A report for
Universitätsklinikum Schleswig-Holstein/Campus Kiel
on Shared Decision Making
for neuropathic pain

Kleijnen Systematic Reviews Ltd

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LIST OF ABBREVIATIONS

AE	Adverse events
CADTH	Canadian Agency for Drugs and Technologies in Health
CDSR	Cochrane Database of Systematic Reviews
DARE	Database of Abstracts of Reviews of Effects
FAQ	Frequently asked questions
GIN	Guidelines International Network
GRADE	Grading of Recommendations, Assessment, Development, and Evaluation
HRQoL	Health-related quality of life
HTA	Health technology assessment
KSR	Kleijnen Systematic Reviews Ltd
NHS	National Health Service
NICE	National Institute for Health and Care Excellence (UK)
NNH	Number needed to harm
NNT	Number needed to treat
NR	Not reported
PDN	Painful diabetic neuropathy
PHN	Postherpetic neuralgia
QoL	Quality of life
RCT	Randomised controlled trial
RR	Relative risk
SSNRI	Selective Serotonin Noradrenalin Reuptake Inhibitor

1. PROJECT OBJECTIVES

The overall aim of this project is to provide tools to support patient decision making across a range of clinical topics. Specifically for each topic of interest, KSR will produce a report containing an evidence table of treatment options and a synthesis of the literature underpinning the evidence table.

The topic of this report is neuropathic pain focusing on antidepressants, antiepileptics and tramadol.

2. METHODS

2.1 INCLUSION CRITERIA

The research question underpinning the literature searches for this topic was developed in conjunction with clinical departments at Universitätsklinikum Schleswig-Holstein/Campus Kiel. The question was framed in terms of participants, interventions, outcomes and study design, see Table 1. Based on clinical input and a preliminary review of the literature, we explicitly focus on neuropathic pain therapies given to patients when conventional analgesics (i.e., non-opioid painkillers such as paracetamol or non-steroidal anti-inflammatory drugs +/- adjuvant therapies) are not sufficiently effective. The included systemic therapies may be accompanied by topical therapies (e.g., Lidocaine, Capsacain) but these are not part of this evidence review.

As detailed below, literature searches were carried out using a stepwise approach to identify relevant studies according to study design. In the first step, searches aimed to identify relevant systematic reviews and guidelines. For this project, no further searches were conducted as relevant results were extracted from the identified literature.

Table 1: Inclusion criteria for searches

PICO	
Patients	Patients with neuropathic pain (i.e. all peripheral neuropathic pain, post-herpetic neuralgia, nerve injuries, polyneuropathy etc.)
Interventions	Anti-depressants - Amitriptyline - Duloxetine Anti-epileptic drugs - Pregabalin - Gabapentin - Carbamazepine Opioid-based analgesics - Tramadol
Outcomes	- Pain symptoms (pain reduction to be expected) - Health-related quality of life - Functionality/ activities of daily living (e.g. fitness to drive, fitness to work) - Adverse effects - Addictive potential - Interactions with other drugs
Study Designs	Systematic reviews and guidelines

2.2 FREQUENTLY ASKED QUESTIONS

The following research questions were identified as frequently asked questions (FAQs):

- FAQ 1: What is it and how do I take this medication?

- FAQ 2: What might be the effects on my everyday activities e.g. fitness to drive, fitness to work?
- FAQ 3: How much improvement can I expect in my pain and when?
- FAQ 4: How will the medication affect my quality of life?
- FAQ 5: What side effects might I experience?
- FAQ 6: Could I become addicted to the drug?

2.3 LITERATURE SEARCHES

Literature searches were carried out using a stepwise approach to identify relevant studies according to study design:

1. Systematic reviews and guidelines
2. Randomised controlled trials
3. Observational studies
4. Supplementary searches

Only in the event of no relevant systematic reviews or guidelines being identified were further searches to be conducted to identify randomised controlled trials (RCTs, step 2), and if no RCTs were identified, only then would searches be undertaken to identify observational studies (Step 3).

The search strategies were developed specifically for each database and the keywords adapted according to the configuration of each database. Searches were limited by date range for systematic reviews and guidelines to 2012-2018. Where appropriate, searches were limited to remove animal studies. Searches were not limited by language or publication status.

Handling of citations

Identified references from the bibliographic database searches were downloaded into Endnote bibliographic management software for further assessment and handling. Individual records within the Endnote libraries were tagged with searching information, such as searcher, date searched, database host, database searched, strategy name and iteration, theme or search question. This enabled the information specialist to track the origin of each individual database record, and its progress through the screening and review process.

Quality assurance within the search process

The main Embase strategy was independently peer reviewed by a second KSR Information Specialist. Strategy peer review was informed by items based on the Canadian Agency for Drugs and Technologies in Health (CADTH) checklist.[1]

2.4 SEARCH SOURCES

1) Systematic reviews and guidelines

The following systematic review specific databases were searched from 2012 to March 2018:

- KSR Evidence (Internet): up to 2018/03/13 (https://ksrevidence.com)
- Cochrane Database of Systematic Reviews (CDSR) (Wiley): issue 3 of 12, March 2018
- Database of Abstracts of Reviews of Effects (DARE) (Wiley): issue 2 of 4, April 2015
- Health Technology Assessment (HTA) database (Wiley): issue 4 of 4, October 2016

The following guidelines resources were searched from 2012 to March 2018:

- Guidelines International Network (GIN) (Internet): up to 2018/03/13 (http://www.g-i-n.net/library/international-guidelines-library)
- NICE Evidence (Internet): up to 2018/03/13 (www.evidence.nhs.uk)

Full details of all search strategies are presented in Appendix 1.

2) RCTs

As the search for secondary sources and, thereby, reference checking was sufficient, no additional searches for primary studies were undertaken.

3) Observational studies

As the search for secondary sources and, thereby, reference checking was sufficient, no additional searches for primary studies were undertaken.

4) Supplementary searches

Reviewers also conducted supplementary hand searches to identify potentially relevant references, e.g. guidance specific to Germany and websites of patient organisations. The bibliographies of included studies and review articles were also checked for additional relevant articles.

2.5 METHODS OF STUDY SELECTION, DATA EXTRACTION AND QUALITY ASSESSMENT

Study selection

Two reviewers independently inspected the title and abstract of each reference identified by the search and determined the potential relevance of each article. For potentially relevant articles, or in cases of disagreement, the full article was obtained, independently inspected, and inclusion criteria applied. Any disagreements were resolved through discussion.

Data extraction

An evidence hierarchy was used to select the most appropriate study(ies) to populate the evidence table. Where more than one study could provide evidence for the table the most relevant studies were extracted using the following criteria: recency (most recent preferred), quality (highest quality preferred), representativeness (populations representative of the general target population preferred). Where there were gaps in the evidence table (no systematic review or guideline available) relevant RCTs were extracted and where no RCTs observational studies were extracted.

For each study, data were extracted by one reviewer and checked by another. Any disagreements were resolved by consensus.

Quality assessment

GRADE evidence profiles were also developed to rate the overall quality of the evidence for each intervention and outcome.

3. RESULTS

3.1 LITERATURE SEARCHES AND INCLUSION ASSESSMENT

For this evidence report, systematic searches for systematic reviews and guidelines were supplemented by hand searches.

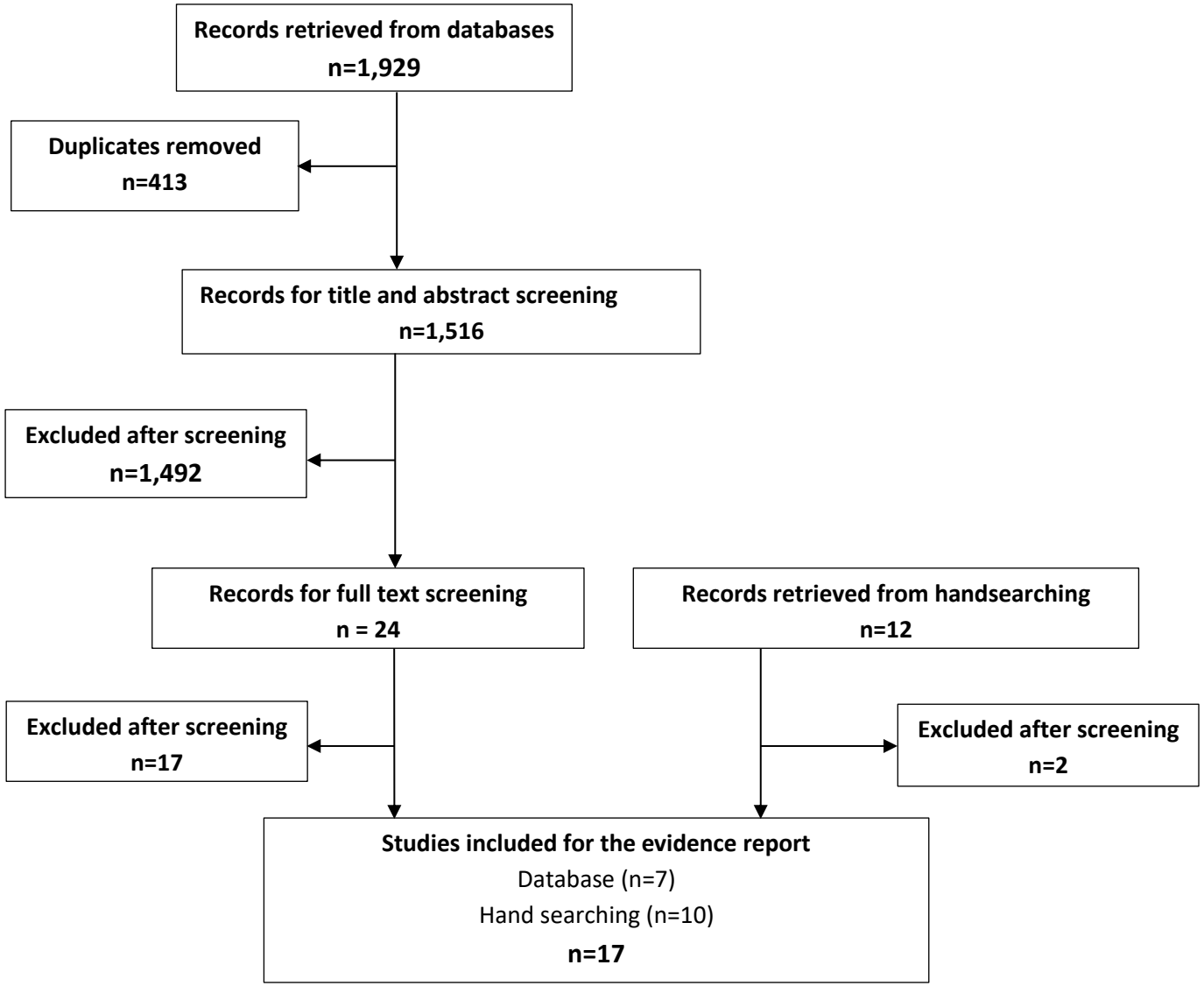
Searches were conducted on 13 March 2018 to identify relevant questions (frequently asked questions; FAQs) and to answer the clinical questions focusing on systematic reviews, meta-analyses and evidence-based guidelines. A total of 1,929 titles and abstracts were retrieved from literature searches. After de-duplication, 1,516 titles and abstracts were screened by two reviewers. From these, 24 full papers were obtained for citations.

Using the criteria described before (see Data extraction), seven reviews were selected as the main sources of evidence in this report.

These searches were supplemented by hand searching to identify additional guidelines (in particular German guidelines) and information by patient organisations which identified patient-driven arguments and prioritisations. A total of ten references were identified from patient organisations, NHS resources and the British National Formulary and were used to provide information on use and addictive potential of the medications. All outcome data on pain, quality of life and adverse events were derived from the seven systematic reviews identified as part of the searches for relevant systematic reviews and guidelines (see step 1 of Search sources).

A summary of the study selection process according to modified PRISMA reporting guidelines is reported in Figure 1.

Figure 1: Flow chart



3.2 OVERVIEW OF THE EVIDENCE

The information identified to answer the patient questions is given below in tables organised by question. Tables are provided showing the underpinning evidence for each question. Data to populate the tables of patient questions were taken from several sources (Table 2).

Where outcomes were assessed using the GRADE tool, the rating is reported.

Table 2: Studies populating the evidence table

Study ID	What is it and how do I take this medication?	What might be the effects on my everyday activities?	How much improvement can I expect in my pain and when?	How will the medication affect my quality of life?	What side effects might I experience?	Could I become addicted to the drug?
Duehmke 2017[2]			✓	✓	✓	
Joint Formulary Committee 2018a[3]						✓
Joint Formulary Committee 2018b[4]						✓
Lunn 2014[5]			✓		✓	
Moore 2015[6]			✓		✓	
NHS 2016[18]	✓					
NHS 2017[7]	✓	✓	✓			✓
NHS 2018[8]	✓	✓	✓			✓
Stewart 2017a[9]	✓					
Stewart 2017b[10]	✓	✓				
Stewart 2018[11]	✓	✓				
Waldfogel 2017[12]				✓		
Wang 2017[13]			✓		✓	
Wiffen 2014[14]	✓	✓	✓		✓	
Wiffen 2017[15]			✓		✓	
Wrightington 2017a[16]	✓		✓			
Wrightington 2017b[17]	✓	✓	✓			✓

FAQ 1: What is it and how do I take this medication?

Table 3 provides an overview of the treatments. Table 4 provides further details on the mode of administration of the treatments.

Table 3: What are the treatments?

Treatment → / **↓ FAQ**	**Tricyclic antidepressants** (amitriptyline)	**SSNRI antidepressants** (duloxetine)	**Calcium channel blocker antiepileptics** (gabapentin, pregabalin)	**Sodium channel blocker antiepileptics** (carbamazepine)	**Tramadol**
What is it?	Amitriptyline is widely used to treat depression but at lower doses it is used to treat pain.[7]	Duloxetine is a medication used to treat depression but is also used to treat some types of persistent pain such as nerve pain.[16]	Gabapentin and Pregabalin are anti-epileptic medicines which can be prescribed for pain.[17]	Carbamazepine is an anti-epileptic medicine which can be prescribed for pain.[14]	Tramadol is an opioid pain killer.[8]

Table 4: How do I take the medications?

Treatment → / **↓ FAQ**	**Tricyclic antidepressants** (amitriptyline)	**SSNRI antidepressants** (duloxetine)	**Calcium channel blocker antiepileptics** (gabapentin, pregabalin)	**Sodium channel blocker antiepileptics** (carbamazepine)	**Tramadol**
How do I take this medication?	Amitriptyline tablets and liquid come in 3 different strengths - 10 mg, 25 mg or 50 mg. The usual starting dose is 10 mg a day. This dose can be increased if you need better pain relief up to a maximum	Duloxetine is prescribed as 30 mg and 60 mg capsules. The usual dose is one capsule of either 30 mg or 60 mg daily. When starting duloxetine, your doctor may give you the lower strength	Gabapentin 300 mg comes in yellow capsules. The number of capsules to be taken is increased over the first few days according to your response and any side effects. You can take gabapentin	Carbamazepine is usually prescribed as a tablet, but chewable tablet, liquid, and suppository formulations are manufactured You'll usually need to take carbamazepine at	Tramadol comes as tablets, capsules and liquid drops that you swallow. It can also be given by injection but this is usually only done in hospital. You may be given fast acting tramadol which starts

Treatment → ↓ FAQ	Tricyclic antidepressants (amitriptyline)	SSNRI antidepressants (duloxetine)	Calcium channel blocker antiepileptics (gabapentin, pregabalin)	Sodium channel blocker antiepileptics (carbamazepine)	Tramadol
	of 75 mg a day. It's usual to take amitriptyline once a day before bedtime because it can make you feel sleepy.[7]	of capsules to begin with, and then increase the strength as you go on. You can take duloxetine either before or after meals.[11]	before or after food.[9] You will be advised to take a low dose when you first start taking pregabalin, and then to increase the dose over the first few weeks. Most people take two or three doses a day once they are on a regular maintenance dose. You can take pregabalin before or after food. If you have been supplied with oral liquid medicine, you will need to use an oral dosing syringe.[10]	a low dose once or twice a day, with the dose being gradually increased and taken up to four times a day until it provides satisfactory pain relief.[18]	to work within 30 to 60 minutes but lasts for only a short time. Some tramadol tablets and capsules are slow-release. This means the tramadol is gradually released into your body over either 12 or 24 hours. This type of tramadol takes longer to start working but lasts longer. You can take tramadol before or after food. It is contraindicated with alcohol.[8]

FAQ 2: What might be the effects on my everyday activities e.g. fitness to drive, fitness to work?

Table 5 gives an overview of effects on everyday activities.

Table 5: What might be the effects on my everyday activities?

Treatment → **↓ FAQ**	**Tricyclic antidepressants** (amitriptyline)	**SSNRI antidepressants** (duloxetine)	**Calcium channel blocker antiepileptics** (gabapentin, pregabalin)	**Sodium channel blocker antiepileptics** (carbamazepine)	**Tramadol**
What might be the effects on my everyday activities e.g. fitness to drive, fitness to work?	Some people feel sleepy while they're taking amitriptyline. It might be best to stop driving and cycling for the first few days of treatment until you know how this medicine makes you feel.[7]	Duloxetine can make you feel dizzy or sleepy. If this happens, do not drive and do not use tools or machines.[11]	With gabapentin avoid operating heavy machinery or driving a car when you first start taking these capsules or if at any time you feel the medicine is making you unfit to do either. The common side effects are drowsiness, unsteadiness and giddiness.[17] Pregabalin can make you feel dizzy or sleepy or you may have blurred or double vision. If this happens do not drive and do not use tools or machines.[10]	Carbamazepine could make you sleepy and dizzy. If this happens, do not drive and do not use tools or machines.[14]	Tramadol can make you feel sick and dizzy which may affect your ability to drive and operate machinery.[8]

FAQ 3: How much improvement can I expect in my pain and when?

Table 6 gives an overview of the data identified relating to improvement in pain. Supporting evidence is presented in Tables 7 to 12. The evidence identified by the reviews was variable in quality. Only evidence relating to duloxetine and gabapentin was rated 'moderate' (providing a good indication of the likely effect) with the evidence on amitriptyline, pregabalin, carbamazepine and tramadol being generally of lower quality. In these circumstances, caution is needed in interpreting the findings.

For those interventions with moderate evidence the following conclusions could be drawn. In relation to duloxetine, review authors found an adequate amount of moderate quality evidence that doses of 60 mg and 120 mg daily are effective for treating pain in diabetic peripheral neuropathy but lower daily doses are not. As regards gabapentin, doses of 1800 mg to 3600 mg daily) can provide good levels of pain relief to some people with postherpetic neuralgia and peripheral diabetic neuropathy. Evidence for other types of neuropathic pain is very limited.

For interventions with lower evidence the following conclusions could be drawn. In relation to amitriptyline, Cochrane review authors concluded that, as there was no good evidence of a lack of effect, amitriptyline could continue to be used in practice but in the knowledge that only a minority of people will achieve satisfactory pain relief. In relation to pregabalin, review authors concluded that pregabalin may be an effective pharmacological approach for the neuropathic pain. However in this review pregabalin was not statistically significantly superior to placebo for numbers of patients with 50% pain relief. Cochrane review authors concluded that carbamazepine is probably effective in some people with chronic neuropathic pain, but trials were no longer than four weeks' duration and studies were small, amongst other issues. The authors of the tramadol review concluded that the evidence did not provide a reliable indication of the likely treatment effect which could be, substantially different from the estimate in the review.

The above variation in quality, taken together with the fact that the reviews covered different populations with neuropathic pain, means that comparing between drugs should be done with caution.

Table 6: Improvement in pain – option data

Treatment → **↓ FAQ**	**Tricyclic antidepressants** (amitriptyline)	**SSNRI antidepressants** (duloxetine)	**Calcium channel blocker antiepileptics** (gabapentin, pregabalin)	**Sodium channel blocker antiepileptics** (carbamazepine)	**Tramadol**
How much improvement can I expect in my pain?[1]	It is not known how many people may have at least 50% reduction in pain with amitriptyline. A Cochrane review concluded that amitriptyline should continue to be used to treat neuropathic pain but that only a small number of people will achieve satisfactory pain relief. (Table 7)	In trials of patients with diabetic peripheral neuropathic pain approximately 45 of 100 patients taking duloxetine had at least 50% pain reduction compared to approximately 26 given a placebo. (Table 8)	In trials of patients with diabetic peripheral neuropathic pain approximately 38 of 100 patients taking gabapentin had at least 50% pain reduction compared to approximately 21 given a placebo. (Figures for post-herpetic neuralgia were 33 and 19) (Table 9). In trials of patients with various neuropathic pain conditions approximately 37 of 100 patients taking pregabalin had at least 50% pain reduction compared to approximately 27 given placebo. (Table 10) but	There is not enough good quality evidence to say how well carbamazepine works in any neuropathic pain condition. Carbamazepine is probably helpful for some people with chronic neuropathic pain but it is not possible to know beforehand who will benefit and who will not. (Table 11)[3]	In trials of patients with various neuropathic pain conditions approximately 53 of 100 patients taking tramadol had at least 50% pain compared to approximately 30 given a placebo (Table 12)[4]

Treatment → ↓ FAQ	Tricyclic antidepressants (amitriptyline)	SSNRI antidepressants (duloxetine)	Calcium channel blocker antiepileptics (gabapentin, pregabalin)	Sodium channel blocker antiepileptics (carbamazepine)	Tramadol
			this difference could be due to chance.[2]		
When might my pain improve?	You may notice a difference after a week or two but it can take 6 weeks for amitriptyline to work as a painkiller.[7]	Duloxetine will not work straight away and could take up to a month to notice any significant benefit. You may need to increase the dose.[16]	A period of four weeks of treatment will allow you to judge whether or not the medicine has helped your pain. If so and if the side effects have not been too troublesome, then you can continue to take the drug.[17]	No information	You will feel less pain 30 to 60 minutes after taking fast-acting tramadol. The pain relief wears off after 4 to 6 hours. Slow acting tramadol tablets and capsules can take a day or two to start working but the pain relief will last for longer.[8]
1.Duloxetine, gabapentin, carbamazepine and tramadol results showed that statistically significantly more people had 50% reduction in pain or more when compared to placebo. Differences were not statistically significant for pregabalin and could not be determined for amitriptyline. 2.Not statistically significant. 3. However the Cochrane review concluded that there was not enough good quality evidence to say how well carbamazepine worked in any neuropathic pain condition and the result cannot be relied upon. 4. The authors of the tramadol review concluded that the evidence did not provide a reliable indication of the likely treatment effect which could be, substantially different from this estimate.					

Table 7: Improvement in pain – Evidence for amitriptyline compared with placebo

Outcome	Probable outcome with placebo	Probable outcome with intervention	NNT or NNH and / or relative effect (95% CI)	No of participants and studies	Quality of the evidence	Comments
At least 50% Improvement of pain	NR	NR	NR	NR	Small studies that were considered very likely to be biased or used outcomes of limited clinical utility, or both)	Amitriptyline should continue to be used but only a small number will get satisfactory pain relief.

Source: Moore 2015[6]
CI = confidence interval; NNH = number needed to harm; NNH = number needed to harm; RR = relative risk

Table 8: Improvement in pain – Evidence for duloxetine compared with placebo

Outcome	Probable outcome with placebo	Probable outcome with intervention	NNT or NNH and / or relative effect (95% CI)	No of participants and studies	Quality of the evidence	Comments
Number of patients with ≥50% improvement of pain at ≤ 12 weeks	257 per 1000	445 per 1000	RR 1.73 (1.44 to 2.08) NNT 5 (4 to 7)	908 participants, 4 studies	Moderate	Based on 11-point Likert score

Source: Lunn (2014)[5]
Patient or population: patients with painful neuropathy or chronic pain from diabetic peripheral neuropathy; **Settings:** primary and secondary care; **Intervention:** duloxetine 60 mg daily.
CI = confidence interval; NNH = number needed to harm; NNH = number needed to harm; RR = relative risk

Table 9: Improvement in pain – Evidence for gabapentin compared with placebo

Outcome	Probable outcome with placebo	Probable outcome with intervention	NNT or NNH and / or relative effect (95% CI)	No of participants and studies	Quality of the evidence	Comments
At least 50% pain intensity reduction (PHN)[1]	190 per 1000	330 per 1000	RR 1.7 (1.4 to 2.0) NNT 6.9 (5.5 to 9.4)	2031 participants, 7 studies	Moderate	Downgraded because of issues around dosing, formulation, and imputation
At least 50% pain intensity reduction (DN)[2]	210 per 1000	380 per 1000	RR 1.9 (1.5 to 2.3) NNT 5.9 (4.6 to 6.3)	1277 participants, 6 studies	Moderate	Downgraded because of issues around dosing, formulation, and imputation

Source: Wiffen 2017[15]

1Patient or population: adults with postherpetic neuralgia; **Settings:** community; **Intervention:** gabapentin 1800 mg daily or gabapentin encarbil 1200 mg daily; **Comparison:** placebo. 2 **Patient or population:** adults with peripheral diabetic neuropathy; **Settings:** community; **Intervention:** gabapentin 1800 mg daily or gabapentin encarbil 1200 mg daily; **Comparison:** placebo.

CI = confidence interval; DN = diabetic neuropathy; NNH = number needed to harm; NNH = number needed to harm; PHN = post-herpetic neuralgia; RR = relative risk

Table 10: Improvement in pain – Evidence for pregabalin compared with placebo

Outcome	Probable outcome with placebo	Probable outcome with intervention	NNT or NNH and / or relative effect (95% CI)	No of participants and studies	Quality of the evidence	Comments
At least 50% pain intensity reduction	267 per 1000	373 per 1000	RR 1.36 (0.91 to 2.04)	5 studies, 1900 participants	Unclear	

Source: Wang 2017[13]
Patient or population: adults with neuropathic pain (spinal cord injury, diabetic peripheral neuropathy, post-herpetic neuralgia, HIV- distal sensory polyneuropathy); **Settings:** community; **Intervention:** pregabalin; **Comparison:** placebo
CI = confidence interval; NNH = number needed to harm; NNH = number needed to harm; RR = relative risk

Table 11: Improvement in pain – Evidence for carbamazepine compared with placebo

Outcome	Probable outcome with placebo	Probable outcome with intervention	NNT or NNH and / or relative effect (95% CI)	No of participants and studies	Quality of the evidence	Comments
"Substantial benefit. At least 50% reduction in pain or equivalent"	94 per 1000	608 per 1000	RR 6.5 (3.4 to 12) NNT 1.9 (1.6 to 2.5)	188 participants, 4 studies	Low	Mixed conditions and doses, small, short studies imputation not reported. Evidence considered 'not reliable'.

Source: Wiffen 2014[14]
Patient or population: adults with neuropathic pain (Trigeminal neuralgia, painful diabetic neuropathy, chronic post stroke pain); **Settings:** community; **Intervention:** oral carbamazepine (100 mg to 2400 mg daily); **Comparison:** placebo
CI = confidence interval; NNH = number needed to harm; NNH = number needed to harm; RR = relative risk

Table 12: Improvement in pain – Evidence for tramadol compared with placebo

Outcome	Probable outcome with placebo	Probable outcome with intervention	NNT or NNH and / or relative effect (95% CI)	No of participants and studies	Quality of the evidence	Comments
At least 50% reduction in pain	300 per 1000	530 per 1000	RR 2.2 (1.02 to 4.6) NNT 4.4 (2.9 to 8.8)	265 participants, 3 studies	Low	Downgraded 2 levels due to small number of studies and participants and relatively few events, and several sources of potential bias.

Source: Duehmke 2017[2]
Patient or population: adults with neuropathic pain (any origin); **Settings:** community; **Intervention:** oral tramadol (typically started at a dose of about 100 mg daily and increased over 1 to 2 weeks to a maximum of 400 mg daily); **Comparison:** placebo
CI = confidence interval; NNH = number needed to harm; NNH = number needed to harm; RR = relative risk

FAQ 4: How will the medication affect my quality of life?

Quality of life is (QoL) not explicitly assessed in the systematic reviews of pain included in this report. It is generally assumed that improvement in pain results in better quality of life for the patient. For example Duehmke states that 'Pain intensity reduction of 50% or more correlates with improvements in co-morbid symptoms, function, and quality of life generally.'[2]

The fact that the systematic reviews did not assess quality of life outcomes may also be explained by poor reporting in the primary studies of these outcomes. In this regard, a recent systematic review by Waldfogel and colleagues aimed to assess the effect of pharmacological treatments of diabetic neuropathy on pain and quality of life.[12] This review identified 32 studies that reported quality of life outcomes (covering a range of pharmacological treatments). However, Waldfogel and colleagues commented that many did not report specific QoL values so that the review authors could only count how many studies had statistically significant findings. They stated that pregabalin had the highest number of studies reporting QoL (10 RCTs) of which four had 'statistically significant' findings (not explicitly stated but presumably in favour of pregabalin). Six did not have statistically significant results. They further stated that anticonvulsants had statistically significant results in seven of 18 studies and SNRIs in one of four studies. Their conclusion was that QoL was poorly reported and recommended that future studies assess this outcome. Given these observations, we decided not to explore the primary studies further for this outcome.

FAQ 5: What side effects might I experience?

Table 13 gives an overview of the data identified relating to adverse events. Supporting evidence is presented in Tables 14 to 19. The evidence identified by the reviews was variable in quality. Only evidence relating to gabapentin was rated 'moderate' or 'high' (providing a good indication of the likely effect) with the remaining evidence being generally of lower quality. The same issues of interpretation of results apply to adverse events as discussed above for efficacy outcomes means that comparing results between drugs should be done with caution.

Table 13: Adverse effects – option data

Treatment → **↓ FAQ**	**Tricyclic antidepressants** (amitriptyline)	**SSNRI antidepressants** (duloxetine)	**Calcium channel blocker antiepileptics** (gabapentin, pregabalin)	**Sodium channel blocker antiepileptics** (carbamazepine)	**Tramadol**
Will I get side effects?[1]	In trials approximately 55 of 100 patients taking amitriptyline had an adverse event (36 in the placebo group). Approximately 16 of 100 taking amitriptyline withdrew from trials due to an adverse event (7 in the placebo group).(Table 14)	In trials approximately 73 of 100 patients taking duloxetine had an adverse event (62 in the placebo group). Approximately 11 of 100 taking duloxetine withdrew from trials due to an adverse event (6 in the placebo group). (Table 15)	In trials approximately 63 of 100 taking gabapentin had an adverse event (49 in placebo group). Approximately 11 of 100 taking gabapentin withdrew from trials due to an adverse event (8 in the placebo group). (Table 16) In trials of pregabalin approximately 16 in 100 withdrew from the trial due to an adverse event (7 in	In trials approximately 66 of 100 taking carba-mazepine had an adverse event (27 in placebo group). Approximately 3 of 11 patients taking carba-mazepine withdrew from trials due to an adverse event (0 in the placebo group). (Table 18)	In trials approximately 58 of 100 taking tramadol had an adverse event (34 in placebo group). Approximately 15 of 100 taking tramadol withdrew from trials due to an adverse event (3 in the placebo group). (Table 19)

Treatment → ↓ FAQ	Tricyclic antidepressants (amitriptyline)	SSNRI antidepressants (duloxetine)	Calcium channel blocker antiepileptics (gabapentin, pregabalin)	Sodium channel blocker antiepileptics (carbamazepine)	Tramadol
			the placebo group) (Table 17)		
What side effects might I experience?	Adverse events might include: urinary retention, constipation, dizziness, confusion, postural hypertension, dry mouth, increased sleep, palpitations or rash.[6]	Adverse events might include: nausea, dry mouth, dizziness, somnolence, fatigue, insomnia, constipation, decreased appetite, sweating and rhinitis.[5]	Adverse events for gabapentin might include: somnolence; dizziness; swelling in legs and feet and lack of coordination.[15] For pregabalin these might include: dizziness; swelling in legs and feet; somnolence; weight gain; vertigo; dry mouth; blurred vision; constipation and euphoria.[13]	Adverse events might include giddiness, dizziness and unsteadiness. Gastrointestinal problems such as constipation and nausea have also been noted.[14]	Adverse events might include: nausea, somnolence, constipation, dry mouth, general malaise, dizziness, tiredness, headache, dyspepsia, diarrhoea, sweating, sleep disorders, and micturition problems.[2]
1.All active drugs had statistically significantly more adverse events and associated withdrawals when compared to placebo.However withdrawals due to adverse events for carbamazepine were not compared statistically between groups. 2. Apart from gabapentin evidence was of low quality.					

Table 14: Adverse events – Evidence for amitriptyline compared with placebo

Outcome	Probable outcome with placebo	Probable outcome with intervention	NNT or NNH and / or relative effect (95% CI)	No of participants and studies	Quality of the evidence	Comments

Any adverse event	356 per 1000	550 per 1000	RR 1.5 (1.3 to 1.8) NNH 5.2 (3.6 to 9.1)	519 participants, 6 studies	Unclear	Few studies with large sample sizes
Any serious adverse event	18 per 1000	66 per 1000	Not calculated	236 participants, 2 studies	Unclear	Few studies with large sample sizes
Withdrawal due to adverse events	69 per 1000	157 per 1000	RR 2.23 (1.11 to 4.45)	303 participants, 3 studies	Unclear	Small studies, poor quality

Source: Moore 2015 [6]

Patient or population: adults with neuropathic pain (Cancer-related neuropathic pain, spinal cord injury, painful diabetic neuropathy, postherpetic neuralgia, mixed neuropathic pain, HIV-related neuropathy, post-stroke pain); **Settings:** community; **Intervention:** oral amitriptyline (10 mg to 125 mg daily); **Comparison:** placebo

CI = confidence interval; NNH = number needed to harm; NNH = number needed to harm; RR = relative risk

Table 15: Adverse events – Evidence for duloxetine compared with placebo

Outcome	Probable outcome with placebo	Probable outcome with intervention	NNT or NNH and / or relative effect (95% CI)	No of participants and studies	Quality of the evidence	Comments
Any adverse event	621 per 1000	727 per 1000	RR 1.15 (1.11 to 1.20)	4837 participants, 14 studies	Low	
Any serious adverse event	18 per 1000	15 per 1000	RR 0.81 (0.53 to 1.25)	Not reported	Unclear	
Withdrawal due to adverse events (at 60mg dose)	56 per 1000	109 per 1000	RR 1.95 (1.6 to 2.37)	4837 participants, 14 studies	Low	

Source: Lunn 2014 [5]
Patient or population: adults with neuropathic pain (Painful diabetic neuropathy, fibromyalgia, painful peripheral neuropathy, central neuropathic pain); **Settings:** community; **Intervention:** duloxetine (20 mg to 120 mg daily)**; Comparison:** placebo
CI = confidence interval; NNH = number needed to harm; NNH = number needed to harm; RR = relative risk

Table 16: Adverse events – Evidence for gabapentin compared with placebo

Outcome	Probable outcome with placebo	Probable outcome with intervention	NNT or NNH and / or relative effect (95% CI)	No of participants and studies	Quality of the evidence	Comments
Any adverse event	490 per 1000	630 per 1000	RR 1.3 (1.2 to 1.4) NNH 7.5 (6.1 to 9.6)	4279 participants, 18 studies	Moderate	Many events. Unlikely that research would change this finding
Any serious adverse event	28 per 1000	32 per 1000	RR 1.2 (0.83 to 1.7) NNH not calculated.	3948 participants, 19 studies	Moderate	Small number of events but no suggestion of

Outcome	Probable outcome with placebo	Probable outcome with intervention	NNT or NNH and / or relative effect (95% CI)	No of participants and studies	Quality of the evidence	Comments
						difference
Withdrawal due to adverse events	82 per 1000	110 per 1000	RR 1.4 (1.1 to 1.7) NNH 30 (20 to 66)	4346 participants, 22 studies	High	Unlikely new research would change this finding.

Source: Wiffen 2017 [15]
Patient or population: adults with neuropathic pain (Postherpetic neuralgia, painful diabetic neuropathy, mixed neuropathic pain, radicular leg pain, nerve injury pain, spinal cord injury, phantom limb pain, cancer-related neuropathic pain, HIV-associated sensory neuropathies); **Settings:** community; **Intervention:** gabapentin (20 mg to 120 mg daily); **Comparison:** placebo
CI = confidence interval; NNH = number needed to harm; NNH = number needed to harm; RR = relative risk

Table 17: Adverse events – Evidence for pregabalin compared with placebo

Outcome	Probable outcome with placebo	Probable outcome with intervention	NNT or NNH and / or relative effect (95% CI)	No of participants and studies	Quality of the evidence	Comments
Withdrawal due to adverse events	67 per 1000	156 per 1000	RR 1.89 (1.07 to 3.34)	8 studies, 2215 participants	Unclear	

Source: Wang 2017 [13]
Patient or population: adults with neuropathic pain (Postherpetic neuralgia, painful diabetic neuropathy, mixed neuropathic pain, radicular leg pain, nerve injury pain, spinal cord injury, phantom limb pain, cancer-related neuropathic pain, HIV-associated sensory neuropathies); **Settings:** community; **Intervention:** pregabalin (unclear dose); **Comparison:** placebo
CI = confidence interval; NNH = number needed to harm; NNH = number needed to harm; RR = relative risk

Table 18: Adverse events – Evidence for carbamazepine compared with placebo

Outcome	Probable outcome with placebo	Probable outcome with intervention	NNT or NNH and / or relative effect (95% CI)	No of participants and studies	Quality of the evidence	Comments
Any adverse event	270 per 1000	660 per 1000	RR 2.4 (1.9 to 3.2) NNH 2.6 (2.1 to 3.5)	346 participants, 4 studies	Low	Cross-over studies. Denominator was all potentially exposed
Any serious adverse event	NR	3	Not calculated	46 participants, 2 studies	Very low	Denominator was all potentially exposed
Withdrawal due to adverse events	0 per 1000	30 per 1000	Not calculated	523 participants, 8 studies	Very low	Cross-over studies. Denominator was all potentially Exposed.

Source: Wiffen 2014[14]
Patient or population: adults with neuropathic pain (Trigeminal neuralgia, painful diabetic neuropathy, chronic post stroke pain); **Settings:** community; **Intervention:** oral carbamazepine (100 mg to 2400 mg daily; **Comparison:** placebo
CI = confidence interval; NNH = number needed to harm; NNH = number needed to harm; RR = relative risk

Table 19: Adverse events – Evidence for tramadol compared with placebo

Outcome	Probable outcome with placebo	Probable outcome with intervention	NNT or NNH and / or relative effect (95% CI)	No of participants and studies	Quality of the evidence	Comments
Any adverse event	340 per 1000	580 per 1000	RR 1.6 (1.2 to 2.1) NNH 4.2 (2.8 to 8.3)	266 participants, 4 studies	Low	Small number of studies and participants and

Outcome	Probable outcome with placebo	Probable outcome with intervention	NNT or NNH and / or relative effect (95% CI)	No of participants and studies	Quality of the evidence	Comments
Any serious adverse event	4 serious adverse events reported in total			Not all studies reported serious adverse events	Very low	relatively few events, and several sources of potential bias.
Withdrawal due to adverse events	30 per 1000	150 per 1000	RR 4.1 (2.0 to 8.4) NNH 8.2 (5.8 to 14)	485 participants, 6 studies	Low	

Source: Duehmke (2017)[2]
Patient or population: adults with neuropathic pain (any origin); **Settings:** community; **Intervention:** oral carbamazepine (100 mg to 2400 mg daily**; Comparison**: placebo
CI = confidence interval; NNH = number needed to harm; NNH = number needed to harm; RR = relative risk

FAQ 6: Could I become addicted to the drug?

Table 20 gives an overview of the data identified relating to addiction potential.

Table 20: Addiction potential – option data

Treatment → **↓ FAQ**	**Tricyclic antidepressants** (amitriptyline)	**SSNRI antidepressants** (duloxetine)	**Calcium channel blocker antiepileptics** (gabapentin, pregabalin)	**Sodium channel blocker antiepileptics** (carbamazepine)	**Tramadol**
Could I become addicted to the drug?	Amitriptyline isn't addictive but you can get extra side effects if you stop taking it suddenly.[7]	Duloxetine is not addictive but to avoid side effects, the dose should be reduced over at least 1 to 2 weeks.[3]	Gabapentin is not addictive but to avoid side effects your medicines should be decreased slowly over a period of time.[17]	Withdrawal symptoms have not been reported.[4]	Tramadol is addictive. If you need to take it for a long time your body can become tolerant to it. That means you need higher doses to control your pain. If you want to stop taking tramadol, talk to your doctor first. The dose will usually be reduced gradually so you don't get unpleasant withdrawal effects.[8]

4. DISCUSSION

4.1 STRENGTH, LIMITATIONS AND UNCERTAINTIES

Hand searching for relevant German guidelines found one relevant guideline on neuropathic pain.[19] As it was undergoing an update at the time of writing this report (October 2018), it was not used as a source of evidence.

The evidence presented in this report is based on recent systematic reviews particularly from Cochrane. For the majority of the reviews the main focus is on the effectiveness of the treatment at reducing pain. In regard to improvements in pain, with the exception of duloxetine and gabapentin, evidence for the treatments investigated was deemed to be of low quality and therefore unreliable. In the case of amitriptyline, it was unclear how much pain could be improved using this agent. Another limitation highlighted by the reviews is that primary studies were often quite short (for example the review of gabapentin indicated that primary studies lasted from 4 to 12 weeks).[15] The effect of treatments in the long-term of chronic pain is less studied.

A further limitation is that the evidence here collected offers little information on changes in functionality and daily activities. Furthermore, the reviews do not generally assess quality of life in any detail. We decided not to explore the primary studies for quality of life outcomes as we found evidence indicating that these outcomes were poorly reported in primary studies.

Although information on adverse effects is available from primary studies, several reviews highlight the poor quality of evidence and the resulting uncertainty around frequency of adverse events (particularly of serious ones). Patients will need to be fully informed of any risks and uncertainties surrounding adverse events. Whilst patients may be able to use the information given to help decide on a course of treatment, clinicians will still need to take account of individual patient contraindications for use and individual risks of severe adverse events. Furthermore, patients will need to be encouraged to report any adverse events they experience during treatment and to know which of these constitute an emergency.

The above variation in quality, taken together with the fact that the reviews covered different populations with neuropathic pain, means that comparing between drugs should be done with caution.

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APPENDIX 1: SEARCH STRATEGY

Systematic reviews and guideline search results

Database	Dates	Results
CDSR	2012 - Issue 3, Mar 2018	500
DARE	2012 - Issue 2, Apr 2015	328
HTA	2012 - Issue 4, Oct 2016	56
NHS Evidence	01/01/2012 - 13/03/2018	477
KSR Evidence	2016 - 2018	304
GIN	all years	264
Total		**1929**
Total after de-duplication		**1516**

Search strategies

Cochrane Database of Systematic Reviews (CDSR) (Wiley): Issue 3 of 12, March 2018
Database of Abstracts of Reviews of Effects (DARE) (Wiley): Issue 2 of 4, April 2015
Health Technology Assessment Database (HTA) (Wiley): Issue 4 of 4, October 2016
Searched: 13.3.18

#1 MeSH descriptor: [Peripheral Nervous System Diseases] explode all trees 81
#2 MeSH descriptor: [Neuralgia] explode all trees 1045
#3 MeSH descriptor: [Diabetic Neuropathies] explode all trees 1391
#4 MeSH descriptor: [Polyneuropathies] explode all trees 324
#5 MeSH descriptor: [Mononeuropathies] explode all trees 853
#6 MeSH descriptor: [Complex Regional Pain Syndromes] explode all trees 238
#7 MeSH descriptor: [Somatosensory Disorders] explode all trees 894
#8 MeSH descriptor: [Pain, Postoperative] explode all trees 12050
#9 (neuralg* or neurodynia* or dysesthesia):ti,ab,kw 1902
#10 ((nerve* or neuropath* or neuro-path* or mononeuropath* or polyneuropath* or diabat* or peripheral or central or multifocal or mixed) near/3 (pain* or hurt or hurting or hurts or sore or soreness or tender* or discomfort* or ache* or aching or agony or nociception or nociperception or algiatry)):ti,ab,kw 5924
#11 (pain* near/3 (post-treatment* or "post treatment*" or posttreatment* or surg* or post-op* or postop* or "post op*")):ti,ab,kw 25479
#12 ((peripheral or central or multifocal or mixed) near/3 ("nerve disease*" or "nerve disorder*" or "nervous system disease*")):ti,ab,kw 1090
#13 ("PNS disease*" or "PNS disorder*"):ti,ab,kw 4
#14 (CRPS* or "complex regional pain syndrome*"):ti,ab,kw 357
#15 ("posttrauma* dystroph*" or "post trauma* dystroph*" or "reflex* neurovascular dystroph*" or "posttrauma* osteoporo*" or "post trauma* osteoporo*"):ti,ab,kw 15
#16 (sympathetic near/2 (syndrom* or dystroph*)):ti,ab,kw 227
#17 ("algo dystroph*" or "algo neurodystroph*" or sudeck* near/2 atroph* or algodystroph* or algoneurodystroph*):ti,ab,kw 34
#18 (("shoulder hand" or "shoulder arm") near/2 (syndrom* or dystroph*)):ti,ab,kw 73
#19 (cervical near/2 "sympathetic dystroph*"):ti,ab,kw 0

#20 (causalgia or (pain* near/2 deafferentation)):ti,ab,kw 39
#21 ((phantom or fantom or amputat* or missing or lost or remov* or absent) near/3 (limb* or extremit* or leg* or arm* or foot or feet or hand* or organ* or breast* or sensation*)):ti,ab,kw 1328
#22 (phantom-limb* or PLP):ti,ab,kw 224
#23 (sensation* near/3 (diminished* or pinprick or "light touch")):ti,ab,kw 172
#24 ("position sense disorder*" or "proprioceptive disorder*"):ti,ab,kw 2
#25 ("sensation disorder*"):ti,ab,kw 292
#26 ((somatosensory or somatic or thermal) near/3 (disorder* or diseas*)):ti,ab,kw 266
#27 #20-#26 Publication Year from 2012 to 2018 14720

CDSR = 500
DARE = 328
HTA = 56

KSR Evidence (Internet): Database last updated 2018 March 13
www.ksrevidence.com
Searched: 13.03.18

(neuropath* AND pain) OR ("peripheral nervous" OR "peripheral nerve" OR neuralgia OR polyneuropath* OR mononeuropath*) **304**

Guideline International Library (GIN) (Internet): up to 13 March 2018
http://www.g-i-n.net

Search terms	**Results: 2012-2018**
pain	247
neuralgia	3
neuropathy	12
neuropathies	3
polyneuropathy	3
polyneuropathies	0
mononeuropathy	0
mononeuropathies	2
"peripheral nervous system"	6
Total retrieved	**276**
Total (without duplicates)	**264**

NICE Evidence Search: limited to guidance and SRs only (Internet): 2018/03/13
Searched 13.3.18
https://www.evidence.nhs.uk/

Search terms	Results (Guidance): 2012-2018/03/13
"neuropathic pain"	332
"neuropathy pain"	31
"peripheral nervous system"	98
neuralgia	218
Total retrieved	**679**
Total (without duplicates)	**477**