Complete Summary

GUIDELINE TITLE

Pharmacologic management of neuropathic pain: evidence-based recommendations.

BIBLIOGRAPHIC SOURCE(S)

Dworkin RH, O'Connor AB, Backonja M, Farrar JT, Finnerup NB, Jensen TS, Kalso EA, Loeser JD, Miaskowski C, Nurmikko TJ, Portenoy RK, Rice AS, Stacey BR, Treede RD, Turk DC, Wallace MS. Pharmacologic management of neuropathic pain: evidence-based recommendations. Pain 2007 Dec 5;132(3):237-51. [135 references] PubMed

GUIDELINE STATUS

This is the current release of the guideline.

This updates a previous version: Dworkin RH, Backonja M, Rowbotham MC, Allen RR, Argoff CR, Bennett GJ, Bushnell MC, Farrar JT, Galer BS, Haythornthwaite JA, Hewitt DJ, Loeser JD, Max MB, Saltarelli M, Schmader KE, Stein C, Thompson D, Turk DC, Wallace MS, Watkins LR, Weinstein SM. Advances in neuropathic pain: diagnosis, mechanisms, and treatment recommendations. Arch Neurol 2003 Nov;60(11):1524-34. [70 references] PubMed

** REGULATORY ALERT **

FDA WARNING/REGULATORY ALERT

Note from the National Guideline Clearinghouse: This guideline references a drug(s) for which important revised regulatory information has been released.

- December 12, 2007, Carbamazepine: The U.S. Food and Drug Administration (FDA) has provided recommendations for screening that should be performed on specific patient populations before starting treatment with carbamazepine.
- May 2, 2007, Antidepressant drugs: Update to the existing black box warning on the prescribing information on all antidepressant medications to include warnings about the increased risks of suicidal thinking and behavior in young adults ages 18 to 24 years old during the first one to two months of treatment.

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

Neuropathic pain (NP)

Note: The treatment of trigeminal neuralgia (tic douloureux), for which there are distinct treatment recommendations, was not considered. On the basis of recent recommendations for the diagnosis of neuropathic pain, conditions for which there is no evidence of lesions affecting nervous system somatosensory pathways (e.g., fibromyalgia, irritable bowel syndrome) were also not considered.

GUIDELINE CATEGORY

Management
Treatment

CLINICAL SPECIALTY

Anesthesiology
Family Practice
Geriatrics
Internal Medicine
Neurological Surgery
Neurology
Obstetrics and Gynecology
Oncology
Orthopedic Surgery
Pharmacology
Physical Medicine and Rehabilitation
Podiatry
Psychiatry
Psychology
Rheumatology
Sports Medicine
Urology

INTENDED USERS

Advanced Practice Nurses
Nurses
Pharmacists
Physician Assistants
Physicians
Podiatrists

GUIDELINE OBJECTIVE(S)

- To briefly review the results of randomized clinical trials (RCTs) examining medications for the treatment of neuropathic pain (NP)
- To present up-to-date evidence-based guidelines for the pharmacologic management of NP that take into account clinical efficacy, adverse effects, impact on health-related quality of life, convenience, and costs
- To provide specific recommendations for the use of these medications

TARGET POPULATION

Adult patients with neuropathic pain

INTERVENTIONS AND PRACTICES CONSIDERED

Diagnosis/Evaluation

1. Assessment including identifying the underlying disease, response to prior therapies, comorbid conditions, and presence of depression and anxiety
2. Frequent reassessment of pain and its adverse effects

Pharmacological Treatment/Management

1. Patient education and support
2. First-line medications
    - Tricyclic antidepressants (TCAs)
    - Selective serotonin and norepinephrine reuptake inhibitors (SSNRIs)
    - Calcium channel alpha 2-delta ligands
    - Topical lidocaine
3. Second-line medications
    - Opioid analgesics
    - Tramadol
4. Third-line medications
    - Antiepileptics
    - Antidepressants
    - Mexiletine, N-methyl- D-aspartate (NMDA) receptor antagonists, and topical capsaicin

MAJOR OUTCOMES CONSIDERED

- Clinical effectiveness, measured by pain relief
- Adverse effects/drug interactions
- Ease of use
- Health-related quality of life

- Cost

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases
Searches of Unpublished Data

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Relevant publications were identified through Medline searches (1966–2007), examination of reference lists of relevant published articles and book chapters, and personal knowledge of the authors. Only studies of oral or topical pharmacotherapy in adults were considered, and the recommendations do not apply to the treatment of pediatric neuropathic pain. The treatment of trigeminal neuralgia (tic douloureux), for which there are distinct treatment recommendations was not considered. On the basis of recent recommendations for the diagnosis of neuropathic pain (NP), conditions for which there is no evidence of lesions affecting nervous system somatosensory pathways (e.g., fibromyalgia, irritable bowel syndrome) were also not considered.

In evaluating the literature and developing recommendations, the Cochrane Database and other recent systematic reviews were emphasized. Efficacy was considered to have been demonstrated if the results of a randomized clinical trial (RCT) found statistically significantly greater pain reduction versus placebo for the primary outcome measure and was evaluated according to the Oxford Centre for Evidence-based Medicine levels of evidence. All medications with efficacy supported by at least one systematic review or positive placebo-controlled or dose-response RCT (levels of evidence criterion 1b or better), in which reduction of chronic NP was a primary or co-primary endpoint were considered for inclusion. Published data, unpublished data (when available), and the clinical experience of the authors were used to evaluate each of these medications in terms of degree of efficacy, safety, tolerability, drug interactions, ease of use, and impact on health-related quality of life.

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

1a: Systematic review (SR) (with homogeneity) of randomized controlled trials

1b: Individual RCT (with narrow Confidence Interval)

1c: All or none (met when all patients died before the treatment because available, but now some survive on it; or when some patients died before the treatment became available, but none now die on it)

2a: SR (with homogeneity) of cohort studies

2b: Individual cohort study (including low quality RCT; e.g., <80% follow-up)

2c: "Outcomes" Research; Ecological studies

3a: SR (with homogeneity) of case-control studies

3b: Individual Case-Control Study

4: Case-series (and poor quality cohort and case-control studies)

5: Expert opinion without explicit critical appraisal, or based on physiology, bench research, or "first principles"

Source: Oxford Centre for Evidence-based Medicine. Levels of evidence and grades of recommendation. Available at: http://www.cebm.net/levels_of_evidence.asp

METHODS USED TO ANALYZE THE EVIDENCE

Review
Review of Published Meta-Analyses

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Not stated

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus (Consensus Development Conference)

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

The consensus meeting on which these treatment recommendations are based and the preparation of this article were conducted under the auspices of the International Association for the Study of Pain (IASP) Neuropathic Pain Special Interest Group with additional support provided by the Neuropathic Pain Institute, both of which have received unrestricted support for their activities from multiple pharmaceutical companies. No individuals employed by pharmaceutical companies were involved in the consensus meeting on which these recommendations are based or in the preparation of this article. Prior to the consensus meeting, all participants were provided with copies of existing treatment guidelines, systematic reviews and meta-analyses, and recently published randomized clinical trials (RCTs). This literature and the authors' clinical and research experience

were reviewed during the consensus meeting. Systematic reviews and RCTs published after the meeting were reviewed subsequently.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

A: Consistent level 1 studies

B: Consistent level 2 or 3 studies ***or*** extrapolations from level 1 studies

C: Level 4 studies ***or*** extrapolations from level 2 or 3 studies

D: Level 5 evidence ***or*** troublingly inconsistent or inconclusive studies of any level

Source: Oxford Centre for Evidence-based Medicine. Levels of evidence and grades of recommendation. Available at: http://www.cebm.net/levels_of_evidence.asp

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Not stated

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Grades of recommendation (A-D) and levels of evidence (1a-5) are defined at the end of the "Major Recommendations" field.

General Management Considerations and Recommendations

Assessment of neuropathic pain (NP) should focus on identifying and treating the underlying disease processes and peripheral or central nervous system lesions, response to prior therapies, and comorbid conditions that can be affected by therapy. Particular attention should be paid to identifying coexisting depression, anxiety, sleep disturbances, and other adverse impacts of NP on health-related quality of life, and both pain and its adverse effects should be reassessed frequently. Patient education and support are critical components of the successful management of NP. Careful explanation of the cause of NP and the treatment plan are essential. Patient and provider expectations regarding treatment effectiveness and tolerability must be discussed, and realistic treatment goals should be established with patients. Non-pharmacologic methods of coping with pain should

be discussed, including the importance of stress reduction, good sleep hygiene, physical therapy, and other potentially useful interventions.

There is insufficient evidence to rank first-line medications for NP by their degree of efficacy or safety. Clinicians must consider several other factors when selecting a specific medication for a patient with NP, including: (1) the potential for adverse outcomes associated with medication-related side effects; (2) potential drug interactions; (3) comorbidities that may also be relieved by the non-analgesic effects of the medication (e.g., sleep disturbance, depression, anxiety); (4) costs associated with therapy; (5) the potential risks of medication abuse; and (6) the risks of intentional and unintentional overdose. These potentially competing factors must be prioritized according to the specific needs of each patient with NP.

Individual variation in the response to the medications used to treat NP is substantial and unpredictable. Although evidence-based recommendations encourage the use of specific medications, the overall approach should be recognized as a stepwise process intended to identify the medication, or medication combination, that provides the greatest pain relief and fewest side effects for a given patient (see the Table below). If an adequate trial of one medication fails to adequately relieve pain or causes intolerable side effects, treatment should be discontinued and a different medication should be selected for a trial. If a medication is well tolerated and provides partial pain relief, it should be continued and a second medication with a distinct mechanism of action added.

In addition to potential additive analgesic benefits, combination therapy may provide analgesia more quickly by combining a medication with a rapid onset of effect with one that requires several weeks of treatment before maximum benefit is achieved. These potential advantages of combination therapy must be weighed against the possibility of additive adverse effects, drug interactions, increased cost, and reduced adherence to a more complex treatment regimen.

Table - Stepwise Pharmacologic Management of Neuropathic Pain (NP)

Step 1 • Assess pain and establish the diagnosis of NP [Dworkin et al., 2003; Cruccu et al., 2004); if uncertain about the diagnosis, refer to a pain specialist or neurologist. • Establish and treat the cause of NP; if uncertain about availability of treatments addressing NP etiology, refer to appropriate specialist. • Identify relevant comorbidities (e.g., cardiac, renal, or hepatic disease, depression, gait instability) that might be relieved or exacerbated by NP treatment, or that might require dosage adjustment or additional monitoring of therapy. • Explain the diagnosis and treatment plan to the patient, and establish realistic expectations. **Step 2** • Initiate therapy of the disease causing NP, if applicable.

- Initiate symptom treatment with one or more of the following:
    - A secondary amine tricyclic antidepressant (TCA) (nortriptyline, desipramine) or a selective serotonin and norepinephrine reuptake inhibitor (SSNRI) (duloxetine, venlafaxine)
    - A calcium channel alpha 2-sigma ligand, either gabapentin or pregabalin
    - For patients with localized peripheral NP: topical lidocaine used alone or in combination with one of the other first-line therapies
    - For patients with acute neuropathic pain, neuropathic cancer pain, or episodic exacerbations of severe pain, and when prompt pain relief during titration of a first-line medication to an efficacious dosage is required, opioid analgesics or tramadol may be used alone or in combination with one of the first-line therapies
- Evaluate patient for non-pharmacologic treatments, and initiate if appropriate.

Step 3

- Reassess pain and health-related quality of life frequently.
- If substantial pain relief (e.g., average pain reduced to $\leq$3/10) and tolerable side effects, continue treatment.
- If partial pain relief (e.g., average pain remains $\geq$4/10) after an adequate trial (see Table 3 in the original guideline document), add one of the other first-line medications.
- If no or inadequate pain relief (e.g., <30% reduction) at target dosage after an adequate trial (see Table 3 in the original guideline document), switch to an alternative first-line medication.

Step 4

If trials of first-line medications alone and in combination fail, consider second- and third-line medications or referral to a pain specialist or multidisciplinary pain center.

First-line Medications

Three medications or medication classes are recommended as first-line treatment for patients with NP (**grade A recommendation**). Table 2 in the original guideline document summarizes treatment selection considerations. Prescribing information for each of these medications—including starting dosage, titration requirements, target dosage, and duration of an adequate trial—is provided in Table 3 of the original guideline document.

Tricyclic Antidepressants (TCAs) and Selective Serotonin and Norepinephrine Reuptake Inhibitors (SSNRIs)

TCAs are typically inexpensive and usually administered once daily. The presence of depression is not required for the analgesic effects of these medications, although they may be particularly useful in patients with inadequately treated depression. The most common side effects of TCAs include sedation, anticholinergic effects (e.g., dry mouth, constipation, and urinary retention), and orthostatic hypotension. Secondary amine TCAs (nortriptyline and desipramine)

are preferred because they are better tolerated than tertiary amine TCAs (amitriptyline and imipramine) but have comparable analgesic efficacy. Amitriptyline in particular should be avoided in elderly patients.

The decision to start a TCA should also consider the possibility of cardiac toxicity. Data suggest that the lowest effective dosage of a TCA should be used in all patients with NP, and that TCAs should be avoided in patients who have ischemic heart disease or an increased risk of sudden cardiac death. A screening electrocardiogram (ECG) is recommended before beginning treatment with TCAs in patients over 40 years of age. TCAs should be used cautiously in patients at risk for suicide or accidental death from overdose. They can cause or exacerbate cognitive impairment and gait disturbances in elderly patients, and may predispose to falls. Toxic TCA levels may result if TCAs are administered together with medications that inhibit cytochrome P450 2D6, such as selective serotonin reuptake inhibitors (SSRIs).

Starting doses of TCAs should be low, and the dosage should be titrated slowly until pain is adequately controlled or side effects limit continued titration (see Table 3 in the original guideline document). Although monitoring medication levels is not usually necessary, it may reduce the risk of cardiac toxicity at dosages greater than 150 mg/day.

Duloxetine is an SSNRI that inhibits the reuptake of both serotonin and norepinephrine. It has demonstrated significantly greater pain relief compared with placebo in patients with painful diabetic peripheral neuropathy (DPN) but it has not been studied in other types of NP. Duloxetine has a generally favorable side effect profile and dosing is simple. Nausea is the most common side effect, but it occurs less frequently if treatment is initiated at 30 mg/day and titrated after one week to 60 mg/day, an efficacious dosage at which pain relief can occur within one week (see Table 3 in the original guideline document). As a new medication, there is limited long-term safety information and efficacy data are limited to studies of painful DPN.

Venlafaxine is an SSNRI that inhibits serotonin reuptake at lower dosages and both serotonin and norepinephrine reuptake at higher dosages. Randomized clinical trials (RCTs) in patients with painful DPN and painful polyneuropathies of various types including DPN demonstrated efficacy at dosages of 150 to 225 mg/day. RCTs in other populations, including those with post-mastectomy pain, various peripheral and central NP conditions, and post herpetic neuropathy (PHN), demonstrated inconsistent or negative results. In one RCT, 5% of venlafaxine-treated patients developed ECG changes, and monitoring is therefore recommended in patients with cardiovascular risk factors. Venlafaxine is available in both short- and long-acting formulations. Two-to-four weeks is often required to titrate to an effective dosage, and patients should be tapered gradually from venlafaxine because of the risk of discontinuation syndrome (see Table 3 in the original guideline document).

Calcium Channel alpha 2-delta Ligands

Gabapentin is generally safe, has no clinically important drug interactions, and is available in generic formulations. The main dose-limiting side effects are somnolence and dizziness, which are reduced by gradual dosage titration, and

peripheral edema. In some patients, particularly the elderly, gabapentin can cause or exacerbate cognitive or gait impairment. Several weeks can be required to reach an effective dosage, which is usually between 1800 and 3600 mg/day (administered in three divided doses, increasing the night-time dose preferentially). Dosage reduction is necessary in patients with renal insufficiency. The onset of activity can be seen as early as the second week of therapy when titration is rapid, but peak effect usually occurs approximately two weeks after a therapeutic dosage is achieved. Therefore, an adequate trial may require two months or more (see Table 3 in the original guideline document).

Pregabalin produces dose-dependent side effects similar to those of gabapentin. It has also demonstrated anxiolytic effects in RCTs of generalized anxiety disorder, which may provide additional benefit in patients with chronic pain. Like gabapentin, it has no clinically important drug interactions but requires dosage reduction in patients with renal impairment. Studies indicate that treatment can be initiated at 150 mg/day (in either two or three divided doses), although a starting dose of 75 mg at bedtime is used by some clinicians to reduce the likelihood of early side effects in elderly patients and in others especially prone to side effects (see Table 3 in the original guideline document). The potential for twice daily dosing and the linear pharmacokinetics of pregabalin may contribute to relatively greater ease of use compared with gabapentin, but the overall efficacy and tolerability of these two medications appear similar. However, onset of pain relief with pregabalin can be more rapid than with gabapentin because its starting dosage of 150 mg/day is efficacious. Upward dosage titration can reach 300 mg/day within one to two weeks, and the maximum benefits typically occur after two weeks of treatment at target dosages of 300 to 600 mg/day. Because it is a new medication, long-term safety of pregabalin is not as well established as it is for gabapentin.

Topical Lidocaine

As a topical preparation, lidocaine patch 5% is recommended for patients with localized peripheral NP but not for patients with central NP. When used as recommended, the only side effects that occur with the lidocaine patch 5% are mild skin reactions (e.g., erythema and localized rash). Blood levels are minimal with the approved maximum dosing of three patches/day applied for 12 h and also when four patches/day are applied for 18 h. Nonetheless, use of the lidocaine patch 5% should be avoided in patients receiving oral Class I antiarrhythmic medications (e.g., mexiletine) and in patients with severe hepatic dysfunction, in whom excessive blood concentrations are theoretically possible.

The efficacy of lidocaine gel was demonstrated in patients with PHN and allodynia, but not in patients with human immunodeficiency virus (HIV) neuropathy. Because of its safety and ease of use, lidocaine gel can be considered when the lidocaine patch 5% is not available, application of a patch is problematic, or the cost of the lidocaine patch 5% precludes its use.

Second-line Medications That Can Be Used for First-line Treatment in Select Clinical Circumstances

Opioid analgesics and tramadol have demonstrated efficacy in multiple RCTs in patients with NP, and when patients do not have a satisfactory response to the

first-line medications alone or in combination, opioid agonists can be used as second-line treatment alone or in combination with the first-line medications (**grade A recommendation**).

In select clinical circumstances, opioid analgesics and tramadol can also be considered for first-line use (see the Table below).

Table – Circumstances in Which Opioid Analgesics and Tramadol Can Be Considered for First-line Treatment of Neuropathic Pain

- During titration of a first-line medication to an efficacious dosage for prompt pain relief
- Episodic exacerbations of severe pain
- Acute neuropathic pain
- Neuropathic cancer pain

Opioid Analgesics

Treatment of chronic NP with opioid agonists should generally be reserved for patients who have failed to respond to or cannot tolerate the first-line medications. This recommendation is consistent with published guidelines for the use of opioids in chronic non-cancer pain that have been prepared by various groups. Opioids can be considered for first-line use in select circumstances (see Table above). Typically, such first-line use of opioids should be reserved for circumstances in which suitable alternatives cannot be identified and should be on a short-term basis to the extent possible.

Before initiating treatment with opioid analgesics, clinicians should identify and address risk factors for abuse, which include active substance abuse, prior history of opioid or other drug abuse, other major psychiatric pathology, and family history of substance abuse. Response to treatment, side effects, and signs of opioid misuse or abuse should be monitored on a regular basis, as has been described in guidelines for opioid use in chronic non-cancer pain. It is recommended that clinicians without opioid expertise obtain consultation from appropriate specialists in developing a treatment plan for challenging patients.

The most common opioid-related side effects are nausea, constipation, and sedation. Although nausea and sedation typically decrease after several weeks of treatment, constipation may not; it usually requires concurrent management, especially in the elderly or other groups with risk factors for this problem. Opioids should be used cautiously in patients at risk for suicide or accidental death from overdose. In elderly patients, opioids can also cause or exacerbate cognitive impairment and gait disturbances, increasing the risk of falls. In contrast to abuse or addiction, physical dependence develops in all patients chronically treated with opioid analgesics, and patients must be advised that they should not discontinue these medications on their own.

The effective opioid dosage varies widely among patients, and either of two strategies for the initiation of treatment can be used depending on the specific clinical circumstances. For opioid-naive patients, treatment can be initiated with

an oral immediate-release opioid at a dose equivalent to 10–15 mg of morphine every 4 h or on an as needed basis, with conversion to a long-acting opioid after a few days, when the approximate daily dosage has been identified (see Table 3 in the original guideline document). Treatment can also be initiated with a long-acting opioid (e.g., extended-release oral morphine or oxycodone, or transdermal fentanyl). Fixed-schedule dosing with a long-acting opioid is generally preferred, although RCTs in patients with NP are needed to compare the efficacy and safety of short versus long-acting opioids. Titration should continue until satisfactory pain relief is achieved or unacceptable side effects persist despite attempts to improve tolerability (e.g., laxatives for constipation). Treatment with a short-acting opioid on an as needed basis may be appropriate to continue in selected patients with NP who have episodes of markedly increased pain; until the role of such "rescue" treatment has been more adequately characterized for patients with NP, treatment approaches used for patients with other types of chronic pain, including cancer pain, can be followed. As with all of the medications recommended for NP, the lowest effective dosages of opioid analgesics should be used. If an adequate trial of therapy has not produced clinically meaningful pain relief, patients should be tapered off their opioid analgesic and an alternative treatment administered.

Tramadol

As with opioids, tramadol is associated with abuse potential; although rates of tramadol abuse have remained very low despite new branded and generic formulations, some recent reports suggest that the rate of recreational tramadol use may be rising.

The most common side effects of tramadol are somnolence, constipation, dizziness, nausea, and orthostatic hypotension, which occur more frequently with rapid dosage escalation. Tramadol can cause or exacerbate cognitive impairment and gait disturbances in elderly patients. It can also precipitate seizures in patients with a history of seizures or in those receiving medications that reduce seizure threshold. Concurrent use of other serotonergic medications (including SSRIs and SSNRIs) may increase the risk of serotonin syndrome, and combination therapy with these medications must be undertaken cautiously.

As for opioid analgesics, tramadol is recommended primarily for patients who have not responded to the first-line medications but it can also be considered for first-line use in select clinical circumstances (see the Table above). Tramadol is available in both short- and long-acting formulations; for the short-acting formulation, the starting dosage is 50 mg once or twice daily, with gradual titration to a maximum of 400 mg/day. Dosage reduction is necessary in patients with renal or hepatic disease and in the elderly (see Table 3 in the original guideline document).

Generally Third-line Medications

There are a number of other medications that would generally be used as third-line treatments but that could also be used as second-line treatments in some circumstances (e.g., when treatment with an opioid agonist is not indicated or when the patient's treatment history suggests greater potential for their effectiveness). These medications include certain other antiepileptic

(carbamazepine, lamotrigine, oxcarbazepine, topiramate, valproic acid) and antidepressant (bupropion, citalopram, paroxetine) medications, mexiletine, N-methyl- D-aspartate (NMDA) receptor antagonists, and topical capsaicin. Recommendations for their use are based on efficacy in a single RCT or inconsistent results from multiple RCTs and the clinical experience of the authors (**grade B recommendation**). Refer to the original guideline document for information regarding third-line medications.

Additional Recommendations for Central NP

Based on the results of a small number of RCTs, the following specific medications should be considered for patients with central NP: TCAs for central post-stroke pain; calcium channel alpha 2-delta ligands for spinal cord injury pain; and cannabinoids for NP associated with multiple sclerosis (**grade B recommendation**). Lack of long-term follow-up data, limited availability, and concerns over precipitating psychosis or schizophrenia, especially in individuals with environmental or genetic risk factors, restrict the use of cannabinoids to second-line therapy for patients with multiple sclerosis NP at present, and additional trials are needed to further establish their efficacy and safety.

Many patients with central NP either do not have one of these diagnoses or require alternative therapy. In these situations, the first- and second-line medications recommended for peripheral NP can be considered for the treatment of central NP (except for topical lidocaine). However, it must be acknowledged that the evidence base for such treatment is limited.

Conclusions

TCAs, SSNRIs, calcium channel alpha 2-delta ligands, and topical lidocaine have demonstrated efficacy in NP and are recommended as first-line medications. In patients who have failed to respond to these first-line medications alone and in combination, opioid analgesics or tramadol can be used as a second-line treatment alone or in combination with one of the first-line medications. Opioid analgesics and tramadol can also be considered for first-line use in select clinical circumstances.

Patients who have not responded adequately to these medications used alone and in combination can be treated with one or more other recommended medications. For patients who have not responded adequately to pharmacologic management or those who have pain that is associated with challenging comorbidities or with a high level of disability or distress, prompt consultation with a pain specialist or multidisciplinary pain management center is recommended, including consideration of a broad array of non-pharmacologic therapies and invasive treatments.

It is important to emphasize that pharmacologic management of the patient with chronic NP should be considered an integral component of a more comprehensive approach that also includes non-pharmacologic treatments. Non-pharmacologic treatments for NP require increased attention and evaluation in controlled trials in which they are administered alone and also in combination with pharmacologic therapies.

Definitions:

Grades of Recommendations

A: Consistent level 1 studies

B: Consistent level 2 or 3 studies ***or*** extrapolations from level 1 studies

C: Level 4 studies ***or*** extrapolations from level 2 or 3 studies

D: Level 5 evidence ***or*** troublingly inconsistent or inconclusive studies of any level

Levels of Evidence

1a: Systematic review (SR) (with homogeneity) of randomized controlled trials

1b: Individual RCT (with narrow Confidence Interval)

1c: All or none (met when all patients died before the treatment because available, but now some survive on it; or when some patients died before the treatment became available, but none now die on it)

2a: SR (with homogeneity) of cohort studies

2b: Individual cohort study (including low quality RCT; e.g., <80% follow-up)

2c: "Outcomes" Research; Ecological studies

3a: SR (with homogeneity) of case-control studies

3b: Individual Case-Control Study

4: Case-series (and poor quality cohort and case-control studies)

5: Expert opinion without explicit critical appraisal, or based on physiology, bench research, or "first principles"

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

REFERENCES SUPPORTING THE RECOMMENDATIONS

References open in a new window

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

- Recommendations for first-line treatments are consistent with the results of multiple randomized clinical trials (RCTs) (Oxford Centre for Evidence-based Medicine grade A recommendation) and the clinical experience of the authors.
- Recommendations for opioid analgesics and tramadol as generally second-line treatments are consistent with the results of multiple RCTs (grade A recommendation), the clinical experience of the authors, and published guidelines and recommendations for their use.
- Recommendations for other medications that would generally be used as third-line treatments but that could also be used as second-line treatments in some circumstances are based on a single positive RCT or inconsistent results from multiple trials (grade B recommendation) and the authors' clinical experience.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Effective and appropriate use of medication for the treatment/management of chronic neuropathic pain based on clinical effectiveness (significant pain reduction), minimal adverse effects, improvement in quality of life, and cost

POTENTIAL HARMS

Drug-related Adverse Effects

Refer to the "Major Recommendations" field, and the original guideline document including Table 3 for detailed discussion of the adverse effects associated with first-, second-, and third-line medications.

CONTRAINDICATIONS

CONTRAINDICATIONS

- Amitriptyline should be avoided in elderly patients.
- Tricyclic antidepressants (TCAs) should be avoided in patients who have ischemic heart disease or an increased risk of sudden cardiac death.
- Use of the lidocaine patch 5% should be avoided in patients receiving oral Class I antiarrhythmic drugs (e.g., mexiletine) and in patients with severe hepatic dysfunction, in whom excessive blood concentrations are theoretically possible.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

The methodology used in randomized clinical trials (RCTs) of neuropathic pain (NP) varies, and there are few head-to-head comparisons of different medications, making it difficult to compare the relative efficacy and safety of many medications. Little is known regarding the treatment response of patients with mild-to-moderate NP because RCTs have typically evaluated chronic NP of

moderate to severe intensity. Moreover, treatment duration has generally not exceeded three months in the RCTs of any treatments for NP, and knowledge of the long-term benefits and risks of treatment is therefore inadequate. Unfortunately, there is insufficient evidence to rank first-line medications for NP by their degree of efficacy or safety.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Living with Illness

IOM DOMAIN

Effectiveness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Dworkin RH, O'Connor AB, Backonja M, Farrar JT, Finnerup NB, Jensen TS, Kalso EA, Loeser JD, Miaskowski C, Nurmikko TJ, Portenoy RK, Rice AS, Stacey BR, Treede RD, Turk DC, Wallace MS. Pharmacologic management of neuropathic pain: evidence-based recommendations. Pain 2007 Dec 5;132(3):237-51. [135 references] PubMed

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2003 Nov (revised 2007 Aug)

GUIDELINE DEVELOPER(S)

Fourth International Conference on the Mechanisms and Treatment of Neuropathic Pain - Independent Expert Panel
International Association for the Study of Pain - Medical Specialty Society

SOURCE(S) OF FUNDING

Support for the consensus meeting on which this article is based was provided by the International Association for the Study of Pain (IASP) Neuropathic Pain Special Interest Group and by the Neuropathic Pain Institute, both of which have received unrestricted support for their activities from multiple pharmaceutical companies.

GUIDELINE COMMITTEE

Not stated

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

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FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

All authors received an honorarium for participation in the consensus meeting from the University of Rochester Office of Professional Education.

RHD has received research support, consulting fees, or honoraria in the past year from Allergan, Balboa, CombinatoRx, Dara, Eli Lilly, Endo, EpiCept, Fralex, GlaxoSmithKline, GW Pharmaceuticals, Johnson & Johnson, KAI Pharmaceuticals, Merck, NeurogesX (also stock options), Ono, Organon, Pfizer, Supernus, US Food and Drug Administration, US National Institute of Health, US Veterans Administration, Wyeth, and XTL Biopharmaceuticals.

ABO has received research support from Endo and the Mayday Fund, and is the recipient of an institutional career development award (T32AG020493-02) from the National Institute on Aging.

MB has received research support, consulting fees, or honoraria in the past year from Allergan, Astellas, Cephalon, Dov, Eli Lilly, Eisia, Endo, Johnson & Johnson, Merck, NeurogesX, Novartis, Pfizer, Schwarz, and Xenoport.

JTF has received research support, consulting fees, or honoraria in the past year from Abbott, Adolor, Allergan, Celgene, Cephalon, Eli Lilly, GW Pharmaceuticals, Ortho McNeil, Pfizer, Philadelphia Health Care Trust, Purdue, and UCB Pharma.

NBF has received research support or honoraria in the past year from Neurosearch A/S and UCB Nordic.

TSJ has received research support, consulting fees, or honoraria in the past year from Eli Lilly, GlaxoSmithKline, Johnson & Johnson, Lundbeck Research Foundation, and Pfizer.

JDL has received a grant from Purdue and honoraria from Endo, Medtronic, Pfizer, and US National Institute of Health.

TJN has received research support, consulting fees, or honoraria in the past year from Eli Lilly, GW Pharmaceuticals, Medtronic, Pain Relief Foundation, Pfizer, Schwarz, UCB Pharma, and UK Department of Health.

RKP has received research support, consulting fees, or honoraria in the past year from Abbott, Ametek, Bayer, Biovail, Cephalon, Cytogel, Endo, Forest, GlaxoSmithKline, GW Pharmaceuticals, Janssen, King, Ligand, Medgenex, Merck, Mylan, Neuromed, Organon, Ortho McNeil, Painceptor, Pfizer, Pharmos, Progenics, Sarentis, Solvay, UCB Pharma, Wex, and Xenon.

ASCR has received research support, consulting fees, honoraria, or travel expenses in the past two years from Amgen, Boehringer Ingelheim, Eisai, Eli Lilly, GlaxoSmithKline, Novartis, Ono Pharma, Organon, Pfizer, Sanofi Pasteur/MSD, Solvay, Spinifex, Trophus, and UCB Pharma.

BRS has received research support, consulting fees, or honoraria from Celgene, DepoMed, Eli Lilly, and Pfizer.

RDT has received research support, consulting fees, or honoraria from Allergan, Boehringer Ingelheim, Bundesministerium fur Bildung und Forschung, Deutsche Forschungsgemeinschaft, GlaxoSmithKline, Grunenthal, Merck Sharpe & Dohme, Pfizer, Schwarz, and US National Institute of Health.

DCT has received consulting fees or honoraria in the past year from Abbott, Alpharma, Astra-Zeneca, Celgene, Eli Lilly, GlaxoSmithKline, PriCara/Ortho-McNeil, Schwarz, and Wyeth.

GUIDELINE STATUS

This is the current release of the guideline.

This updates a previous version: Dworkin RH, Backonja M, Rowbotham MC, Allen RR, Argoff CR, Bennett GJ, Bushnell MC, Farrar JT, Galer BS, Haythornthwaite JA, Hewitt DJ, Loeser JD, Max MB, Saltarelli M, Schmader KE, Stein C, Thompson D, Turk DC, Wallace MS, Watkins LR, Weinstein SM. Advances in neuropathic pain: diagnosis, mechanisms, and treatment recommendations. Arch Neurol 2003 Nov;60(11):1524-34. [70 references] PubMed

GUIDELINE AVAILABILITY

Electronic copies: Not available at this time.

Print copies: Available from Robert H. Dworkin, PhD, Department of Anesthesiology, University of Rochester School of Medicine and Dentistry, 601 Elmwood Avenue, Box 604, Rochester, NY 14642; Email: robert_dworkin@urmc.rochester.edu.

AVAILABILITY OF COMPANION DOCUMENTS

None available

PATIENT RESOURCES

None available

NGC STATUS

This NGC summary was completed by ECRI on May 4, 2004. The information was verified by the guideline developer on May 20, 2004. This summary was updated on May 3, 2005 following the withdrawal of Bextra (valdecoxib) from the market and the release of heightened warnings for Celebrex (celecoxib) and other nonselective nonsteroidal anti-inflammatory drugs (NSAIDs). This summary was updated by ECRI on June 16, 2005, following the U.S. Food and Drug Administration advisory on COX-2 selective and non-selective non-steroidal anti-inflammatory drugs (NSAIDs). This summary was updated by ECRI on October 3, 2005, following the U.S. Food and Drug Administration advisory on Paxil (paroxetine). This summary was updated by ECRI on December 12, 2005, following the U.S. Food and Drug Administration advisory on Paroxetine HCL - Paxil and generic paroxetine. This summary was updated by ECRI on May 31, 2006 following the U.S. Food and Drug Administration advisory on Paxil (paroxetine hydrochloride). This summary was updated by ECRI on November 15, 2006, following the FDA advisory on Lamictal (lamotrigine). This summary was updated by ECRI on November 22, 2006, following the FDA advisory on Effexor (venlafaxine HCl). This summary was updated by ECRI Institute on November 6, 2007, following the U.S. Food and Drug Administration advisory on Antidepressant drugs. This NGC summary was updated by ECRI Institute on February 14, 2008. The updated information was verified by the guideline developer on February 20, 2008.

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Date Modified: 11/3/2008