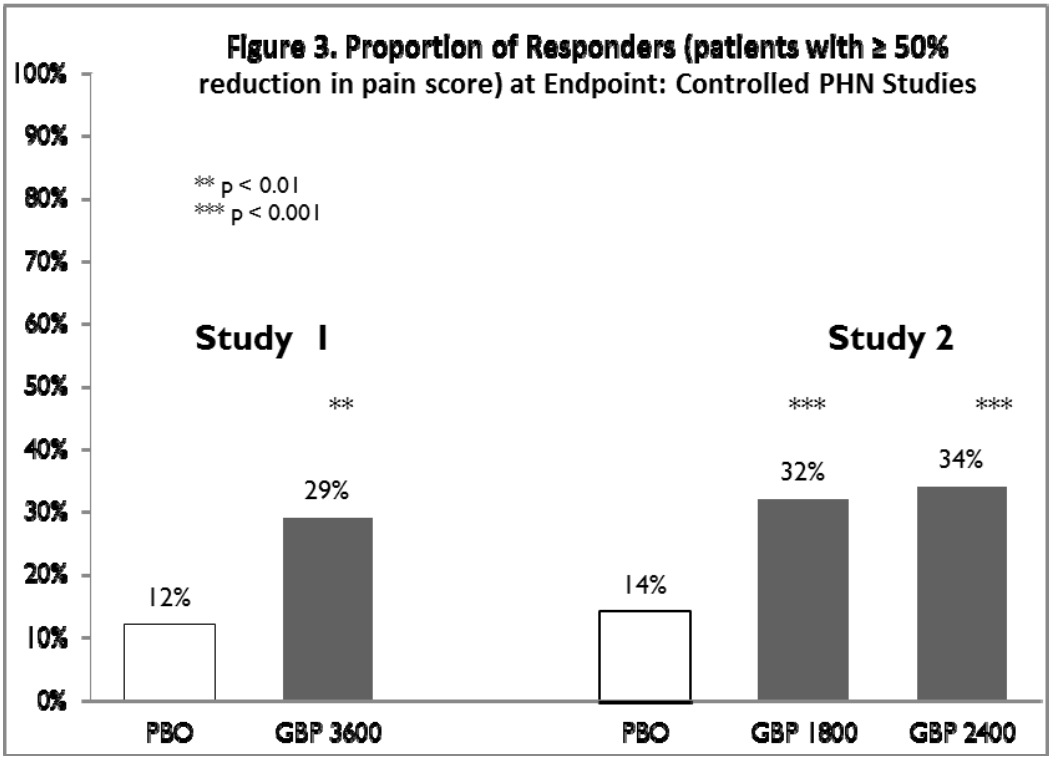


Figure 3. Proportion of Responders (patients with ≥50% reduction in pain score) at Endpoint: Controlled PHN Studies

14.2 Epilepsy for Partial Onset Seizures (Adjunctive Therapy)

The effectiveness of NEURONTIN as adjunctive therapy (added to other antiepileptic drugs) was established in multicenter placebo-controlled, double-blind, parallel-group clinical trials in adult and pediatric patients (3 years and older) with refractory partial seizures.

Evidence of effectiveness was obtained in three trials conducted in 705 patients (age 12 years and above) and one trial conducted in 247 pediatric patients (3 to 12 years of age). The patients enrolled had a history of at least 4 partial seizures per month in spite of receiving one or more antiepileptic drugs at therapeutic levels and were observed on their established antiepileptic drug regimen during a 12-week baseline period (6 weeks in the study of pediatric patients). In patients continuing to have at least 2 (or 4 in some studies) seizures per month, NEURONTIN or placebo was then added on to the existing therapy during a 12-week treatment period. Effectiveness was assessed primarily on the basis of the percent of patients with a 50% or greater reduction in seizure frequency from baseline to treatment (the "responder rate") and a derived measure called response ratio, a measure of change defined as (T - B)/(T + B), in which B is the patient's baseline seizure frequency and T is the patient's seizure frequency during treatment. Response ratio is distributed within the range -1 to +1. A zero value indicates no change while complete elimination of seizures would give a value of -1; increased seizure rates would give positive values. A response ratio of -0.33 corresponds to a 50% reduction in seizure frequency. The

results given below are for all partial seizures in the intent-to-treat (all patients who received any doses of treatment) population in each study, unless otherwise indicated.

One study compared NEURONTIN 1200 mg/day, in three divided doses with placebo. Responder rate was 23% (14/61) in the NEURONTIN group and 9% (6/66) in the placebo group; the difference between groups was statistically significant. Response ratio was also better in the NEURONTIN group (-0.199) than in the placebo group (-0.044), a difference that also achieved statistical significance.

A second study compared primarily NEURONTIN 1200 mg/day, in three divided doses (N=101), with placebo (N=98). Additional smaller NEURONTIN dosage groups (600 mg/day, N=53; 1800 mg/day, N=54) were also studied for information regarding dose response. Responder rate was higher in the NEURONTIN 1200 mg/day group (16%) than in the placebo group (8%), but the difference was not statistically significant. The responder rate at 600 mg (17%) was also not significantly higher than in the placebo, but the responder rate in the 1800 mg group (26%) was statistically significantly superior to the placebo rate. Response ratio was better in the NEURONTIN 1200 mg/day group (-0.103) than in the placebo group (-0.022); but this difference was also not statistically significant ($p = 0.224$). A better response was seen in the NEURONTIN 600 mg/day group (-0.105) and 1800 mg/day group (-0.222) than in the 1200 mg/day group, with the 1800 mg/day group achieving statistical significance compared to the placebo group.

A third study compared NEURONTIN 900 mg/day, in three divided doses (N=111), and placebo (N=109). An additional NEURONTIN 1200 mg/day dosage group (N=52) provided dose-response data. A statistically significant difference in responder rate was seen in the NEURONTIN 900 mg/day group (22%) compared to that in the placebo group (10%). Response ratio was also statistically significantly superior in the NEURONTIN 900 mg/day group (-0.119) compared to that in the placebo group (-0.027), as was response ratio in 1200 mg/day NEURONTIN (-0.184) compared to placebo.

Analyses were also performed in each study to examine the effect of NEURONTIN on preventing secondarily generalized tonic-clonic seizures. Patients who experienced a secondarily generalized tonic-clonic seizure in either the baseline or in the treatment period in all three placebo-controlled studies were included in these analyses. There were several response ratio comparisons that showed a statistically significant advantage for NEURONTIN compared to placebo and favorable trends for almost all comparisons.

Analysis of responder rate using combined data from all three studies and all doses (N=162, NEURONTIN; N=89, placebo) also showed a significant advantage for NEURONTIN over placebo in reducing the frequency of secondarily generalized tonic-clonic seizures.

In two of the three controlled studies, more than one dose of NEURONTIN was used. Within each study, the results did not show a consistently increased response to dose. However, looking across studies, a trend toward increasing efficacy with increasing dose is evident (see Figure 4).

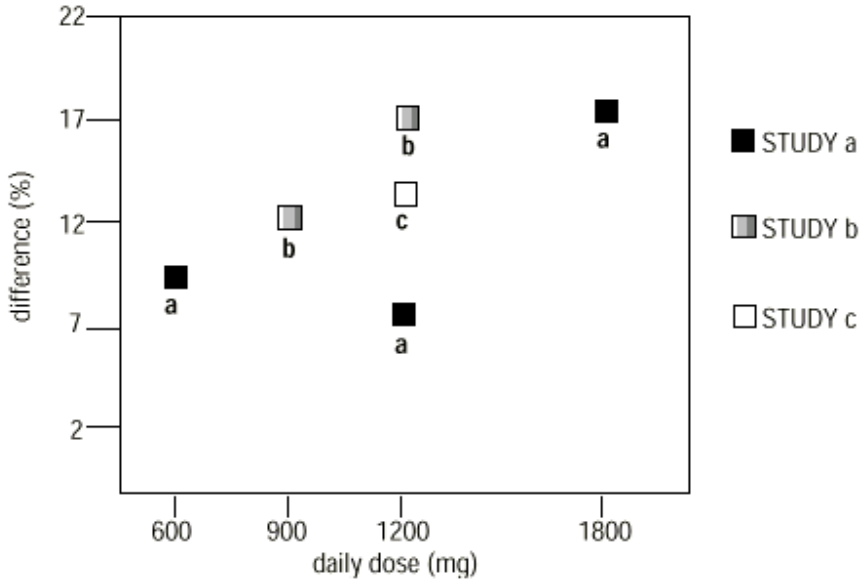


Figure 4. Responder Rate in Patients Receiving NEURONTIN Expressed as a Difference from Placebo by Dose and Study: Adjunctive Therapy Studies in Patients ≥12 Years of Age with Partial Seizures

In the figure, treatment effect magnitude, measured on the Y axis in terms of the difference in the proportion of gabapentin and placebo-assigned patients attaining a 50% or greater reduction in seizure frequency from baseline, is plotted against the daily dose of gabapentin administered (X axis).

Although no formal analysis by gender has been performed, estimates of response (Response Ratio) derived from clinical trials (398 men, 307 women) indicate no important gender differences exist. There was no consistent pattern indicating that age had any effect on the response to NEURONTIN. There were insufficient numbers of patients of races other than Caucasian to permit a comparison of efficacy among racial groups.

A fourth study in pediatric patients age 3 to 12 years compared 25 –35 mg/kg/day NEURONTIN (N=118) with placebo (N=127). For all partial seizures in the intent-to-treat population, the response ratio was statistically significantly better for the NEURONTIN group (-0.146) than for the placebo group (-0.079). For the same population, the responder rate for NEURONTIN (21%) was not significantly different from placebo (18%).

A study in pediatric patients age 1 month to 3 years compared 40 mg/kg/day NEURONTIN (N=38) with placebo (N=38) in patients who were receiving at least one marketed antiepileptic drug and had at least one partial seizure during the screening period (within 2 weeks prior to baseline). Patients had up to 48 hours of baseline and up to 72 hours of double-blind video EEG monitoring to record and count the occurrence of seizures. There were no statistically significant differences between treatments in either the response ratio or responder rate.

Appendix 7

NEURONTIN

Summary of product information (ANNEX III)

European Medicines Agency (EMA)

European Union

Updated: September 2006

Access online

1. NAME OF THE MEDICINAL PRODUCT

Neurontin and associated names 100 mg hard capsule
Neurontin and associated names 300 mg hard capsule
Neurontin and associated names 400 mg hard capsule
Neurontin and associated names 600 mg film-coated tablet
Neurontin and associated names 800 mg film-coated tablet

[See Annex I - To be completed nationally]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 100 mg hard capsule contains 100 mg of gabapentin.

Each 300 mg hard capsule contains 300 mg of gabapentin.

Each 400 mg hard capsule contains 400 mg of gabapentin.

Each 600 mg film-coated tablet contains 600 mg of gabapentin.

Each 800 mg film-coated tablet contains 800 mg of gabapentin.

Excipients:

Each 100 mg hard capsule contains 13 mg lactose (as monohydrate).

Each 300 mg hard capsule contains 41 mg lactose (as monohydrate).

Each 400 mg hard capsule contains 54 mg lactose (as monohydrate).

For a full list of excipients, see section 6.1.

[To be completed nationally]

3. PHARMACEUTICAL FORM

Capsule, hard

Film-coated tablet

[Description to be completed nationally]

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Epilepsy

Gabapentin is indicated as adjunctive therapy in the treatment of partial seizures with and without secondary generalization in adults and children aged 6 years and above (see section 5.1).

Gabapentin is indicated as monotherapy in the treatment of partial seizures with and without secondary generalization in adults and adolescents aged 12 years and above.

Treatment of peripheral neuropathic pain

Gabapentin is indicated for the treatment of peripheral neuropathic pain such as painful diabetic neuropathy and post-herpetic neuralgia in adults.

4.2 Posology and method of administration

For oral use.

Gabapentin can be given with or without food and should be swallowed whole with sufficient fluid-intake (e.g. a glass of water).

For all indications a titration scheme for the initiation of therapy is described in Table 1, which is recommended for adults and adolescents aged 12 years and above. Dosing instructions for children under 12 years of age are provided under a separate sub-heading later in this section.

Table 1		
DOSING CHART – INITIAL TITRATION		
Day 1	Day 2	Day 3
300 mg once a day	300 mg two times a day	300 mg three times a day

Epilepsy

Epilepsy typically requires long-term therapy. Dosage is determined by the treating physician according to individual tolerance and efficacy. When in the judgment of the clinician there is a need for dose reduction, discontinuation, or substitution with an alternative medication, this should be done gradually over a minimum of one week.

Adults and adolescents:

In clinical trials, the effective dosing range was 900 to 3600 mg/day. Therapy may be initiated by titrating the dose as described in Table 1 or by administering 300 mg three times a day (TID) on Day 1. Thereafter, based on individual patient response and tolerability, the dose can be further increased in 300 mg/day increments every 2-3 days up to a maximum dose of 3600 mg/day. Slower titration of gabapentin dosage may be appropriate for individual patients. The minimum time to reach a dose of 1800 mg/day is one week, to reach 2400 mg/day is a total of 2 weeks, and to reach 3600 mg/day is a total of 3 weeks. Dosages up to 4800 mg/day have been well tolerated in long-term open-label clinical studies. The total daily dose should be divided in three single doses, the maximum time interval between the doses should not exceed 12 hours to prevent breakthrough convulsions.

Children aged 6 years and above:

The starting dose should range from 10 to 15 mg/kg/day and the effective dose is reached by upward titration over a period of approximately three days. The effective dose of gabapentin in children aged 6 years and older is 25 to 35 mg/kg/day. Dosages up to 50 mg/kg/day have been well tolerated in a long-term clinical study. The total daily dose should be divided in three single doses, the maximum time interval between doses should not exceed 12 hours.

It is not necessary to monitor gabapentin plasma concentrations to optimize gabapentin therapy. Further, gabapentin may be used in combination with other antiepileptic medicinal products without concern for alteration of the plasma concentrations of gabapentin or serum concentrations of other antiepileptic medicinal products.

Peripheral neuropathic pain

Adults

The therapy may be initiated by titrating the dose as described in Table 1. Alternatively, the starting dose is 900 mg/day given as three equally divided doses. Thereafter, based on individual patient response and tolerability, the dose can be further increased in 300 mg/day increments every 2-3 days up to a maximum dose of 3600 mg/day. Slower titration of gabapentin dosage may be appropriate for individual patients. The minimum time to reach a dose of 1800 mg/day is one week, to reach 2400 mg/day is a total of 2 weeks, and to reach 3600 mg/day is a total of 3 weeks.

In the treatment of peripheral neuropathic pain such as painful diabetic neuropathy and post-herpetic neuralgia, efficacy and safety have not been examined in clinical studies for treatment periods longer than 5 months. If a patient requires dosing longer than 5 months for the treatment of peripheral neuropathic pain, the treating physician should assess the patient's clinical status and determine the need for additional therapy.

Instruction for all areas of indication

In patients with poor general health, i.e., low body weight, after organ transplantation etc., the dose should be titrated more slowly, either by using smaller dosage strengths or longer intervals between dosage increases.

Use in elderly patients (over 65 years of age)

Elderly patients may require dosage adjustment because of declining renal function with age (see Table 2). Somnolence, peripheral oedema and asthenia may be more frequent in elderly patients.

Use in patients with renal impairment

Dosage adjustment is recommended in patients with compromised renal function as described in Table 2 and/or those undergoing haemodialysis. Gabapentin 100 mg capsules can be used to follow dosing recommendations for patients with renal insufficiency.

Table 2	
DOSAGE OF GABAPENTIN IN ADULTS BASED ON RENAL FUNCTION	
Creatinine Clearance (ml/min)	Total Daily Dose[a] (mg/day)
≥80	900-3600
50-79	600-1800
30-49	300-900
15-29	150[b]-600
<15[c]	150[b]-300

[a] Total daily dose should be administered as three divided doses. Reduced dosages are for patients with renal impairment (creatinine clearance < 79 ml/min).
[b] To be administered as 300 mg every other day.
[c] For patients with creatinine clearance <15 ml/min, the daily dose should be reduced in proportion to creatinine clearance (e.g., patients with a creatinine clearance of 7.5 ml/min should receive one-half the daily dose that patients with a creatinine clearance of 15 ml/min receive).

Use in patients undergoing haemodialysis

For anuric patients undergoing haemodialysis who have never received gabapentin, a loading dose of 300 to 400 mg, then 200 to 300 mg of gabapentin following each 4 hours of haemodialysis, is recommended. On dialysis-free days, there should be no treatment with gabapentin.

For renally impaired patients undergoing haemodialysis, the maintenance dose of gabapentin should be based on the dosing recommendations found in Table 2. In addition to the maintenance dose, an additional 200 to 300 mg dose following each 4-hour haemodialysis treatment is recommended.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

4.4 Special warnings and precautions for use

If a patient develops acute pancreatitis under treatment with gabapentin, discontinuation of gabapentin should be considered (see section 4.8).

Although there is no evidence of rebound seizures with gabapentin, abrupt withdrawal of anticonvulsants in epileptic patients may precipitate status epilepticus (see section 4.2).

As with other antiepileptic medicinal products, some patients may experience an increase in seizure frequency or the onset of new types of seizures with gabapentin.

As with other anti-epileptics, attempts to withdraw concomitant anti-epileptics in treatment refractory patients on more than one anti-epileptic, in order to reach gabapentin monotherapy have a low success rate.

Gabapentin is not considered effective against primary generalized seizures such as absences and may aggravate these seizures in some patients. Therefore, gabapentin should be used with caution in patients with mixed seizures including absences.

No systematic studies in patients 65 years or older have been conducted with gabapentin. In one double blind study in patients with neuropathic pain, somnolence, peripheral oedema and asthenia occurred in a somewhat higher percentage in patients aged 65 years or above, than in younger patients. Apart from these findings, clinical investigations in this age group do not indicate an adverse event profile different from that observed in younger patients.

The effects of long-term (greater than 36 weeks) gabapentin therapy on learning, intelligence, and development in children and adolescents have not been adequately studied. The benefits of prolonged therapy must therefore be weighed against the potential risks of such therapy.

Laboratory tests
False positive readings may be obtained in the semi-quantitative determination of total urine protein by dipstick tests. It is therefore recommended to verify such a positive dipstick test result by methods based on a different analytical principle such as the Biuret method, turbidimetric or dye-binding methods, or to use these alternative methods from the beginning.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine *[this text will only be included in the capsules SPC]*.

4.5 Interaction with other medicinal products and other forms of interaction

In a study involving healthy volunteers (N=12), when a 60 mg controlled-release morphine capsule was administered 2 hours prior to a 600 mg gabapentin capsule, mean gabapentin AUC increased by 44% compared to gabapentin administered without morphine. Therefore, patients should be carefully observed for signs of CNS depression, such as somnolence, and the dose of gabapentin or morphine should be reduced appropriately.

No interaction between gabapentin and phenobarbital, phenytoin, valproic acid, or carbamazepine has been observed.

Gabapentin steady-state pharmacokinetics are similar for healthy subjects and patients with epilepsy receiving these antiepileptic agents.

Coadministration of gabapentin with oral contraceptives containing norethindrone and/or ethinyl estradiol, does not influence the steady-state pharmacokinetics of either component.

Coadministration of gabapentin with antacids containing aluminium and magnesium, reduces gabapentin bioavailability up to 24%. It is recommended that gabapentin be taken at the earliest two hours following antacid administration.

Renal excretion of gabapentin is unaltered by probenecid.

A slight decrease in renal excretion of gabapentin that is observed when it is coadministered with cimetidine is not expected to be of clinical importance.

4.6 Pregnancy and lactation

Risk related to epilepsy and antiepileptic medicinal products in general

The risk of birth defects is increased by a factor of 2 – 3 in the offspring of mothers treated with an antiepileptic medicinal product. Most frequently reported are cleft lip, cardiovascular malformations and neural tube defects. Multiple antiepileptic drug therapy may be associated with a higher risk of congenital malformations than monotherapy, therefore it is important that monotherapy is practised whenever possible. Specialist advice should be given to women who are likely to become pregnant or who are of childbearing potential and the need for antiepileptic treatment should be reviewed when a woman is planning to become pregnant. No sudden discontinuation of antiepileptic therapy should be undertaken as this may lead to breakthrough seizures, which could have serious consequences for both mother and child. Developmental delay in children of mothers with epilepsy has been observed rarely. It is not possible to differentiate if the developmental delay is caused by genetic, social factors, maternal epilepsy or the antiepileptic therapy.

Risk related to gabapentin

There are no adequate data from the use of gabapentin in pregnant women.

Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown. Gabapentin should not be used during pregnancy unless the potential benefit to the mother clearly outweighs the potential risk to the foetus.

No definite conclusion can be made as to whether gabapentin is associated with an increased risk of congenital malformations when taken during pregnancy, because of epilepsy itself and the presence of concomitant antiepileptic medicinal products during each reported pregnancy.

Gabapentin is excreted in human milk. Because the effect on the breast-fed infant is unknown, caution should be exercised when gabapentin is administered to a breast-feeding mother. Gabapentin should be used in breast-feeding mothers only if the benefits clearly outweigh the risks.

4.7 Effects on ability to drive and use machines

Gabapentin may have minor or moderate influence on the ability to drive and use machines. Gabapentin acts on the central nervous system and may cause drowsiness, dizziness or other related symptoms. Even, if they were only of mild or moderate degree, these undesirable effects could be potentially dangerous in patients driving or operating machinery. This is especially true at the beginning of the treatment and after increase in dose.

4.8 Undesirable effects

The adverse reactions observed during clinical studies conducted in epilepsy (adjunctive and monotherapy) and neuropathic pain have been provided in a single list below by class and frequency (very common (≥ 1/10), common (≥1/100, <1/10), uncommon (≥1/1000, ≤1/100) and rare (≥1/10,000; ≤1/1,000). Where an adverse reaction was seen at different frequencies in clinical studies, it was assigned to the highest frequency reported.

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Infections and infestations
Very Common: Viral infection
Common: Pneumonia, respiratory infection, urinary tract infection, infection, otitis media

Blood and the lymphatic system disorders
Common: leucopenia
Rare: thrombocytopenia

Immune system disorders
Rare: allergic reactions (e.g. urticaria)

Metabolism and Nutrition Disorders
Common: anorexia, increased appetite

Psychiatric disorders
Common: hostility, confusion and emotional lability, depression, anxiety, nervousness, thinking abnormal
Rare: hallucinations

Nervous system disorders
Very Common: somnolence, dizziness, ataxia,
Common: convulsions, hyperkinesias, dysarthria, amnesia, tremor, insomnia, headache, sensations such as paresthesia, hypaesthesia, coordination abnormal, nystagmus, increased, decreased, or absent reflexes
Rare: movement disorders (e.g. choreoathetosis, dyskinesia, dystonia)

Eye disorders
Common: visual disturbances such as amblyopia, diplopia

Ear and Labyrinth disorders
Common: vertigo
Rare: tinnitus

Cardiac disorders
Rare: palpitations

Vascular disorder
Common: hypertension, vasodilatation

Respiratory, thoracic and mediastinal disorders
Common: dyspnoea, bronchitis, pharyngitis, cough, rhinitis

Gastrointestinal disorders
Common: vomiting, nausea, dental abnormalities, gingivitis, diarrhea, abdominal pain, dyspepsia, constipation, dry mouth or throat, flatulence
Rare: pancreatitis

Hepatobiliary disorders
Rare: hepatitis, jaundice

Skin and subcutaneous tissue disorders
Common: facial oedema, purpura most often described as bruises resulting from physical trauma, rash, pruritus, acne
Rare: Stevens-Johnson syndrome, angioedema, erythema multiforme, alopecia

Musculoskeletal, connective tissue and bone disorders
Common: arthralgia, myalgia, back pain, twitching

Renal and urinary disorders
Common: incontinence
Rare: acute renal failure

Reproductive system and breast disorders
Common: impotence

General disorders and administration site conditions
Very Common: fatigue, fever
Common: peripheral or generalized oedema, abnormal gait, asthenia, pain, malaise, flu syndrome
Rare: withdrawal reactions (mostly anxiety, insomnia, nausea, pains, sweating), chest pain. Sudden unexplained deaths have been reported where a causal relationship to treatment with gabapentin has not been established.

Investigations
Common: WBC (white blood cell count) decreased, weight gain
Rare: Blood glucose fluctuations in patients with diabetes, elevated liver function tests

Injury and poisoning
Common: accidental injury, fracture, abrasion

Under treatment with gabapentin cases of acute pancreatitis were reported. Causality with gabapentin is unclear (see section 4.4).

Respiratory tract infections, otitis media, convulsions and bronchitis were reported only in clinical studies in children. Additionally, in clinical studies in children, aggressive behaviour and hyperkinesias were reported commonly.

4.9 Overdose

Acute, life-threatening toxicity has not been observed with gabapentin overdoses of up to 49 g. Symptoms of the overdoses included dizziness, double vision, slurred speech, drowsiness, lethargy and mild diarrhoea. All patients recovered fully with supportive care. Reduced absorption of gabapentin at higher doses may limit drug absorption at the time of overdosing and, hence, minimize toxicity from overdoses.

Although gabapentin can be removed by haemodialysis, based on prior experience it is usually not required. However, in patients with severe renal impairment, haemodialysis may be indicated.

An oral lethal dose of gabapentin was not identified in mice and rats given doses as high as 8000 mg/kg. Signs of acute toxicity in animals included ataxia, laboured breathing, ptosis, hypoactivity, or excitation.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic groups: Other antiepileptics ATC code: N03AX12

The precise mechanism of action of gabapentin is not known.
Gabapentin is structurally related to the neurotransmitter GABA (gamma-aminobutyric acid) but its mechanism of action is different from that of several other active substances that interact with GABA synapses including valproate, barbiturates, benzodiazepines, GABA transaminase inhibitors, GABA uptake inhibitors, GABA agonists, and GABA prodrugs. *In vitro* studies with radiolabeled gabapentin have characterized a novel peptide binding site in rat brain tissues including neocortex and hippocampus that may relate to anticonvulsant and analgesic activity of gabapentin and its structural derivatives. The binding site for gabapentin has been identified as the alpha$_2$-delta subunit of voltage-gated calcium channels.

Gabapentin at relevant clinical concentrations does not bind to other common drug or neurotransmitter receptors of the brain including $GABA_A$, $GABA_B$, benzodiazepine, glutamate, glycine or N-methyl-d-aspartate receptors.

Gabapentin does not interact with sodium channels *in vitro* and so differs from phenytoin and carbamazepine. Gabapentin partially reduces responses to the glutamate agonist N-methyl-D-aspartate (NMDA) in some test systems *in vitro*, but only at concentrations greater than 100 µM, which are not achieved *in vivo*. Gabapentin slightly reduces the release of monoamine neurotransmitters *in vitro*. Gabapentin administration to rats increases GABA turnover in several brain regions in a manner similar to valproate sodium, although in different regions of brain. The relevance of these various actions of gabapentin to the anticonvulsant effects remains to be established. In animals, gabapentin readily enters the brain and prevents seizures from maximal electroshock, from chemical convulsants including inhibitors of GABA synthesis, and in genetic models of seizures.

A clinical trial of adjunctive treatment of partial seizures in paediatric subjects, ranging in age from 3 to 12 years, showed a numerical but not statistically significant difference in the 50% responder rate in favour of the gabapentin group compared to placebo. Additional post-hoc analyses of the responder rates by age did not reveal a statistically significant effect of age, either as a continuous or dichotomous variable (age groups 3-5 and 6-12 years). The data from this additional post-hoc analysis are summarised in the table below:

Response (≥ 50% Improved) by Treatment and Age MITT* Population			
Age Category	Placebo	Gabapentin	P-Value
< 6 Years Old	4/21 (19.0%)	4/17 (23.5%)	0.7362
6 to 12 Years Old	17/99 (17.2%)	20/96 (20.8%)	0.5144

*The modified intent to treat population was defined as all patients randomised to study medication who also had evaluable seizure diaries available for 28 days during both the baseline and double-blind phases.

5.2 Pharmacokinetic properties

Absorption

Following oral administration, peak plasma gabapentin concentrations are observed within 2 to 3 hours. Gabapentin bioavailability (fraction of dose absorbed) tends to decrease with increasing dose. Absolute bioavailability of a 300 mg capsule is approximately 60%. Food, including a high-fat diet, has no clinically significant effect on gabapentin pharmacokinetics.

Gabapentin pharmacokinetics are not affected by repeated administration. Although plasma gabapentin concentrations were generally between 2 µg/ml and 20 µg/ml in clinical studies, such concentrations were not predictive of safety or efficacy. Pharmacokinetic parameters are given in Table 3.

Table 3
Summary of gabapentin mean (%CV) steady-state pharmacokinetic parameters following every eight hours administration

Pharmacokinetic parameter	300 mg (N = 7)		400 mg (N = 14)		800 mg (N=14)	
	Mean	%CV	Mean	%CV	Mean	%CV
C_{max} (µg/ml)	4.02	(24)	5.74	(38)	8.71	(29)
t_{max} (hr)	2.7	(18)	2.1	(54)	1.6	(76)
T1/2 (hr)	5.2	(12)	10.8	(89)	10.6	(41)
AUC (0-8) µg•hr/ml)	24.8	(24)	34.5	(34)	51.4	(27)
Ae% (%)	NA	NA	47.2	(25)	34.4	(37)

C_{max} = Maximum steady state plasma concentration
t_{max} = Time for C_{max}
T1/2 = Elimination half-life
AUC(0-8) = Steady state area under plasma concentration-time curve from time 0 to 8 hours postdose
Ae% = Percent of dose excreted unchanged into the urine from time 0 to 8 hours postdose
NA = Not available

Distribution

Gabapentin is not bound to plasma proteins and has a volume of distribution equal to 57.7 litres. In patients with epilepsy, gabapentin concentrations in cerebrospinal fluid (CSF) are approximately 20% of

corresponding steady-state trough plasma concentrations. Gabapentin is present in the breast milk of breast-feeding women.

Metabolism

There is no evidence of gabapentin metabolism in humans. Gabapentin does not induce hepatic mixed function oxidase enzymes responsible for drug metabolism.

Elimination

Gabapentin is eliminated unchanged solely by renal excretion. The elimination half-life of gabapentin is independent of dose and averages 5 to 7 hours.

In elderly patients, and in patients with impaired renal function, gabapentin plasma clearance is reduced. Gabapentin elimination-rate constant, plasma clearance, and renal clearance are directly proportional to creatinine clearance.

Gabapentin is removed from plasma by haemodialysis. Dosage adjustment in patients with compromised renal function or undergoing haemodialysis is recommended (see section 4.2).

Gabapentin pharmacokinetics in children were determined in 50 healthy subjects between the ages of 1 month and 12 years. In general, plasma gabapentin concentrations in children > 5 years of age are similar to those in adults when dosed on a mg/kg basis.

Linearity/Non-linearity

Gabapentin bioavailability (fraction of dose absorbed) decreases with increasing dose which imparts non-linearity to pharmacokinetic parameters which include the bioavailability parameter (F) e.g. Ae%, CL/F, Vd/F. Elimination pharmacokinetics (pharmacokinetic parameters which do not include F such as CLr and T1/2), are best described by linear pharmacokinetics. Steady state plasma gabapentin concentrations are predictable from single-dose data.

5.3 Preclinical safety data

Carcinogenesis

Gabapentin was given in the diet to mice at 200, 600, and 2000 mg/kg/day and to rats at 250, 1000, and 2000 mg/kg/day for two years. A statistically significant increase in the incidence of pancreatic acinar cell tumors was found only in male rats at the highest dose. Peak plasma drug concentrations in rats at 2000 mg/kg/day are 10 times higher than plasma concentrations in humans given 3600 mg/day. The pancreatic acinar cell tumors in male rats are low-grade malignancies, did not affect survival, did not metastasize or invade surrounding tissue, and were similar to those seen in concurrent controls. The relevance of these pancreatic acinar cell tumors in male rats to carcinogenic risk in humans is unclear.

Mutagenesis

Gabapentin demonstrated no genotoxic potential. It was not mutagenic *in vitro* in standard assays using bacterial or mammalian cells. Gabapentin did not induce structural chromosome aberrations in mammalian cells *in vitro* or *in vivo*, and did not induce micronucleus formation in the bone marrow of hamsters.

Impairment of Fertility

No adverse effects on fertility or reproduction were observed in rats at doses up to 2000 mg/kg (approximately five times the maximum daily human dose on a mg/m^2 of body surface area basis).

Teratogenesis

Gabapentin did not increase the incidence of malformations, compared to controls, in the offspring of mice, rats, or rabbits at doses up to 50, 30 and 25 times respectively, the daily human dose of 3600 mg, (four, five or eight times, respectively, the human daily dose on a mg/m^2 basis).

Gabapentin induced delayed ossification in the skull, vertebrae, forelimbs, and hindlimbs in rodents, indicative of fetal growth retardation. These effects occurred when pregnant mice received oral doses of 1000 or 3000 mg/kg/day during organogenesis and in rats given 500, 1000, or 2000 mg/kg prior to and during mating and throughout gestation. These doses are approximately 1 to 5 times the human dose of 3600 mg on a mg/m^2 basis.

No effects were observed in pregnant mice given 500 mg/kg/day (approximately 1/2 of the daily human dose on a mg/m^2 basis).

An increased incidence of hydroureter and/or hydronephrosis was observed in rats given 2000 mg/kg/day in a fertility and general reproduction study, 1500 mg/kg/day in a teratology study, and 500, 1000, and 2000 mg/kg/day in a perinatal and postnatal study. The significance of these findings is unknown, but they have been associated with delayed development. These doses are also approximately 1 to 5 times the human dose of 3600 mg on a mg/m^2 basis.

In a teratology study in rabbits, an increased incidence of post-implantation fetal loss, occurred in doses given 60, 300, and 1500 mg/kg/day during organogenesis. These doses are approximately 1/4 to 8 times the daily human dose of 3600 mg on a mg/m^2 basis.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

[To be completed nationally]

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

[To be completed nationally]

6.4 Special precautions for storage

[To be completed nationally]

6.5 Nature and contents of container

[To be completed nationally]

Capsules: 20, 30, 50, 84, 90, 98, 100, 200, 500, 1000

Tablets: 20, 30, 45, 50, 84, 90, 100, 200, 500

Also supplied as a titration pack for treatment of neuropathic pain containing 40 x 300 mg capsules and 10 x 600 mg tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

[To be completed nationally]

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[To be completed nationally]

10. DATE OF REVISION OF THE TEXT