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.

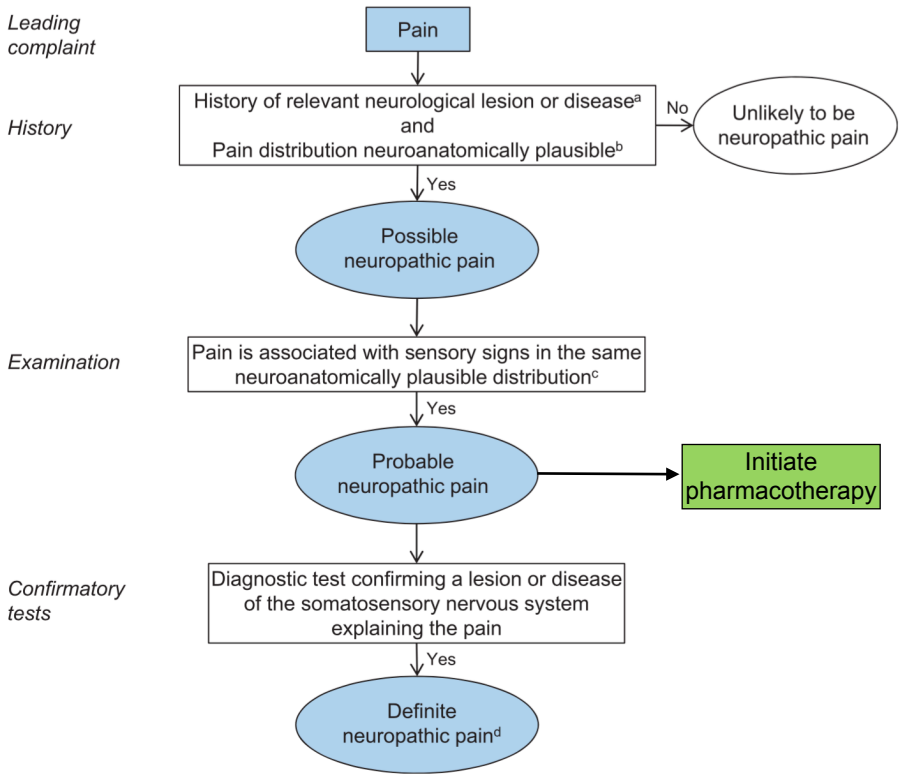

Figure 1: *Diagnosis and grading of diagnostic certainty of neuropathic pain. The level of "probable" is usually sufficient to initiate treatment according to neuropathic pain guidelines. The level "definite" is useful in specialist contexts and when a causal treatment of the underlying lesion or disease 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].

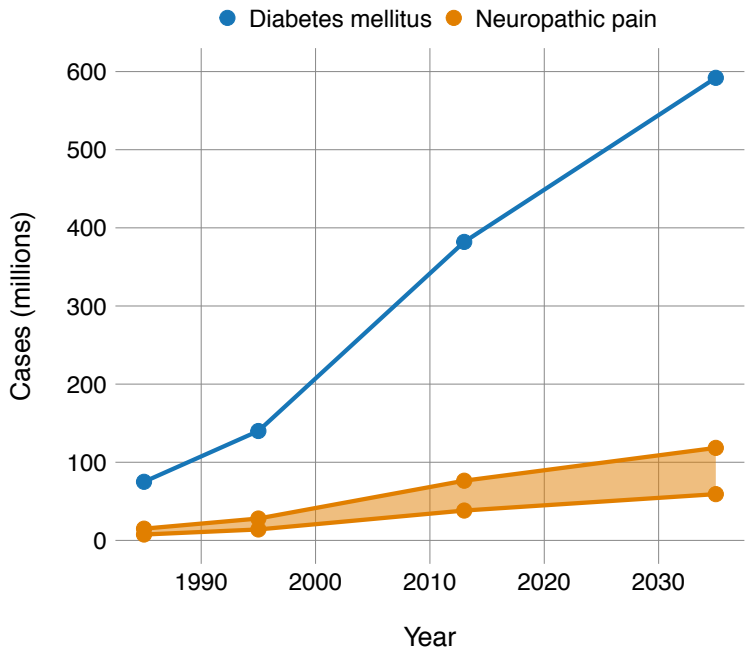

Figure 2: *Estimated and projected number of cases of diabetes mellitus (blue) between 1985 and 2035, and the number of cases of painful diabetic polyneuropathy (orange) over the same period based on conservative estimates of between 10 and 20% of individuals with diabetes developing a painful neuropathy.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

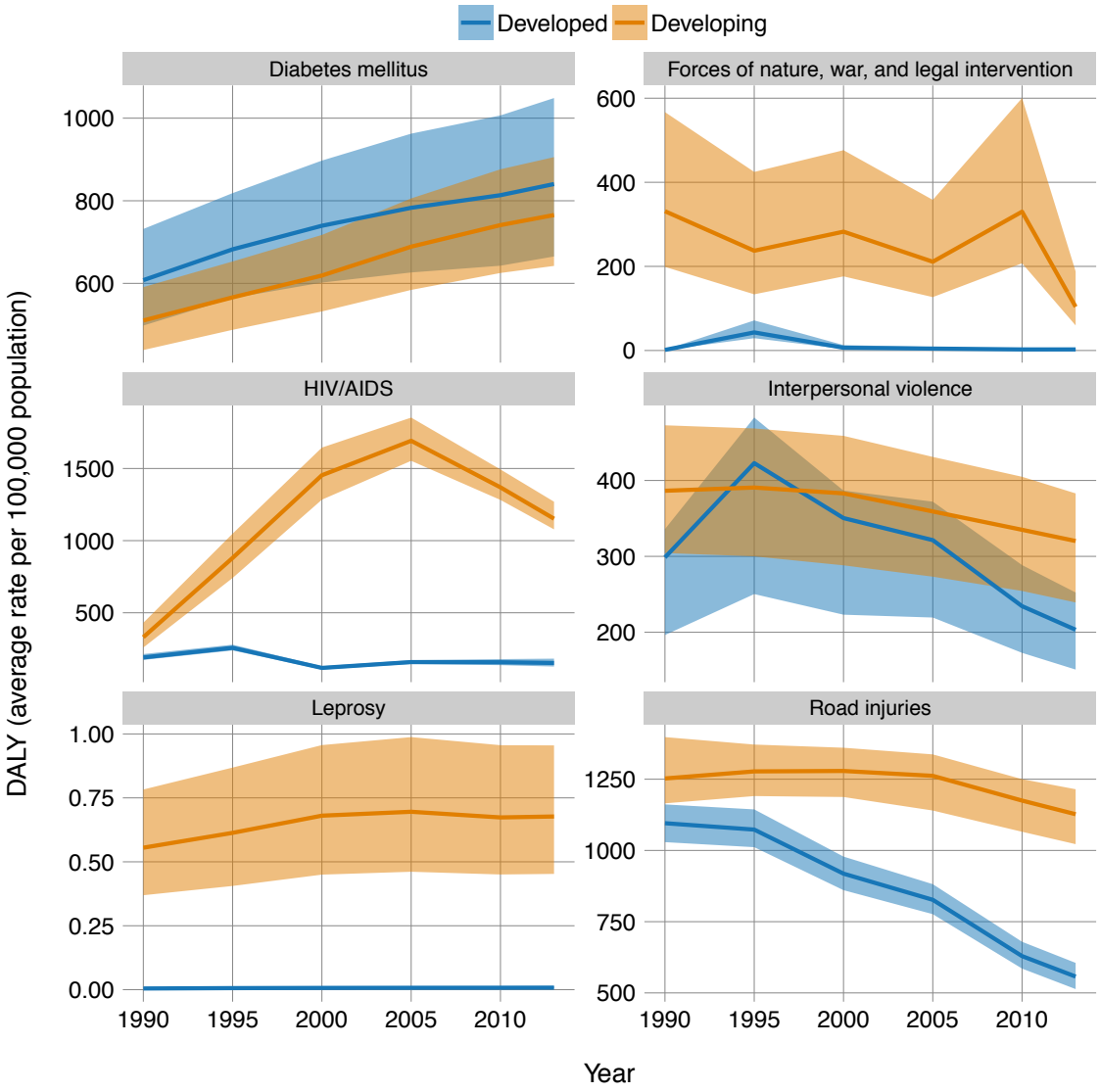

Figure 3: *Disability Adjusted Life Years (DALY) in high income (orange), and low and middle income (blue) countries associated with diabetes mellitus, HIV/AIDS, leprosy, road injuries, interpersonal violence, and forces of nature, war, and legal intervention for the period 1990 and 2013. The shaded 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].

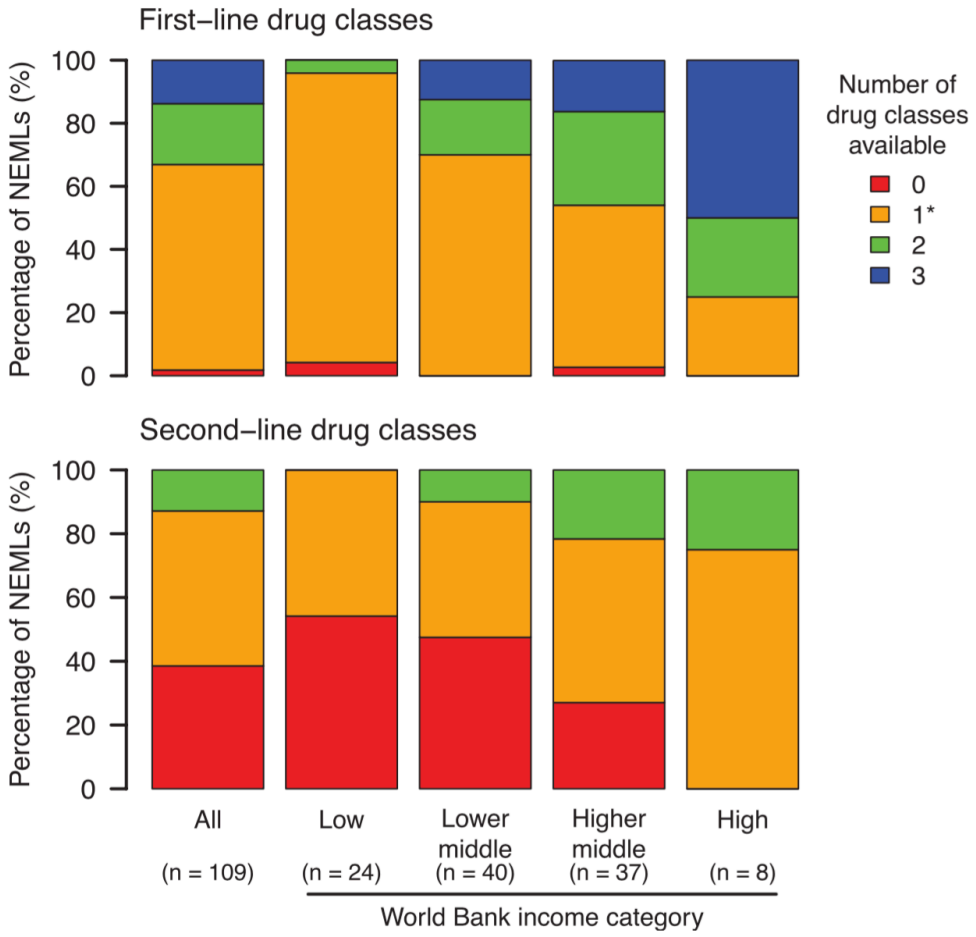

Figure 4: *Percentage of national essential medicine lists (NEMLs) that included 0, 1, 2, or 3 medicine classes recommended for the treatment of neuropathic pain. Data are shown grouped according to World Bank income category and for all countries (n = 109, data from the Cook Islands, Nauru, and Niue 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.

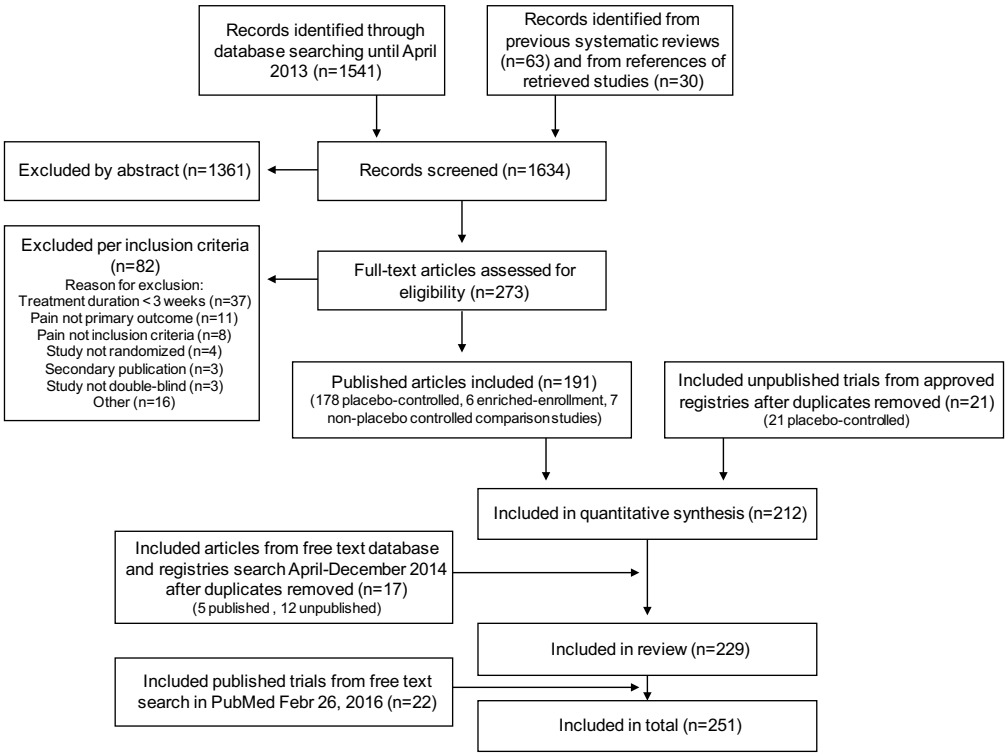

Figure 5: *Flow chart of study selection. Updated from Finnerup et al., 2015 [3] on 26 February 2016.*

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]

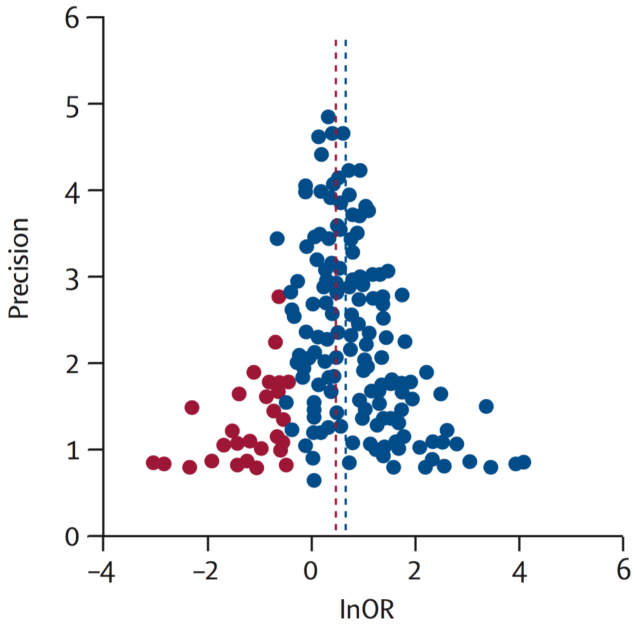

Figure 6: *Funnel plot showing the precision (inverse of standard error) against the effect size (natural log of the odds ratio, LnOR). Blue circles are individual studies. Missing studies imputed by trim and fill are shown in red. The blue vertical line indicates the uncorrected estimate of the effect 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.*

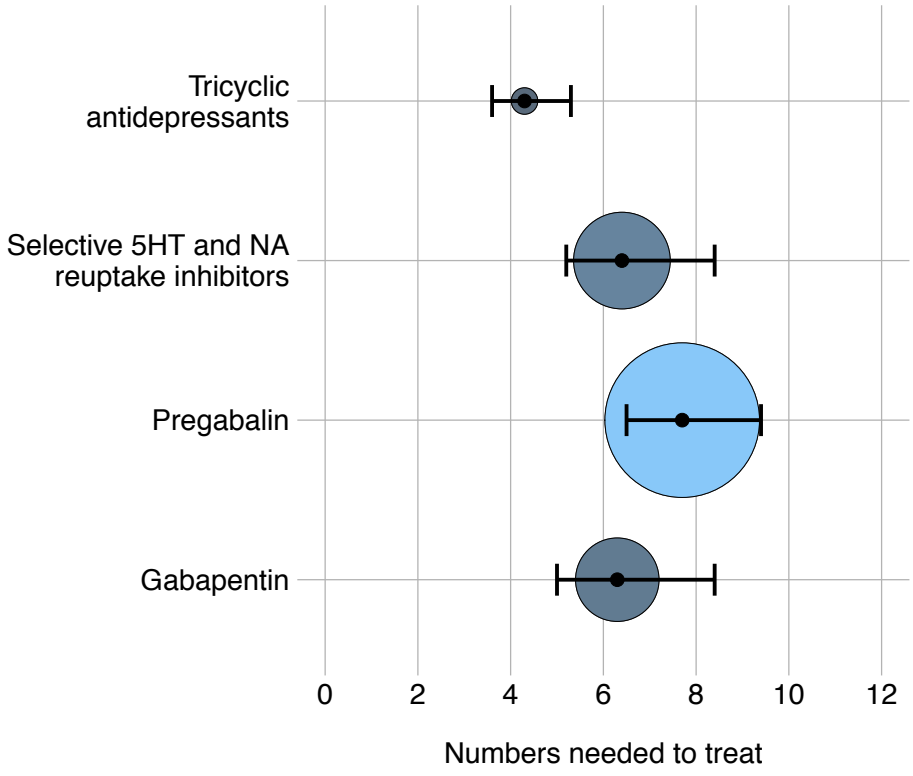

Figure 9: *Mean (95% CI) numbers needed to treat (NNT) for first-line medications recommended by Finnerup et al., 2015 [3]. The size of the coloured circles indicate the relative number of individuals randomized in trials for a particular medication. Data from Finnerup et al., 2015 were updated to include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

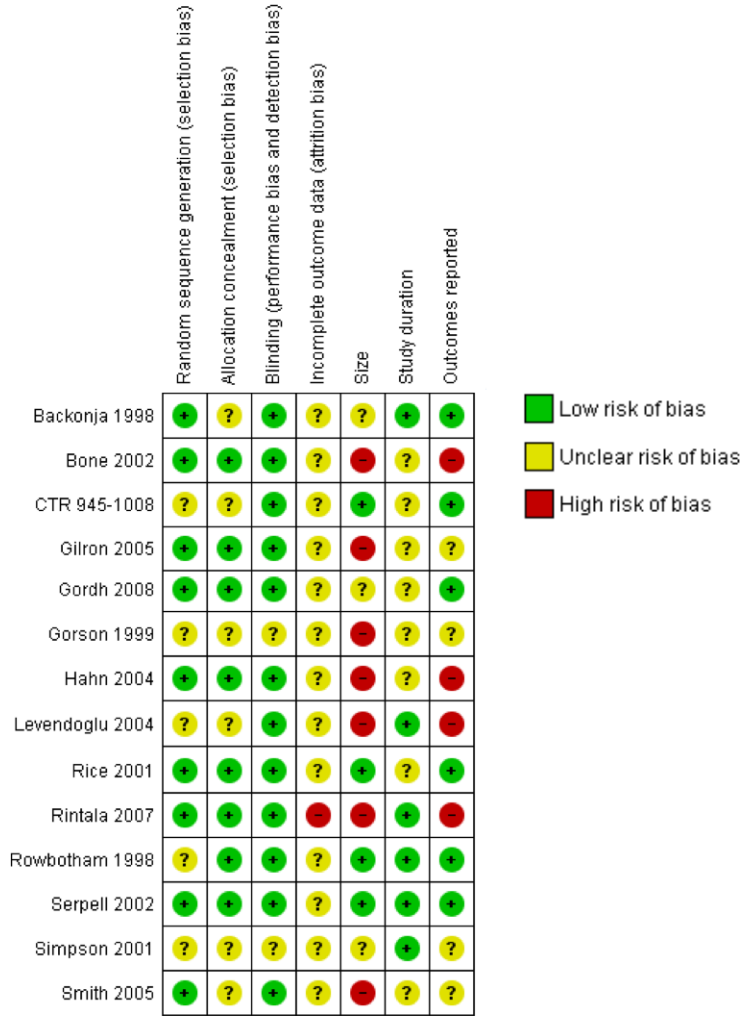

Figure 10: *Summary of the methodological quality of 14 studies of gabapentin for the management of neuropathic pain included in the GRADE analysis. The summaries are derived from a 2014 Cochrane review of the evidence for the use of gabapentin for neuropathic pain and fibromyalgia by Moore and colleagues [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*

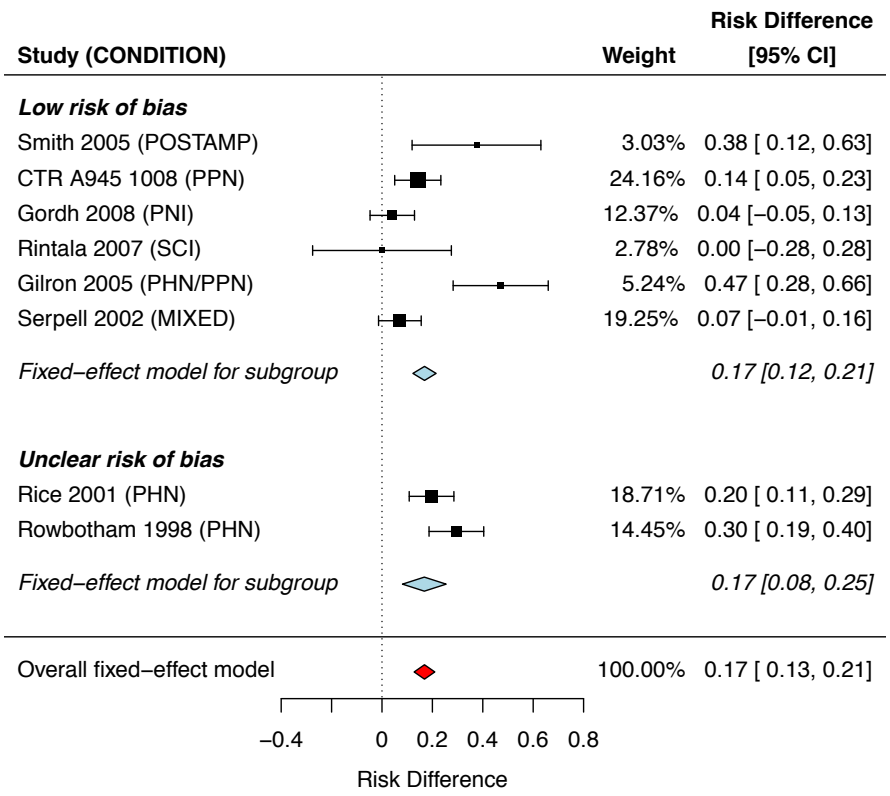

Figure 11: *Absolute risk difference (95% CI) between gabapentin and placebo for the management of neuropathic pain. Positive values indicate greater benefit for gabapentin over placebo. Data are shown for individual studies (black squares), subgroup effects (low and unclear risk of allocation bias; 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].*

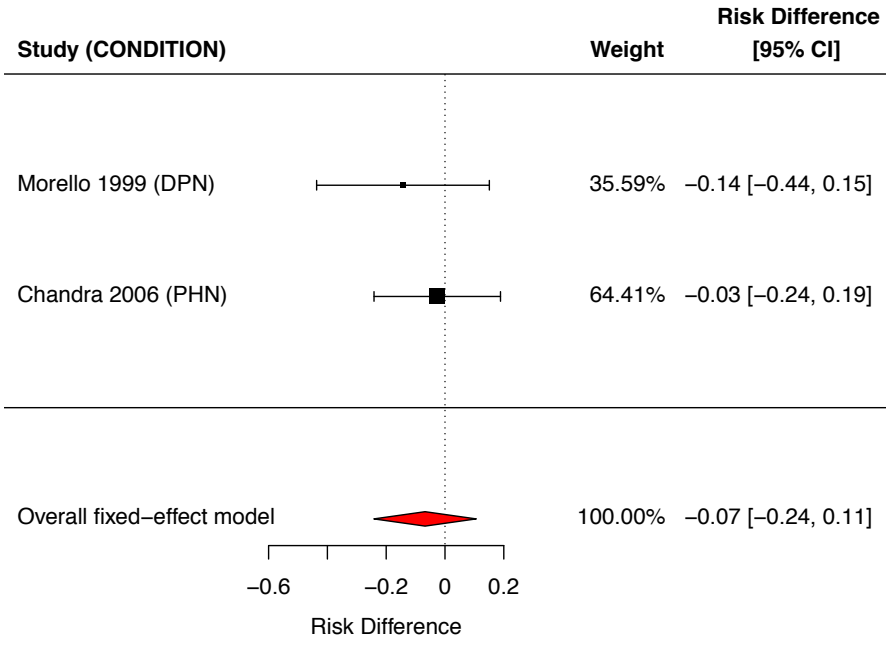

Figure 12: *Absolute risk difference (95% CI) between gabapentin and amitriptyline (Morello 1999 [89]), and gabapentin and nortriptyline (Chandra 2006 [88]) for the management of neuropathic pain. Positive values indicate greater benefit for gabapentin over the TCAs. Data are shown for individual studies (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].

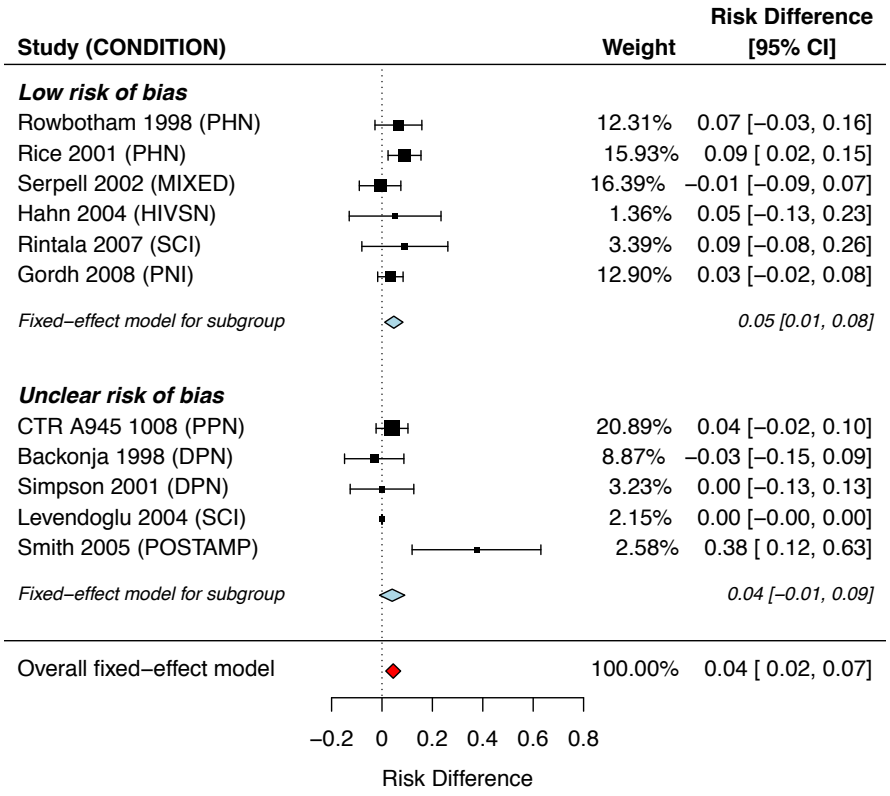

Figure 13: *Withdrawal due to adverse reactions: Absolute risk difference (95% CI) between gabapentin and placebo for study drop-outs because of adverse events. Positive values indicate greater harm for gabapentin over placebo. Data are shown for individual studies (black squares), subgroup effects (low 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].*

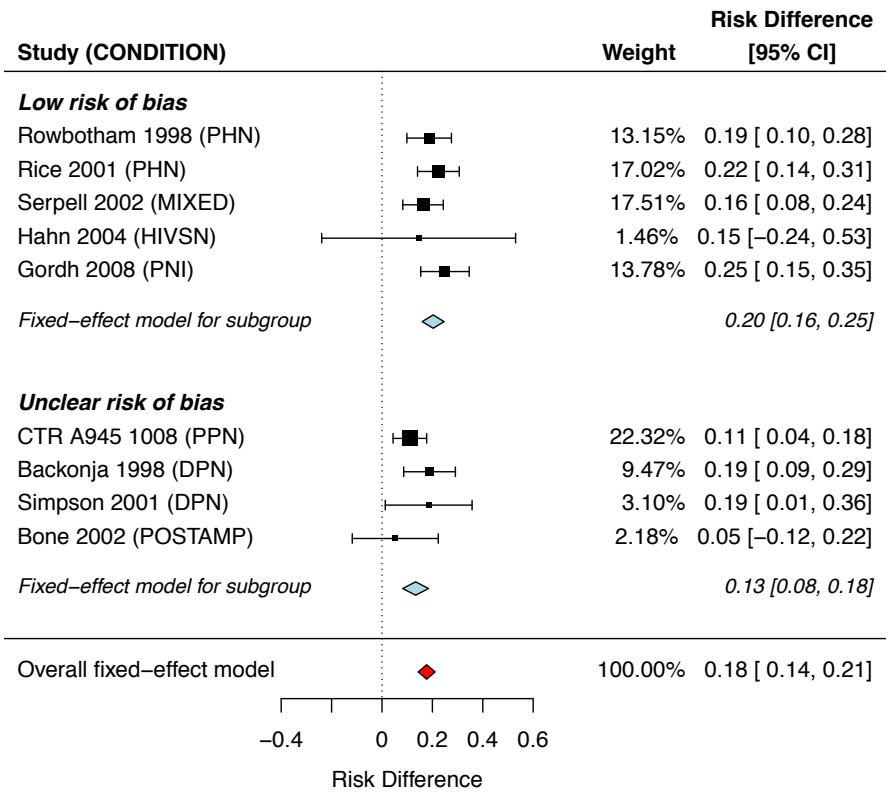

Figure 14: *Dizziness: Absolute risk difference (95% CI) between gabapentin and placebo for participants reporting dizziness. Positive values indicate greater harm for gabapentin over placebo. Data are shown for individual studies (black squares), subgroup effects (low and unclear risk of allocation 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].*

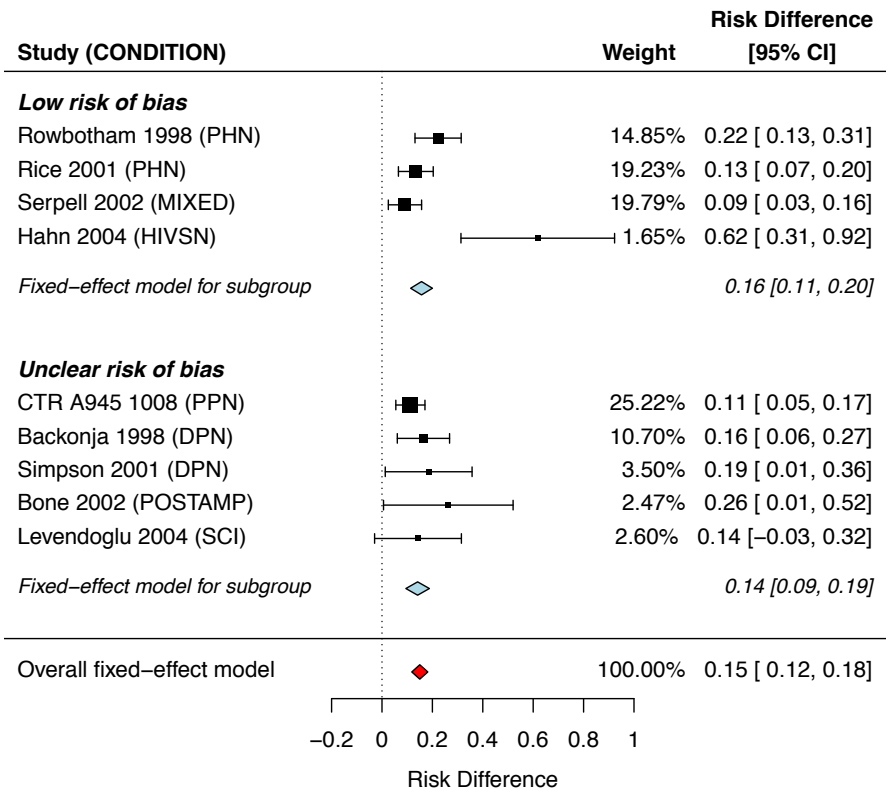

Figure 15: *Somnolence: Absolute risk difference (95% CI) between gabapentin and placebo for participants reporting somnolence. Positive values indicate greater harm for gabapentin over placebo. Data are shown for individual studies (black squares), subgroup effects (low and unclear risk of allocation 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

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