

# Gabapentin for Neuropathic Pain

*An application to the 21<sup>st</sup> 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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## 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 developing 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, developing countries are disproportionately 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 include: tricyclic antidepressants (TCAs),  $\alpha_2\delta$  calcium channel ligands (gabapentin and pregabalin), and serotonin and noradrenaline reuptake inhibitors (SNRIs, duloxetine and venlafaxine) as first-line agents. 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 drugs with proven efficacy in treating neuropathic pain. The Model List includes only one medicine with evidence-based recommendations as a first-line treatment (amitriptyline), and no agents that are recommended as second-line treatments. 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 developing and emerging 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 inclusion of morphine, both being necessary for the treatment of pain.

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

**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)

- World Medical Association
- International Society for Physical and Rehabilitative Medicine
- National Pain Societies
  - Belgian Pain Society
  - Chinese Association for the Study of Pain
  - Indian Society for Study of Pain
  - Lebanese Society for the Study of Pain
  - PainSA, South Africa
  - Society for the Study of Pain, Nigeria

**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.<sup>2</sup>

<sup>2</sup> 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.

### **Core List**

- Tablets: 100mg, 200mg, 300mg, 400mg, 600mg, 800mg
- Capsules: 100mg, 300mg, 400mg, 600mg

### **Complementary List**

- Oral solution: 50 mg/ml (150-470ml bottle sizes available through different manufacturers)

### **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 emerging or developing countries by the International Monetary Fund [20].

The 17 developing or emerging 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  
(emerging and developing nations 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	Rambaxy
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

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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	Neugabrin	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
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	Gabriion	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

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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
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

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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
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	Nervoptyn	capsules / tablets	Abbott
India	Nervuptin	capsules / tablets	Piramal
India	Nervz-G	capsules / tablets	Intas
India	Nerwin-GT	capsules / tablets	Arrowin
India	Neupert 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

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India	Neurotop-G	capsules / tablets	Novaduo
India	Nexcob-G	capsules / tablets	Nitro Cadineur
India	Novomine-GB	capsules / tablets	Novogen
India	NTOmech-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
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

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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
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

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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
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.

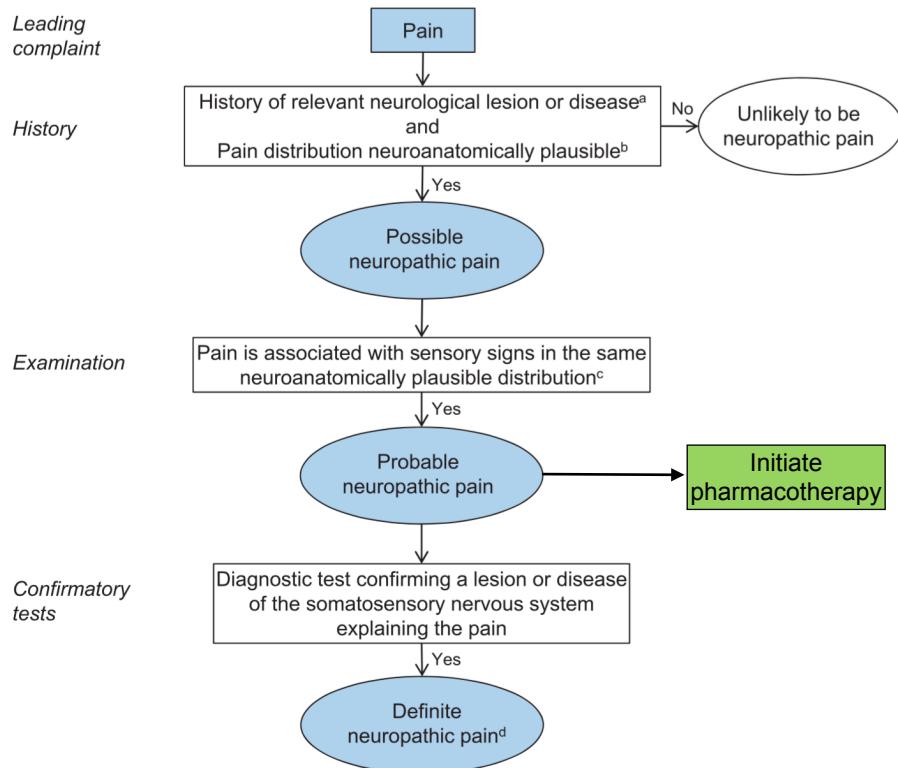
## **Treatment details, public health relevance and evidence appraisal and synthesis**

### **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].



**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. <sup>a</sup> 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. <sup>b</sup> The pain distribution reported by the patient is consistent with the suspected lesion or disease. <sup>c</sup> 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. <sup>d</sup> The term "definite" in this context means "probable neuropathic pain with confirmatory tests". Adapted from: Finnerup et al., 2016 [17].

## 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).

### Dosage and administration

Usual dosage range:

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

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

The FDA and the EMA recommend the following titration schedule for neuropathic pain:

- Day 1: Single 300mg dose
- Day 2: 600mg/day (300mg two times a day)
- Day 3: 900mg/day (300mg three times a day)

Thereafter, based on therapeutic response and tolerability, the dose can be increased in 300mg/day increments every 2 to 3 days up to a maximum dose of 1800mg/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. In analgesic clinical trials of gabapentin in neuropathic pain, the clinical effect (separation from placebo) typically was evident by the end of first week of treatment.

In clinical studies, efficacy was demonstrated over a range of doses from 1800mg/day to 3600mg/day with comparable effects across the dose range. However, the additional benefit of using doses greater than 1800mg/day was not demonstrated.

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

### ***Special populations***

**Children:** Gabapentin does not have regulatory approval for managing neuropathic pain in paediatric patients, but does have approval for use as adjunctive therapy or mono-therapy for partial seizures in children aged 3 to 11 years. Dosing recommendations for this indication are not presented here.

**Elderly:** The total number of patients treated with gabapentin in clinical trials in patients with post-herpetic 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 or older 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. Nevertheless, care should be taken in dose selection, in the elderly, and dose should be adjusted based on creatinine clearance values in these patients. The types and incidence of adverse reactions were similar across age groups except for peripheral oedema and ataxia, which tended to increase in incidence with age.

**Renal impairment:** Gabapentin undergoes almost exclusive renal clearance, and therefore it is recommended that the dose of gabapentin is reduced in patients with renal impairment or undergoing haemodialysis (paediatric patients with renal insufficiency have not been studied). Recommended dosage adjustments are shown in Table 3.

**Pregnancy:** Gabapentin is classified as *Pregnancy Category C*; use during pregnancy only if the potential benefit justifies the potential risk to the fetus. There are no adequate and well-controlled studies in pregnant women. In pre-clinical 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. However, observational data indicates that the rate of fetal malformations in women taking gabapentin is not greater than that reported in the general population [28,29].

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

**Other:** Although no formal studies have been conducted, neither sex, race nor hepatic impairment have been reported to affect the pharmacokinetics of gabapentin.

**Table 3:** Gabapentin dosage based on renal function

Renal function: creatinine clearance (ml/min)*	Total daily dose range (mg/day)	Regimen: <sup>†</sup>				
		A	B	C	D	E
≥ 60	900 to 3600	300 <sub>tid</sub>	400 <sub>tid</sub>	600 <sub>tid</sub>	800 <sub>tid</sub>	1200 <sub>tid</sub>
30 to 59	400 to 1400	200 <sub>bid</sub>	300 <sub>bid</sub>	400 <sub>bid</sub>	500 <sub>bid</sub>	700 <sub>bid</sub>
15 to 29	200 to 700	200 <sub>qd</sub>	300 <sub>qd</sub>	400 <sub>qd</sub>	500 <sub>qd</sub>	700 <sub>qd</sub>
< 15 <sup>‡</sup>	100 to 300	100 <sub>qd</sub>	125 <sub>qd</sub>	150 <sub>qd</sub>	200 <sub>qd</sub>	300 <sub>qd</sub>

	Post-haemodialysis supplemental dose (mg) <sup>§</sup>				
Haemodialysis	125	150	200	250	350

<sup>†</sup> : *tid* = three times a day, *bid* = two times a day, *qd* = single daily dose

<sup>‡</sup> : For patients with creatinine clearance < 15ml/min, reduce daily dose in proportion to creatinine clearance (e.g., patients with a creatinine clearance of 7.5ml/min should receive one-half the daily dose that patients with a creatinine clearance of 15ml/min receive).

<sup>§</sup> : Patients on haemodialysis should receive maintenance doses based on estimates of creatinine clearance as indicated in the upper portion of the table and a supplemental post-haemodialysis dose administered after each 4 hours of haemodialysis as indicated in the lower portion of the table.

\* : In out-patients with stable renal function, creatinine clearance (CLCr) can be reasonably well estimated using the equation of Cockcroft and Gault:

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

### Pharmacokinetics

**Oral Bioavailability:** Gabapentin bio-availability is not dose proportional. That is, as dose is increased, bio-availability decreases. Bio-availability 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. Although gabapentin can be administered with or without food, its administration with food increases the rate and extent of its absorption [14% increase in area under the curve (AUC) and maximum plasma concentration (Cmax)].

**Distribution:** Less than 3% of gabapentin circulates bound to plasma protein. The apparent volume of distribution of gabapentin after 150mg intravenous administration is 58 ± 6 l (mean ± SD). In patients with epilepsy, the minimum concentrations (Cmin) of gabapentin in cerebrospinal fluid were approximately 20% of the corresponding plasma concentrations.

**Elimination:** All pharmacological actions following gabapentin administration are due to the activity of the parent compound. Gabapentin is not appreciably metabolised in humans, and is eliminated from the systemic circulation by renal excretion as unchanged drug. As such, gabapentin elimination rate constant, plasma clearance, and renal clearance are directly proportional to creatinine clearance. Gabapentin elimination half-life is 5 to 7 hours and is unaltered by dose or following multiple dosing.

In elderly patients, and in patients with impaired renal function, gabapentin plasma clearance is reduced. If required, gabapentin can be removed from plasma by haemodialysis.

**Long-term use and overdose:** The EMA documentation notes that the efficacy and safety of gabapentin has not been examined in clinical studies for treatment periods longer than five

months, and if a patient requires dosing for longer periods that the treating physician should assess the patient's clinical status and determine the need for additional therapy.

A lethal dose of gabapentin was not identified in mice and rats receiving single oral doses as high as 8000mg/kg. Signs of acute toxicity in animals included ataxia, laboured breathing, ptosis, sedation, hypoactivity, or excitation. Acute oral overdoses of gabapentin up to 49000mg have been reported. In these cases, double vision, slurred speech, drowsiness, lethargy, and diarrhoea 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 gabapentin.

### **Drug interactions**

**In vitro studies:** *In vitro* studies investigating the effect of gabapentin on major cytochrome P450 enzymes (CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4) found that the only isoform inhibited was CYP2A6, and only at the highest dose tested (171 $\mu$ g/ml, ~15 times the Cmax at 3600mg/day). Even then, the level of inhibition was modest (14 to 30%).

**In vivo studies:** *In vivo* drug interaction studies for gabapentin have involved healthy adults and adult patients with epilepsy. The following medicines displayed no interaction with gabapentin:

- Carbamazepine
- Naproxen (*Doses of gabapentin and naproxen used were lower than the therapeutic doses for both drugs. The magnitude of interaction within the recommended dose ranges of either drug is not known.*)
- Phenobarbital
- Phenytoin
- Probenecid (*Probenecid is a blocker of renal tubular secretion, but did not alter gabapentin pharmacokinetic parameters, indicating that gabapentin does not undergo renal tubular secretion by the pathway that is blocked by probenecid.*)
- Valproic Acid
- Zolpidem

Of importance, there are no known interactions between gabapentin and agents recommended for the treatments of:

- HIV infection in adults or children (lamivudine, abacavir, zidovudine, tenofovir, stavudine, lopinavir/ritonavir, darunavir, dolutegravir, efavirenz, emtricitabine, nevirapine) [30]
- tuberculosis infection (isoniazid, rifampicin, streptomycin, ethambutol, pyrazinamide) [31],
- diabetes mellitus (insulin, metformin, sulfonylureas) [14].

- malaria (amodiaquine, artemether/lumefantrine, artesunate, dihydroartemisinin, meoquine, piperaquine, sulfadoxine–pyrimethamine) [32]
- leprosy (clofazimine, dapsone, minocycline, ofloxacin, rifampicin) [33]

Interactions have been shown with the following medicines:

- Antacid: Administration of antacid containing aluminium hydroxide and magnesium hydroxide reduced the mean bio-availability of gabapentin by about 20%. This decrease in bio-availability was about 10% when gabapentin was administered 2 hours after the antacid.
- Cimetidine: Administration of cimetidine (300mg, three times daily), was associated with a 14% reduction in the clearance of gabapentin. Creatinine clearance fell by 10%, indicating that cimetidine may alter the renal excretion of both gabapentin and creatinine. 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.
- Felbamate: Gabapentin administration was associated with decreased elimination of the entiepileptic drug felbamate. The half-life of felbamate was decreased by 46%, and clearance decreased by 37%.
- Hydrocodone: Co-administration of gabapentin (125 to 500mg) decreased hydrocodone (10 mg) Cmax and AUC values in a dose-dependent manner. Cmax and AUC values were 3% to 4% lower, respectively, after administration of 125mg gabapentin, and 21% to 22% lower, respectively, after administration of 500mg gabapentin. Hydrocodone increased gabapentin AUC values by 14%. The magnitude of the interaction at other doses is not known.
- Oral contraceptive: The AUC and half-life of multiple-dose pharmacokinetic profiles of norethindrone (50 $\mu$ g) and ethinyl estradiol (2.5mg) were similar with and without co-administration of gabapentin (400mg three times a day). However, the Cmax of norethindrone was 13% higher when co-administered with gabapentin. This interaction is not expected to be of clinical importance.
- Morphine: A literature article reported that when a 60mg controlled-release morphine capsule was administered 2 hours before 600mg of gabapentin, mean gabapentin AUC increased by 44% compared to gabapentin administered without morphine. Morphine pharmacokinetic parameters were not affected by administration gabapentin. The magnitude of the interaction at other doses is not known.

### ***Drug abuse and dependence***

Gabapentin is not a scheduled drug.

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. 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. Consequently, the FDA recommends that patients with a history of drug abuse should be carefully evaluated before starting gabapentin. And, they should be observed for signs and symptoms of gabapentin misuse or abuse (e.g., development of tolerance, self-dose escalation, and drug-seeking behaviour). The FDA recommendation is consistent with a review of the literature by Schifano [34], which concluded that the risk of misuse of  $\alpha_2\delta$  calcium channel ligands is low when the drugs are administered at therapeutic doses to individuals with no history of substance misuse.

**Dependence:** There are rare post-marketing 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. These symptoms 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.

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

### Guideline recommendations

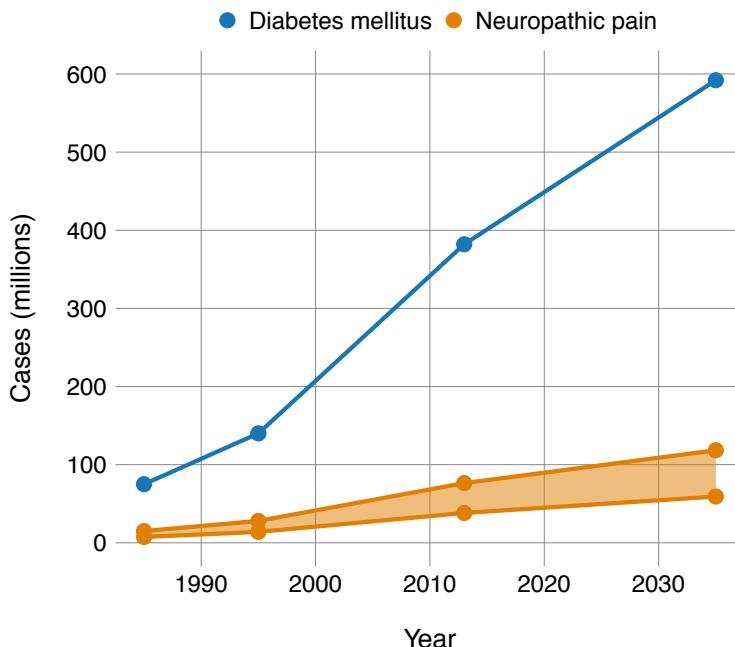
We are unaware of any WHO guidelines for the treatment of neuropathic pain, but several reputable organizations that are independent of the WHO have developed evidence-based guidelines. These include:

- 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, drug 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*” [35,36]. It is commonly associated with back pain (e.g., lumbar or cervical



**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 time period based on conservative estimates of between 10 and 20% of individuals with diabetes developing a painful neuropathy.

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 [37].

In the absence of a ‘gold standard’ for defining cases and a clinical code for routine health-care use, it is impossible to identify the precise prevalence of neuropathic pain, for example through the Global Burden of Disease 2013 study [38]. 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 [38], and projected to rise further [39]). Approximately 26% of those with diabetes mellitus have painful polyneuropathy [7,40], equating to 107 million individuals. Figure 2 shows estimates and projected prevalence data for diabetes mellitus from 1985 to 2030 [39,41], with the estimated number of coincident cases of painful polyneuropathy [42].
- HIV/AIDS (29 million prevalent cases globally, increasing by 275% since 1990 [38]). Approximately 35% of people with HIV/AIDS have painful neuropathy [8], equating to 10 million individuals. The incidence [43,44] and prevalence [45] of the neuropathy has decreased since the introduction of newer antiretroviral regimens that forego neurotoxic medicines such as stavudine, but remains high [46].

- Chronic low back pain (651 million prevalent cases globally, increasing by 57% since 1990 [38]). Approximately 37% of those with chronic low back pain have been shown to experience neuropathic pain [47], 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 developing countries than in developed countries [38], 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).

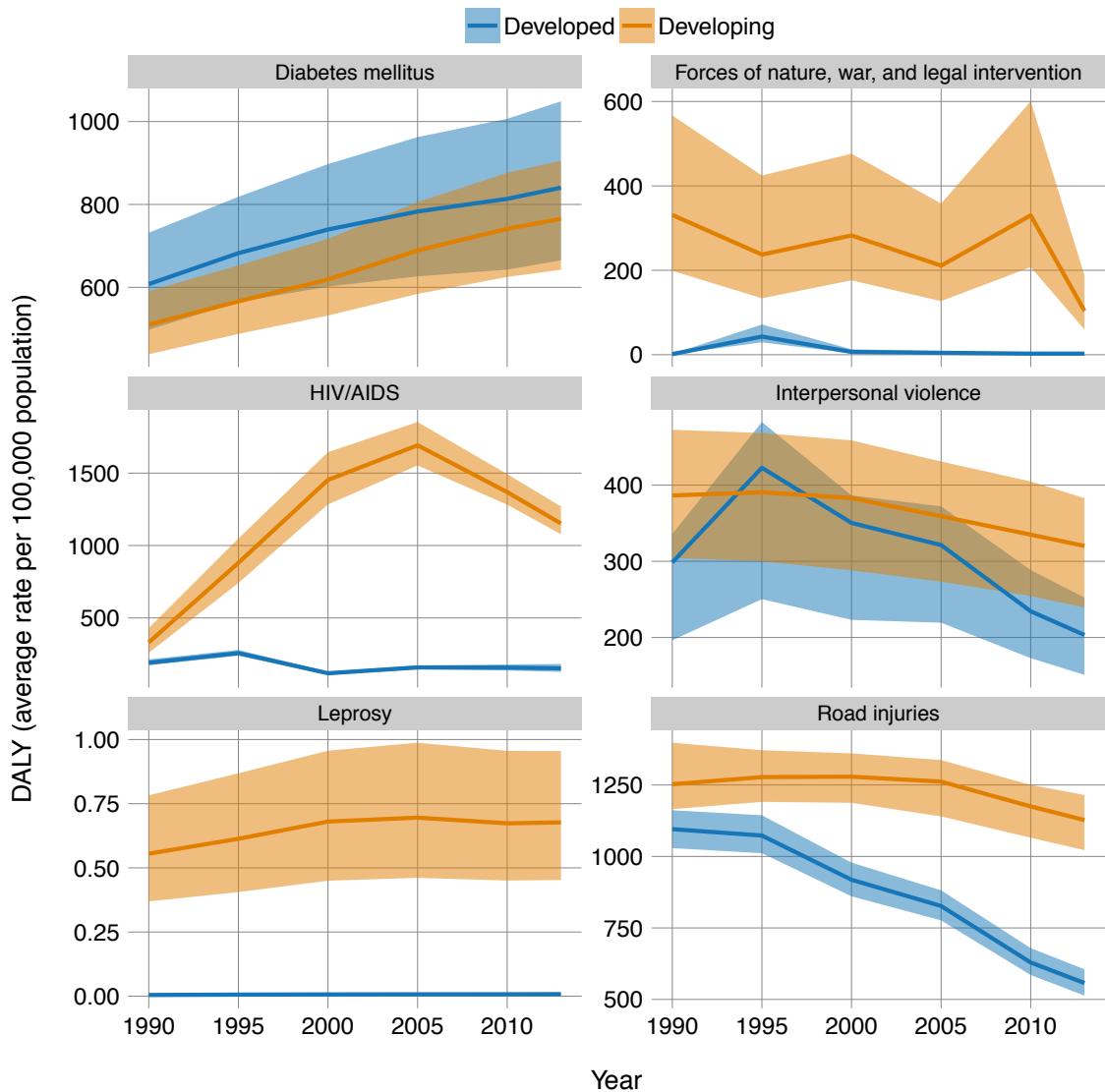
Older age is one of the most important risk factors for neuropathic pain [48]. The ageing population worldwide, as well as the separate rising prevalence of underlying conditions such as diabetes mellitus [38,39] mean that neuropathic pain is likely to increase in prevalence and importance in the future.

Neuropathic pain has a significant adverse impact on all measured aspects of life, health and function [49]. This impact is greater than the impact of chronic, non-neuropathic pain, even when adjusting for pain intensity [50], 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 [50].

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 [51]), and specific classes of medication are required. Gabapentin is recommended as a first-line treatment for neuropathic pain in many national and international guidelines [3–6,52]. 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 [53]; (c) combi-



**Figure 3:** Disability Adjusted Life Years (DALY) in developed (orange), and developing (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.

nation 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.

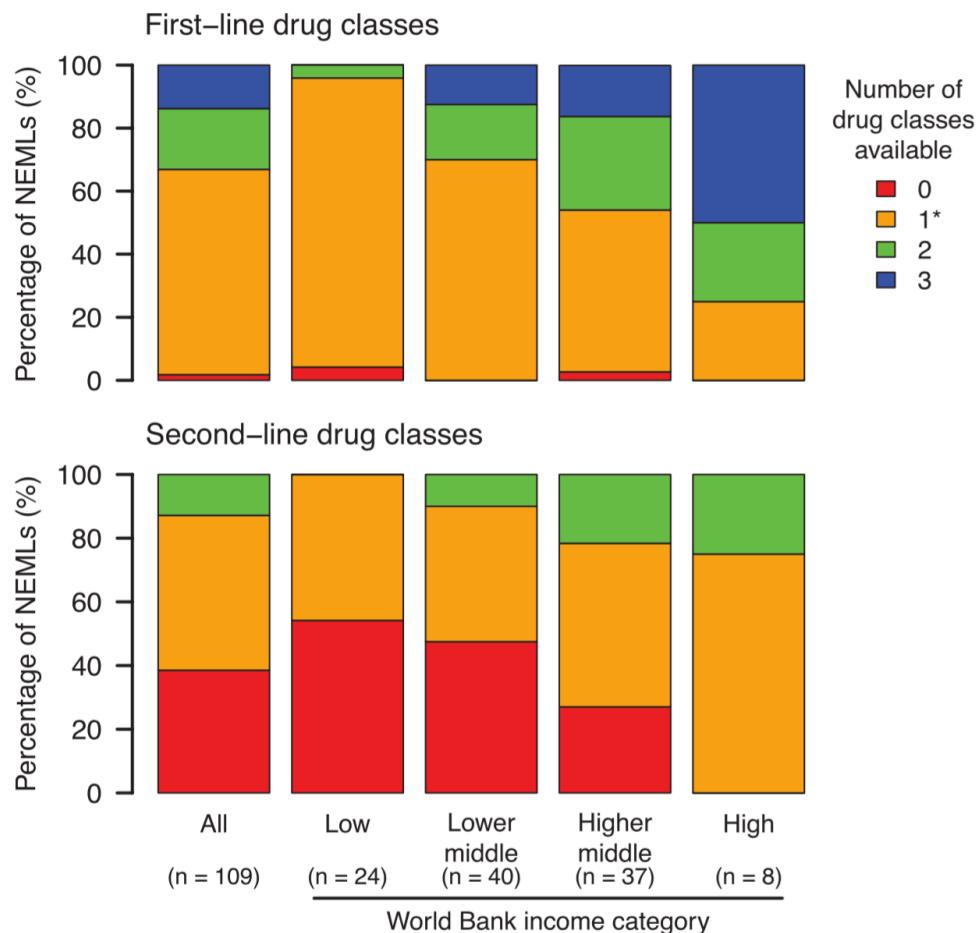
Our review of national essential medicine lists for medications recommended as first- or second-line treatments for neuropathic pain identified that the majority of countries reviewed only had one class of first-line treatment listed (typically a TCA), and about 40% had no second-line treatments listed (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 [6,54], 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, the majority of the 104 developing and emerging 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 essential medicines for the management of symptoms, including pain,*".

### **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 psychological or behaviour-based therapies.

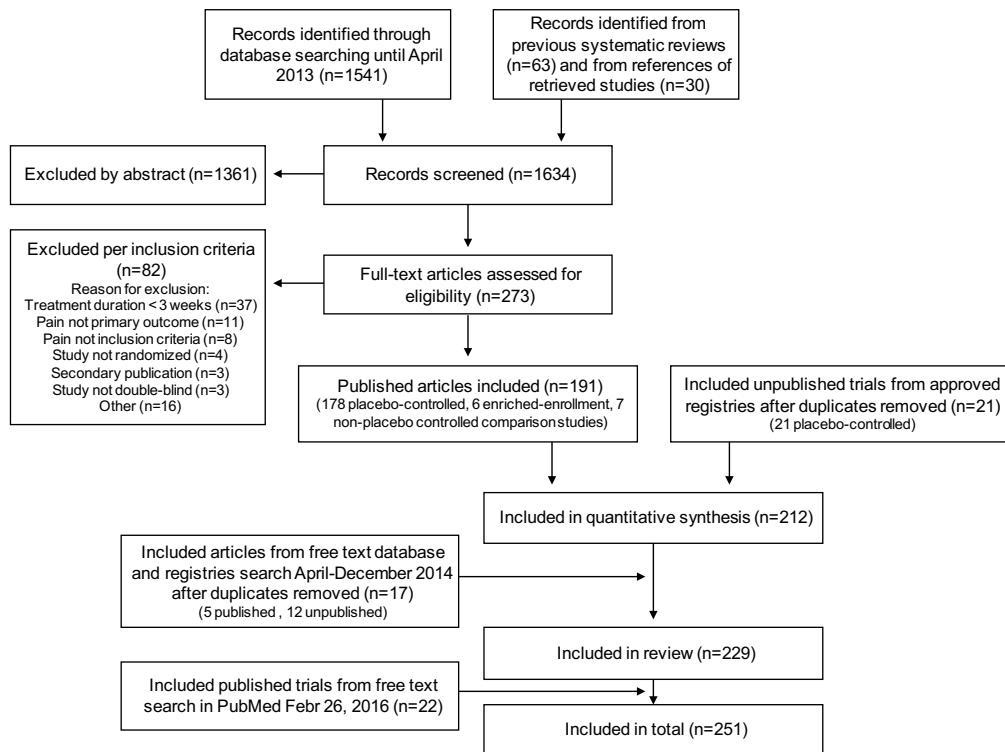
For pharmacological interventions the evidence supporting this application is based upon our recent systematic review, meta-analysis and GRADE based clinical guideline formulation [3]. The systematic review of the literature used a standardised review and data extraction protocol (*for the full protocol 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: [*drug 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.



**Figure 4:** 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  $\alpha_2\delta$  calcium channel ligands. Second-line drug classes include: opioids (including 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. From: Kamerman et al., 2015 [13].

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



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

the somatosensory nervous system) [35]:<sup>3</sup>

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 drugs generally proposed 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 included a composite score of pain and paraesthesia or paraesthesia only.

<sup>3</sup> 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 drug treatment is generally distinct from other neuropathic pains.

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, and carry-over effects in crossover trials. 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  $I^2$  statistic, and 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.

### **Evidence summary and reporting**

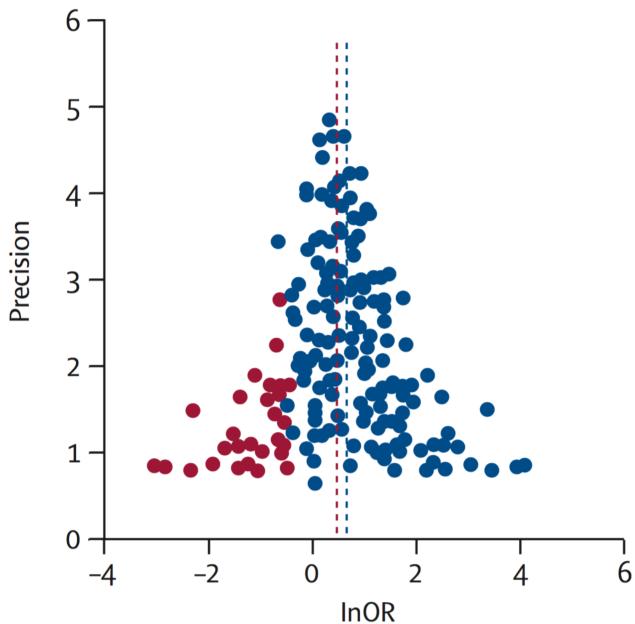
The GRADE classification system was used to summarise the evidence and formulate clinical guidelines [62,63] with final quality of evidence rated as strong or weak from the summary of available data (appraisal of quality, outcome measures, summary of results).

A total of 229 reports, across a number of agents, were included in the published meta-analysis [3].<sup>4</sup> 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).

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

<sup>4</sup> 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 drugs, and combination therapies.



**Figure 6:** Funnel plot showing the precision (inverse of standard error) against the effect size (natural log of the odds ratio,  $\ln\text{OR}$ ). 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].

line),<sup>5</sup> serotonin–adrenaline re-uptake inhibitors (SNRIs; mainly duloxetine),<sup>6</sup> pregabalin<sup>7</sup> and gabapentin could be considered to be first-line drugs (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 drug classes, the evidence-base for the use of TCAs and SNRIs is not evaluated further in this section of the application.<sup>8</sup> 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 drugs 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, combi-

<sup>5</sup> 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).

<sup>6</sup> 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).

<sup>7</sup> 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.

<sup>8</sup> 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.

	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:** 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. § Including gabapentin extended release and enacarbil. Adapted from: Finnerup et al., 2015 [3].

nations 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, the ability to use gabapentin together with 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 $\alpha2\delta$ calcium channel ligands**

#### **Pregabalin**

Eight new reports were identified in the 2016 supplementary search of which one was an enriched-enrollment trial and five provided dichotomous data for NNT calculation. In a mixed peripheral neuropathy population, Holbech and colleagues [67] showed modest analgesic effects for pregabalin (300mg/day) versus placebo and Liu et al 2015 [68] found an effect in PHN. The other studies (Simpson et al 2014 [69], Huffman et al. 2015 [70], Raskin et al. 2016 [71], Chappell et al. 2014 [72], and Ziegler et al. 2015 [73]) 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 [69] used a 300 mg daily dose of pregabalin. In total, 32 randomized controlled trials of pregabalin for neuropathic pain were identified after our updated search. 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

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.

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). 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. Combined NNT was 6.3 (95% CI: 5.0 to 8.3) for gabapentin. There was no evidence of a dose-response effect.

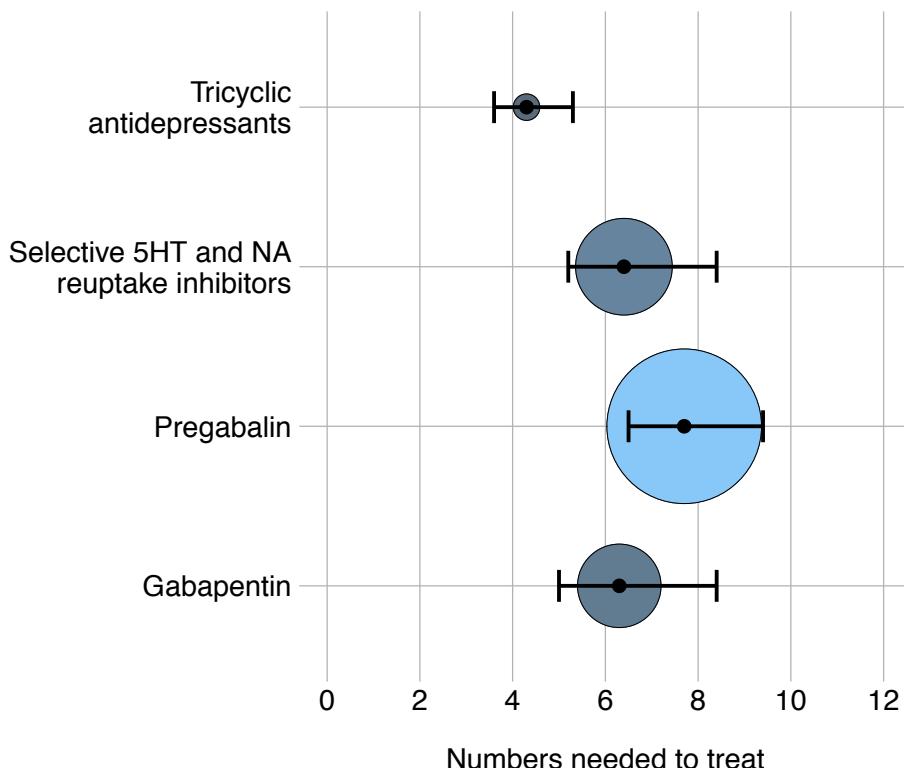
Our data are largely concordant with a recent Cochrane review that evaluated the evidence for the use of gabapentin in chronic neuropathic pain and fibromyalgia in adults [74]. The authors concluded on the basis of second tier evidence that gabapentin was efficacious in post-herpetic neuralgia (NNT 8.0, 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.

### 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).

### Contraindications

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



**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.

### Warnings and precautions

**Drug reaction with eosinophilia and systemic symptoms (DRESS):** Although very rare, DRESS has been associated with use of gabapentin. Some of these reactions have been fatal or life-threatening. If signs or symptoms consistent with DRESS present, the patient should be evaluated immediately, and gabapentin discontinued if an alternative aetiology for the signs or symptoms cannot be established.

**Anaphylaxis and angioedema:** Gabapentin can cause anaphylaxis and angioedema after the first dose or at any time during treatment. Patients should discontinue using gabapentin and seek immediate medical care should they experience signs or symptoms of anaphylaxis or angioedema.

**Effects on driving and operating heavy machinery:** Patients taking gabapentin should not drive until they have gained sufficient experience to assess whether the medication impairs their ability to drive. Driving performance studies conducted with a pro-drug of gabapentin (gabapentin enacarbil, 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 gabapentin may be imperfect. The duration of the driving impairment after starting therapy with gabapentin is unknown. Whether the impairment is related to somnolence or other effects of gabapentin is unknown.

Moreover, because gabapentin causes somnolence and dizziness patients should be advised not to operate complex machinery until they have gained sufficient experience on gabapentin to assess whether it impairs their ability to perform such tasks.

**Withdrawal precipitated seizure:** Anti-epileptic drugs should not be abruptly discontinued because of the possibility of increasing seizure frequency in individuals with epilepsy. In randomized controlled trials of gabapentin for epilepsy, the incidence of status epilepticus did not differ significantly between participants receiving gabapentin and those receiving placebo. This warning pertains primarily to the use of gabapentin in the context of managing epilepsy rather than neuropathic pain.

**Suicidal behaviour and ideation:** Anti-epileptic drugs (AEDs), including gabapentin, increase the risk of suicidal thoughts or behaviour 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 behaviour, and/or any unusual changes in mood or behaviour. 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 of suicidal thinking or behaviour compared to patients randomized to placebo (adjusted relative risk 1.8, 95% CI: 1.2 to 2.7).

**Tumorigenic potential:** An oral carcinogenicity study of gabapentin in rats increased the incidence of pancreatic acinar cell. The clinical significance of this finding is unknown.

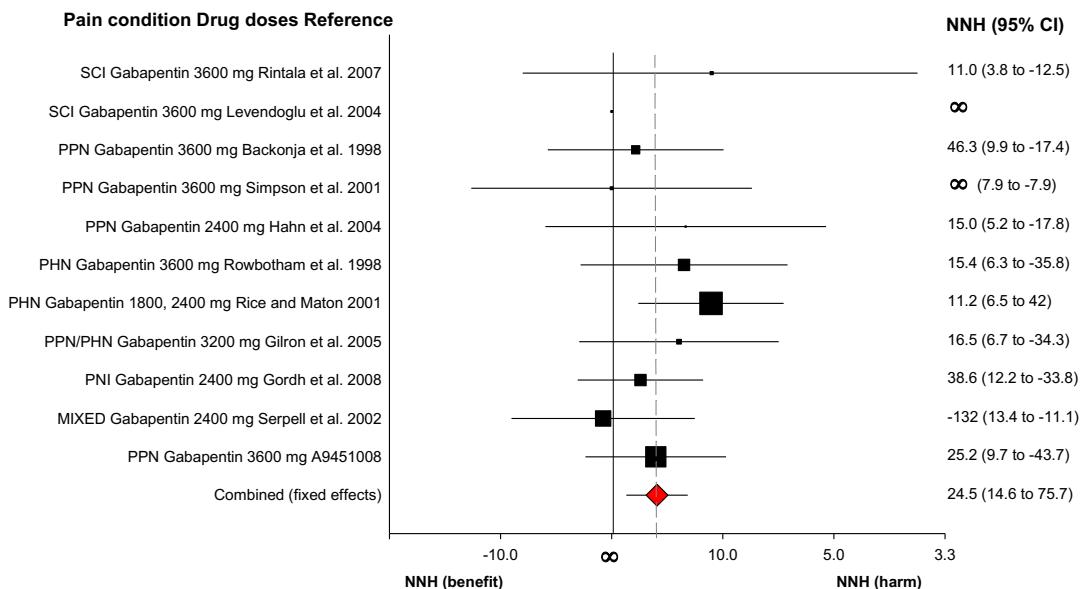
**Sudden and unexplained death in patients with epilepsy:** Eight sudden and unexplained deaths were recorded among a cohort of 2203 epilepsy patients treated with gabapentin, a rate of 0.0038 deaths per patient-year. Although this rate exceeds that expected in a healthy population matched for age and sex, it is within the range of estimates for the incidence of sudden unexplained deaths in patients with epilepsy not receiving gabapentin.

**Somnolence/sedation and dizziness:** In clinical trials for epilepsy, adults receiving doses of up to 1800mg daily of gabapentin reported somnolence, dizziness, and ataxia at a greater rate compared to those receiving placebo (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 gabapentin in patients older than 12 years of age.

#### ***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 literature search in February 2016 did not identify additional studies. Of the 14 studies, one study used only a low dose of gabapentin (900mg) and two studies did not provide numbers of drop-outs due to side effect, thus the combined number needed to harm (NNH) was based on 11 studies (Figure 10). 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



**Figure 10:** Numbers needed to harm (NNH; 95% CI) for trial drop-outs due to adverse effects. Data are derived from 11 trials of gabapentin for neuropathic pain. The bottom red diamond shows the combined effect across the 11 trials. The size of the filled squares indicate the relative number of individuals randomized in each trial.

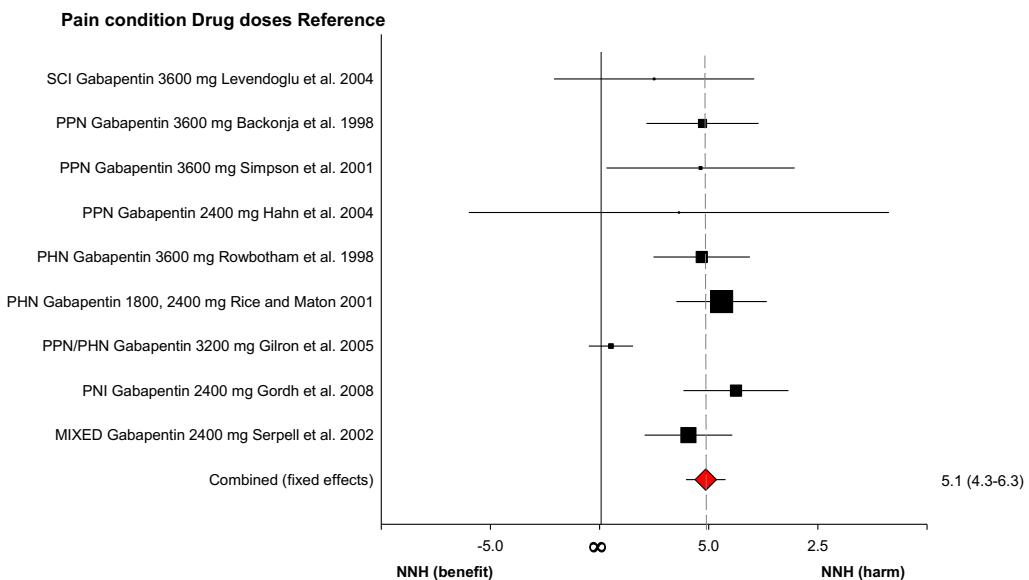
prevalence than in the placebo group. The NNH for dizziness was 5.1 (95% CI: 4.3 to 6.3) and for somnolence 7.1 (95% CI: 5.7 to 9.4) (Figures 11 and 12).

In a Cochrane review of gabapentin in fibromyalgia and neuropathic pain [74], 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) [74]. 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 an NNH of 13 (95% CI: 9 to 24; 544 participants) [74].

## Summary of efficacy and safety across first-line medications

Table 4 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]. 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. 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.

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 13 presents a summary



**Figure 11:** Numbers needed to harm (NNH; 95% CI) for dizziness. Data are derived from nine trials of gabapentin for neuropathic pain. The bottom red diamond shows the combined effect across the nine trials (5.1, 95% CI: 4.3 to 6.3). The size of the filled squares indicate the relative number of individuals randomized in each trial.

**Table 4:** Summary of efficacy and adverse events [10]

	Number needed to treat (50% 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	24.5	5.1	7.1	-
Pregabalin	8.8	13.9	-	-	-
SNRI	6.4	11.8	-	-	-

TCA: Tricyclic antidepressants; SNRI: Serotonin and noradrenaline reuptake inhibitors;

\* : Withdrawal from study as a result of adverse events;

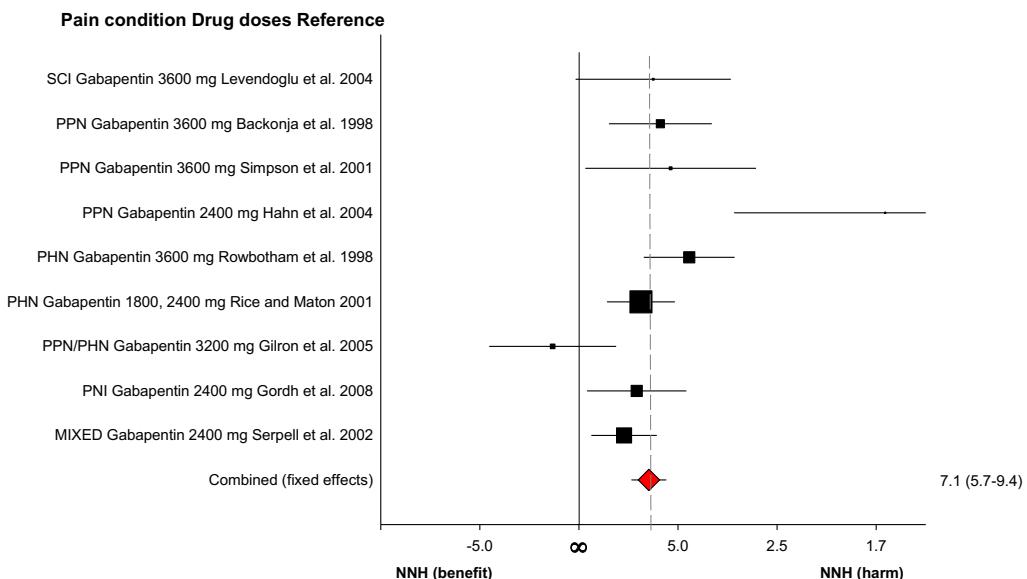
† : Excluding gabapentin extended release / encarbil

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 [75]. 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



**Figure 12:** Numbers needed to harm (NNH; 95% CI) for somnolence. Data are derived from nine trials of gabapentin for neuropathic pain. The bottom red diamond shows the combined effect across the nine trials (7.1, 95% CI: 5.7 to 9.4). The size of the filled squares indicate the relative number of individuals randomized in each trial.

is recommended for the treatment of trigeminal neuralgia [6]<sup>9</sup>. The data are reported as unit price of the medications (Table 5), price when prescribed at the defined daily dose for each 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

<sup>9</sup> 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].



**Figure 13:** 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].

## 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:<sup>10</sup>

- 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 neuropathic pain) for inclusion in the analysis;
- For a drug 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;

<sup>10</sup> For full details on the methodology, please see NICE CG173 guideline [4]: [Appendix F](#).

**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

**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

- 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).

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 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

**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 ?? for registered neuropathic pain indications<sup>11</sup>). 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 [76]. This deficiency in the ICD-10 hampers the collection of accurate epidemiological data on adverse reactions, as well as prescribing, dispensing, and billing informations 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:

<sup>11</sup> 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.

- 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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## **Appendix 1**

**Organizations supporting the application**

**Includes**

**Page count**

## **Appendix 2**

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

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### **Supplementary data**

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

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

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## Summary

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**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 (5·9–9·2) 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,<sup>1</sup> has a substantial effect on quality of life and is associated with a high economic burden for the individual and society.<sup>2–4</sup> It is now regarded as a distinct clinical entity despite a large variety of causes.<sup>5</sup>

Epidemiological surveys have shown that many patients with neuropathic pain do not receive appropriate treatment.<sup>2,6,7</sup> 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.<sup>8</sup> 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<sup>9–11</sup> or specific neuropathic pain disorders, particularly painful diabetic neuropathies and post-herpetic neuralgia.<sup>12–14</sup> 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.<sup>13,15,16</sup> To address these inconsistencies, the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) was introduced in 2000<sup>17,18</sup> 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.<sup>17,18</sup> 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.<sup>19</sup> Non-pharmacological management strategies such as neurostimulation techniques were beyond the scope of this work.<sup>20</sup>

## 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.<sup>21</sup> 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.<sup>22</sup> 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.<sup>23</sup>

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):<sup>1</sup> 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.<sup>1</sup> Trigeminal neuralgia was assessed separately because the response to drug treatment was generally distinct from other neuropathic pain.<sup>10,24</sup>

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<sup>20</sup>).

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.<sup>25</sup> 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).<sup>25</sup> A minimum score of 2 of 5 (randomised and double-blind study) was required for inclusion.<sup>25</sup> 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),<sup>17,18</sup> 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,<sup>16</sup> 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,<sup>26</sup> Egger's regression,<sup>27</sup> and Duval and Tweedie's non-parametric trim-and-fill approach<sup>28</sup> to assess publication bias (appendix). Additionally, we estimated the susceptibility to bias for individual drug classes.<sup>29,30</sup> 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'Abbe plot<sup>31</sup> and as the *I*<sup>2</sup> 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

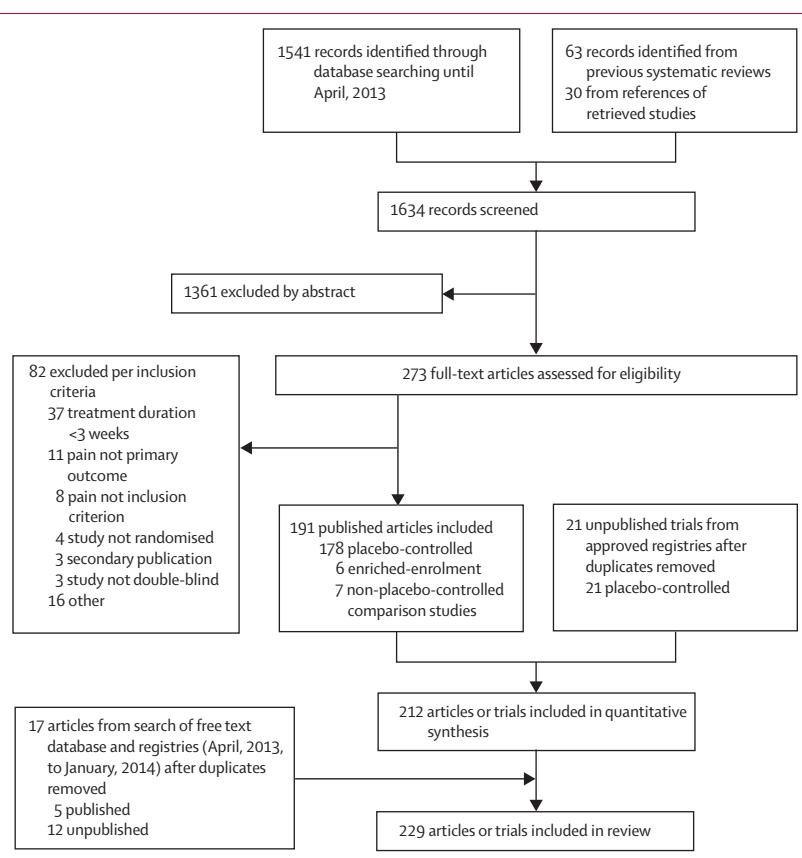


Figure 1: Flow chart of study selection

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

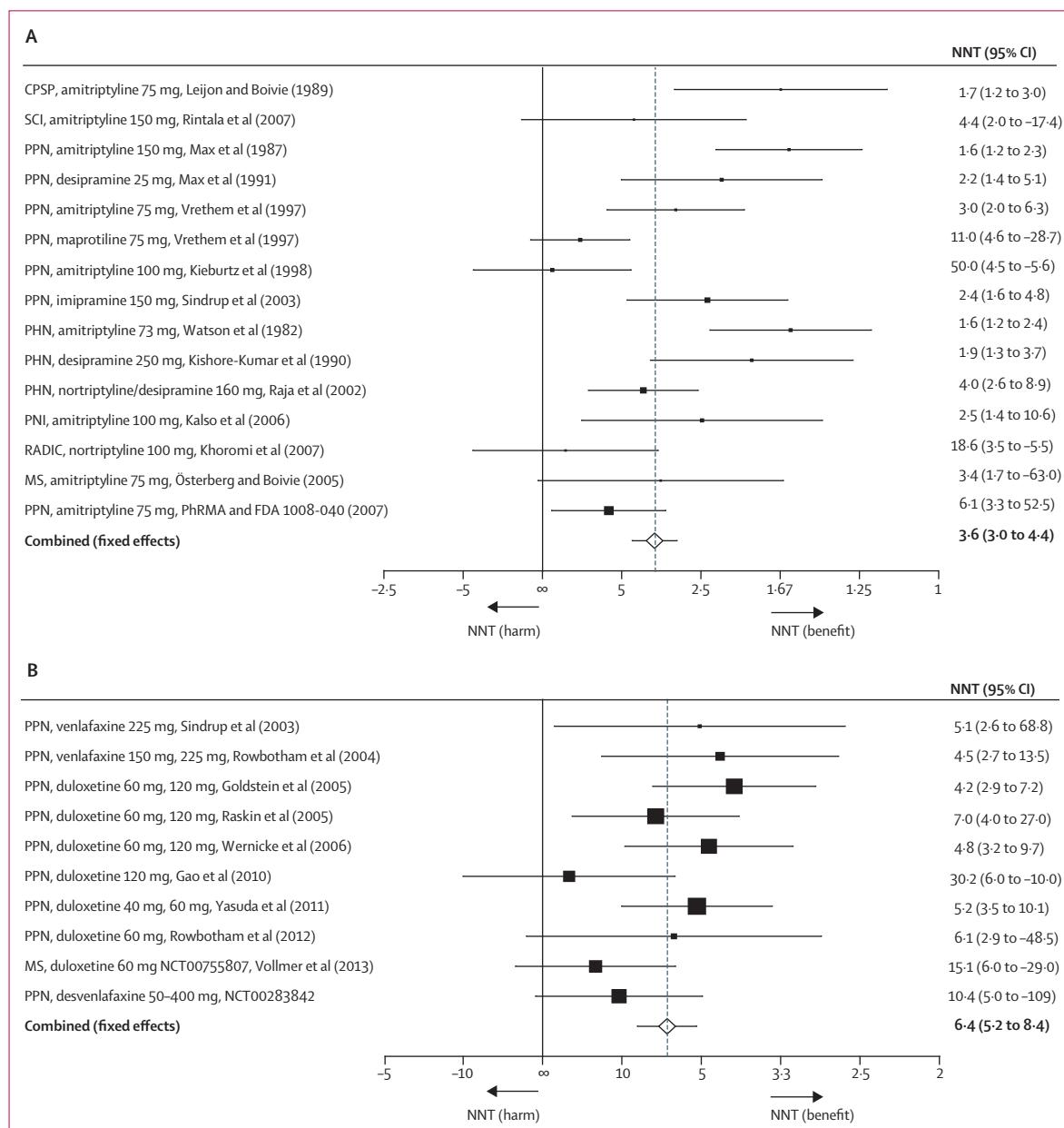


Figure 2: Forest plot of data for tricyclic antidepressants (A) and serotonin-noradrenaline reuptake inhibitors (B) included in the meta-analysis

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

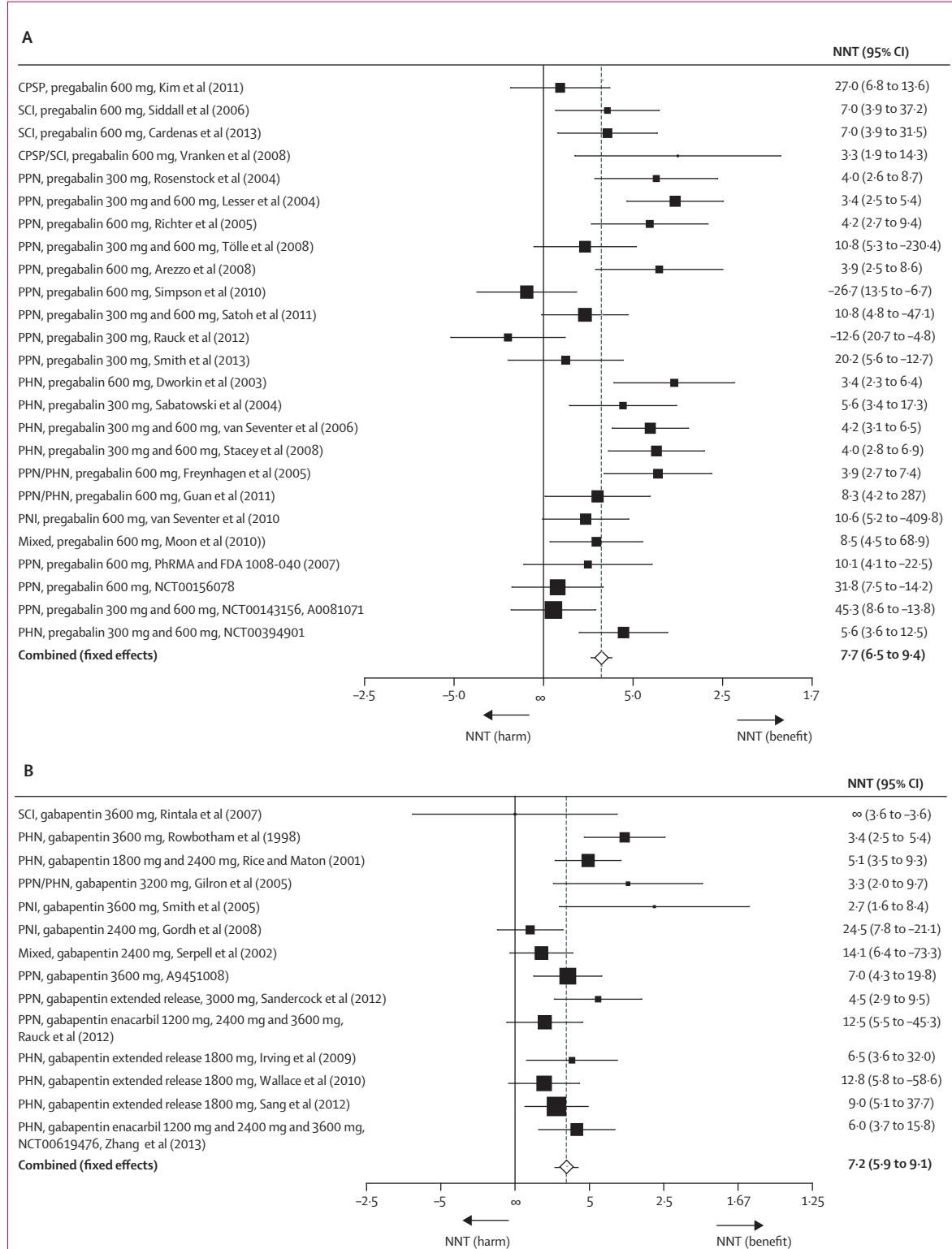
non-significant effect if studies with no effect were published. Using meta-regression, we identified that for studies published in peer-reviewed journals the

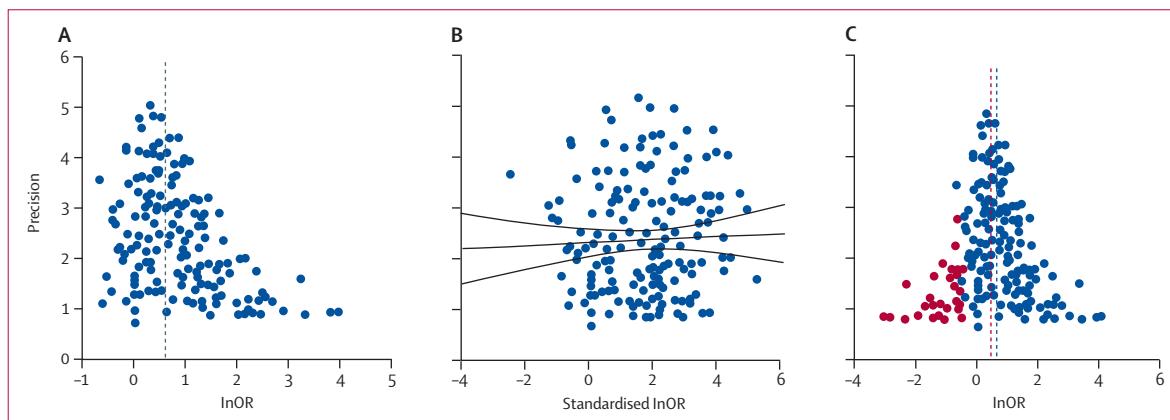
**Figure 3: Forest plot of data for pregabalin (A) and gabapentin including extended release and encarbil (B) included in the meta-analysis**

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. CPS=central post-stroke pain. SCI=spinal cord injury pain. PPN=painful peripheral neuropathy. 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  $\mu$  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  $\Delta$ -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.<sup>23</sup>

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).

#### 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). \*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;<sup>33</sup> an increased risk of sudden cardiac death has been reported with tricyclic antidepressants at doses greater than 100 mg daily.<sup>34</sup> ‡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.<sup>35–37</sup>

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

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;<sup>33</sup> an increased risk of sudden cardiac death has been reported with tricyclic antidepressants at doses greater than 100 mg daily.<sup>34</sup> ‡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.<sup>35–37</sup>

**Table 2:** Drugs or drug classes with strong or weak recommendations for use based on 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.<sup>10,24</sup> 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.<sup>32</sup> 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).<sup>38,39</sup>

The GRADE recommendations for tapentadol, other antiepileptics, capsaicin cream, topical clonidine, selective serotonin reuptake inhibitor antidepressants, NMDA antagonists, and combination therapy<sup>40–42</sup> 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).

## Discussion

In accordance with previous reports,<sup>23</sup> 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.<sup>43</sup> 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,<sup>44</sup> a distinct clinical phenotype in subgroups of patients with radiculopathy,<sup>45</sup> 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<sup>29</sup> and unpublished trials. Publication bias can occur if studies with positive results are published whereas those with no data or negative results are not.<sup>29</sup> It might lead to a major overestimation of efficacy in therapeutic studies.<sup>46</sup> 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.<sup>47</sup> 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.<sup>48</sup> However, our results might also indicate insufficient assay sensitivity in clinical trials of neuropathic pain (table 4).<sup>55</sup> 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.<sup>56</sup> Placebo response was higher in HIV-related neuropathies,<sup>44</sup> and in patients with low or variable pain scores at inclusion.<sup>54</sup> Conversely, it seems to be lower in post-herpetic neuralgia.<sup>44</sup> Another issue is the

NeuPSIG recommendation for future trials in neuropathic pain	
<b>Patient population (appendix)</b>	
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†
<b>Characteristics of the trials (appendix)</b>	
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 <sup>44</sup>

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);<sup>49,50</sup> 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<sup>51,52</sup> and post-hoc analyses of recent clinical trials<sup>53</sup> 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,<sup>54,49</sup> 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

heterogeneous diagnostic criteria for neuropathic pain in several trials (detailed descriptions of the individual studies are available on request). The use of diagnostic algorithms<sup>49</sup> and screening methods<sup>50</sup> 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.<sup>57–59</sup> 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.<sup>51–53</sup>

Like previous NeuPSIG recommendations,<sup>19</sup> 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.<sup>9–13,15–16,19,60</sup> 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.<sup>19,60</sup> This stems mainly from the consideration of potential risk of abuse, particularly with high doses,<sup>35</sup> 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.<sup>61–63</sup> 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.<sup>64</sup> 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.<sup>65–70</sup>

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.<sup>6</sup> By contrast, a recent large study of general practitioners' adherence to current French

recommendations noted a paucity of appropriate recall of first-line drugs.<sup>8</sup> It will be important to facilitate the dissemination of the present recommendations and subsequently to assess their real-life implementation in various countries.<sup>7</sup>

#### 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, Peripheragen, 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, Xenopore, 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 3

Kameran 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?**

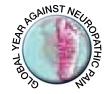
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### Supplementary data

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

[Access repository](#)



# 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<sup>5</sup> 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,<sup>6,24,26</sup> 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.<sup>7,13,15,18,20</sup> The pain is associated with significant decreases in quality of life and socioeconomic well-being, even more so than nonneuropathic chronic pain.<sup>9,19,21</sup> Developing and emerging countries share the greatest burden of conditions that are associated with the development of neuropathic pain<sup>5,10</sup> and can ill afford the negative consequences of this pain.

There are medicines with proven efficacy in the treatment of neuropathic pain.<sup>11,12</sup> 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.<sup>2,4</sup> 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/](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.<sup>14,17</sup> However, none of the analgesic medicines included in the WHO model list is recommended as first-line treatments for neuropathic pain.<sup>11</sup> 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.<sup>17</sup> 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/](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.<sup>11</sup> 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%.

*Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.*

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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.<sup>3,11</sup> 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.<sup>11</sup>

### 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.<sup>16</sup> 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.<sup>22</sup> 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  $\chi^2$  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.<sup>22</sup> 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  $\alpha 2\delta$  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  $\alpha 2\delta$  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<sup>11</sup>), 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.<sup>30,32</sup> Indeed, the WHO<sup>31</sup> 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

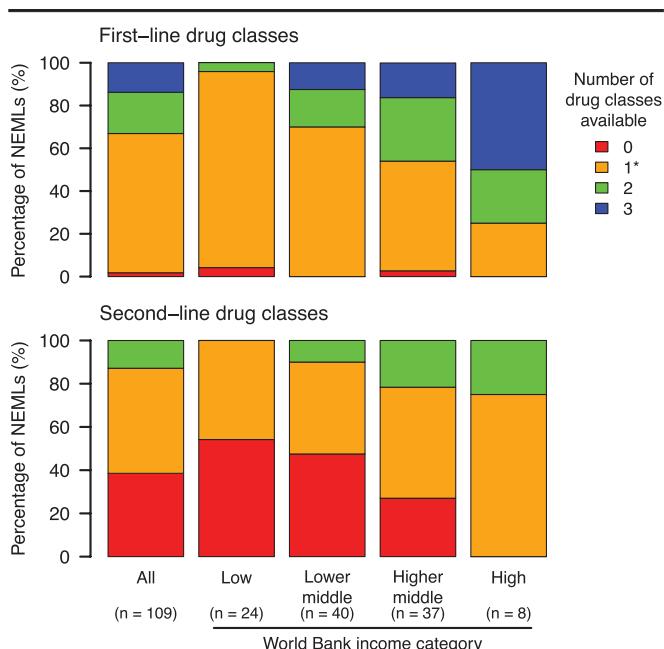
**Table 1**  
**Drug listings on the national essential medicines lists of 112 developing countries.**

	Overall listing, n (%)	Listing by World Bank income category, n (% countries within a category)			Other* (n = 3)
		Low (n = 24)	Upper middle (n = 37)	High (n = 8)	
<b>First-line medications</b>					
TCA					
Amitriptyline	105 (94)	23 (96)	38 (89)	8 (100)	
Clomipramine	53 (47)	11 (46)	21 (52)	5 (62)	0 (0)
Desipramine	2 (2)	0 (0)	1 (2)	0 (0)	0 (0)
Imipramine†	46 (41)	3 (12)	17 (42)	20 (54)	0 (0)
Nortriptyline	10 (9)	1 (4)	2 (5)	6 (16)	1 (12)
SNRI					
Duloxetine	5 (5)	0 (0)	3 (8)	1 (12)	0 (0)
Venlafaxine	19 (17)	0 (0)	7 (18)	4 (50)	0 (0)
α2δ antagonist					
Gabapentin†	33 (30)	1 (4)	10 (25)	6 (75)	0 (0)
Pregabalin	11 (10)	0 (0)	3 (8)	1 (12)	1 (33)
<b>Second-line medications</b>					
Opioid					
Tramadol	61 (55)	8 (33)	19 (48)	26 (70)	1 (33)
Topical					
8% capsaicin	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
5% lidocaine	22 (20)	3 (12)	6 (15)	9 (24)	3 (38)
<b>Strong opioid medications</b>					
Methadone†	34 (30)	4 (17)	8 (20)	16 (43)	6 (75)
Morphine	106 (95)	22 (92)	40 (100)	33 (89)	8 (100)
Oxycodone	15 (13)	0 (0)	4 (10)	9 (24)	2 (25)
<b>Other anticonvulsant medications</b>					
Carbamazepine	109 (97)	22 (92)	40 (100)	36 (97)	8 (100)
Oxcarbazepine†	15 (13)	0 (0)	3 (8)	8 (22)	4 (50)
Sodium valproate	107 (95)	22 (92)	40 (100)	35 (95)	7 (88)

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

†  $P < 0.05$  for  $\chi^2$  test for trend listing vs income category.

α2δ antagonist, α2δ calcium channel antagonists; SNRI, serotonin and norepinephrine 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.<sup>27,28</sup> 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.<sup>23,25,29</sup> 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.<sup>1,8</sup> 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. Hietarharju 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 Mitsubishi 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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