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Topical review

How is neuropathic cancer pain assessed in randomised controlled trials?

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1. Introduction

The prevalence of neuropathic cancer pain is estimated to be between 40% and 80% [9,16,26] and may be directly caused by tumour infiltration or compression (92.5%), or by chemotherapy, radiotherapy, and surgery (20.8%) [9,28]. Neuropathic cancer pain has long been suggested to reduce opioid responsiveness [25] and has been claimed to be a major prognostic factor for poor pain control [8].

According to the International Association for the Study of Pain, neuropathic pain has been defined as "pain initiated or caused by a primary lesion or dysfunction in the nervous system" [22]; however, this definition has been criticized for lack of both diagnostic specificity and precision [29]. Treede et al. [29] recently presented a definition of neuropathic pain as pain related to abnormal somatosensory processing in the peripheral and/or central nervous system. Although not free of controversy, their definition of neuropathic pain is "pain arising as a direct consequence of a lesion or disease affecting the somatosensory system" and provides 4 specific criteria for grading the certainty of the diagnosis [29].

The European Federation of Neurological Societies has recently revised their guidelines on neuropathic pain assessment [11]. They concluded that history and bedside examination are still essential for correct diagnosis, whereas screening tools and questionnaires are useful for indicating neuropathic pain [11].

The aim of this study is to examine the criteria used for assessing neuropathic pain in previous published randomized controlled trials (RCTs) of neuropathic pain in advanced cancer.

2. Methods

2.1. Search strategy

The search was performed in the PubMed, Embase, and Cochrane Central Register of Controlled Trials databases in October/November 2010. The research question "How is neuropathic pain in advanced cancer assessed in RCTs of pharmacological interventions?" guided the construction of the search strategy [23] and included the MESH (medical subject headings) and free terms listed below:

- neoplasms or cancer and,
- pain and,
- neuralgia or deafferentation pain or neuropathic pain or neuropathic or neuropathy or neurogenic pain and,
- palliative care or treatment or placebos or therapeutics or therapy or treatment outcome or treatment failure or clinical protocols or analgesics or analgesics, opioids or analgesia or anticonvulsants or antidepressive agents or anaesthetics.

Searches were narrowed to humans, RCTs, and English language in PubMed and Embase.

2.2. Articles selection

Articles were selected by 2 of the authors and double-checked by 2 other authors according to the following inclusion criteria: patients with advanced cancer, chronic neuropathic pain related to cancer disease, RCTs in which primary endpoint was to study (pharmacological) interventions for neuropathic pain with oral, subcutaneous, intravenous or transdermal analgesics, and English language. Studies about acute neuropathic pain related to recent anticancer treatment and exclusively due to infections, as well as reviews and studies published only as abstracts, were excluded.

2.3. Analyses of studies

Studies were analysed using the grading system for neuropathic pain proposed by Treede et al. [29], which grades the certainty for the presence of neuropathic pain based on 4 criteria:

(1) Pain with a distinct neuroanatomically plausible distribution (sensory examination).
(2) A history suggestive of a relevant lesion or disease affecting the peripheral or central somatosensory system (evidence for disease or neural damage).
(3) Demonstration of the distinct neuroanatomically plausible distribution by at least one confirmatory test (clinical examination with demonstration of neurological signs [negative

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Table 1
Operational definitions of neuropathic pain, pain characteristics and analgesic effect described in the RCTs.

Author	Evidence level/ grade	N	Operational definition – inclusion criteria for neuropathic pain	Pain characteristics						Documented nerve lesion	Medication	Documented analgesic effect on pain characteristics
				Sensory loss	Aesthesia	Hypersensitivity	Pain descriptor	Motor dysfunction	Other			
Ellemann et al. [13]	2b/B	10	Known cancer disease and associated cutaneous allodynia (evoked pain resulting from a low intensity stimulation)	Numbness	Paraesthesia	Allodynia	–	–	–	–	Lidocaine	Yes (only allodynia)
Bruera et al. [7]	2b/B	11	Pain due to direct tumor invasion of nerve plexus	Numbness	Pins and needles	Allodynia	Burning	–	–	Yes 10/11 (CT)	Lidocaine	No
Mercadante et al. [20]	2b/B	10	–	–	–	–	–	–	–	–	Ketamine	No
Mercadante et al. [21]	2b/B	16	Diagnosis made on the basis of the underlying pain cause and when the following most accepted classical features were evident: pain and other symptoms in the distribution of peripheral nerve; constant or intermittent burning, aching or lacerating pain; sensory changes, including hypesthesia, diminished reflexes, hyperesthesia and allodynia; weakness and muscle atrophy; autonomic and trophic skin changes	Hypoaesthesia	–	Allodynia, hyperaesthesia	Burning, aching, lacerating	Hyporeflexia, weakness and muscle atrophy	Autonomic and trophic skin changes	–	Amitriptyline	No
Dellemijn et al. [12]	2b/B	20	Malignant nerve pain caused by tumour involvement of the nerve root(s) or plexus (radicular pain or plexus pain, for less than four weeks radiating along the proximal course of one or more nerve roots or parts of the brachial or lumbosacral plexus with a corresponding sensory deficit (...)	–	–	–	–	–	–	Yes (X-ray, CT, myelography)	Naproxen	No
Caraceni et al. [10]	2b/B	121	Active cancer lesion causing pain by infiltration or compression of nervous structures, and at least one of the following symptoms or signs referred to the pain area: burning pain, shooting/ lancinating pain episodes, dysaesthesia, or allodynia	–	Dysaesthesia	Allodynia	Burning, shooting, lancinanting	–	–	Yes (CT, MRI, US, other)	Gabapentin	Yes
Arbaiza et al. [2]	2b/B	36	Cancer or cancer treatment related neuropathic pain (pain described as burning or like an electric current in an area of distribution around the damage nerve, together with hyporeflexia, hypoaesthesia, dysaesthesia or allodynia or clinical examination)	Hypoaesthesia	Dysaesthesia	Allodynia	Burning, electric current	Hyporeflexia	–	Yes (SEPS)	Tramadol	Yes

Keskinbora et al. [19]	2b/B	75	Pain associated with nerve compression, direct neoplastic invasion of the peripheral nerves or spinal cord, or a neuropathy caused by chemotherapy. Patients with both burning and shooting pain (eletric shock-like), (…), with or without allodynia, were regarded as having neuropathic pain	–	–	Allodynia	Burning, shooting	–	–	Yes (radio/ electrophysiological tests)	Gabapentin	Yes
Arai et al. [1]	2b/B	52	Neuropathic pain defined as pain associated with nerve compression or direct neoplastic invasion of the peripheral nerves or spinal cord. Patients with both sharp pain and burning or shooting pain (electric-shock-like) with or without allodynia	–	–	Allodynia	Burning, shooting, sharp	–	–	–	Gabapentin ± imipramine	No

"–" = not mentioned, CT = computed tomography, MRI = magnetic resonance imaging, US = ultrasound, SEPS = somatosensory evoked potentials.

or positive sensory signs] that support the presence of a lesion or disease consistent with the distribution of pain. Some tests can serve a dual purpose of determining the distribution of pain [criterion 3], and document a relevant lesion [criterion 4]. Suggested confirmatory tests: questionnaires, quantitative sensory testing, electrophysiology, biopsies, neuroimaging, etc).

(4) Demonstration of the relevant lesion or disease by at least one confirmatory test (magnetic resonance imaging or computed tomography confirmation of stroke, surgical or radiological confirmation of nerve compression, laboratory confirmation of diabetes or multiple sclerosis, or nerve biopsy confirmation of neuropathy).

Thus, patients who present all 4 criteria have *definite* neuropathic pain; patients with criteria 1, 2, plus 3 or 4 have *probable* neuropathic pain; and patients with criteria 1 and 2, without evidence of 3 or 4, have *possible* neuropathic pain.

Other information about neuropathic pain definitions in the studies, type of assessment tools for identification/evaluation of neuropathic pain and neuropathic pain descriptors, were also analysed. Moreover, the trials were classified according to the level of evidence and grade of recommendation [24] based on their design, randomization, homogeneity (similar groups for comparison), equal treatment, blinding, losses to follow-up, sample size, and outcomes from each study. According to this classification, RCTs are by definition studies level 1b/grade A, which means evidence with strong consistency [24]. However, studies with flaws in any of the characteristics mentioned above had their level of evidence reduced to 2b/grade B, which means moderate consistency.

3. Results

The literature search resulted in 500 abstracts, from which 69 citations were found in PubMed, 326 in Embase, and 105 in Cochrane databases. Relevant articles were selected and duplicates were excluded. Nine RCTs fulfilled the eligibility criteria and were included in our analysis.

3.1. Study characteristics

The 9 RCTs – published between 1989 and 2010 – studied the analgesic efficacy of different medications (Table 1). Four studies were crossover, double-blinded, and placebo-controlled [7,13,20,21], one study was crossover and double-blinded [12], 2 were double-blinded, placebo-controlled with parallel groups [10], and matched-pair [2], and 2 were open trials with parallel groups [1,19]. Significant results in favour of the intervention were reported in 6 articles [1,2,10,12,19,20].

All studies had random allocation or assignment. Patient groups were considered similar regarding their characteristics in 8 trials [1,2,7,12,13,19–21]. Aside from the allocation of treatments, the groups of patients were considered as treated equally, but in some studies, information about type and doses of adjuvant analgesics was missing. In 3 studies, losses to follow-up higher than 20% were observed [2,10,12]. Based on their methodological characteristics, all studies reached evidence level 2b and grade B of recommendation (Table 1).

3.2. Definitions and characteristics of neuropathic pain

In 8 studies, an operational definition of neuropathic pain was given [1,2,7,10,12,13,19,21]. Six studies considered neuropathic pain associated with the existence of nerve injury [1,2,7,10,12,19]. Other frequent characteristics were hypersensitivity (hyperalgesia

Table 2
Grading of neuropathic pain in the RCTs.

Author/year	Grading system for neuropathic pain				Presence of neuropathic pain	Neuropathic pain assessment repeated after intervention			
	Criterion 1 neuroanatomically distribution	Criterion 2 history of lesion or disease	Criterion 3 neuroanatomically distribution confirmatory test	Criterion 4 lesion or disease confirmatory test		Neurological examination	Assessment tool	Sensory examination	Paraclinical exams
Ellemann et al. [13]	Yes	Yes	Yes	–	Definite	Yes	VAS	–	–
Bruera et al. [7]	Yes	Yes	–	Yes 10/11	Probable	–	VAS	–	–
Mercadante et al. [20]	Yes[a]	Yes[a]	–	–	Possible	–	NRS	–	–
Mercadante et al. [21]	Yes	Yes	Yes	–	Probable	–	NRS	–	–
Dellemijn et al. [12]	Yes	Yes	Yes	Yes	Definite	–	NRS, 6 points pain relief scale	–	–
Caraceni et al. [10]	Yes[b]	Yes	Yes	Yes	Definite	Yes	NRS	–	–
Arbaiza et al. [2]	Yes[b]	Yes	Yes	Yes	Definite	–	NRS	Somatosensory evoked potentials	Sensory and motor neuroconduction tests
Keskinbora et al. [19]	Yes[b]	Yes	Yes	Yes	Definite	–	NRS	Presence/absence allodynia	–
Arai et al. [1]	Yes	Yes	–	–	Possible	–	NRS, pain episodes	–	–

"–" = not mentioned, VAS = visual analogue scale, NRS = numerical rating scale.
[a] Not specified, referred to as clinical examination.
[b] Not specified, but if criteria 3 and 4 are referred to, criterion 1 is considered implicit.

and allodynia) [1,2,7,10,13,19,21] and pain descriptors (burning and shooting, among others) [1,2,7,10,19,21] (Table 1).

The most common cited pain descriptors were burning [1,2,7,10,19,21] and shooting [1,10,19]. Other findings as motor dysfunction and autonomic changes were described in 2 studies [2,21] (Table 1). Documented nerve lesion was cited in 5 studies [2,7,10,12,19], and analyses of the effect of analgesics on neuropathic pain characteristics were described in 3 studies [2,10,13] (Table 1).

3.3. Assessment and grading of neuropathic pain

Information about distinct and accurate sensory examination, neuroanatomical distribution of pain (criterion 1), history of lesion or disease (criterion 2), and confirmatory tests (criteria 3 and 4) were not clearly described in 8 studies [1,2,7,10,13,19–21] (Table 2). In 5 studies, patients were graded as definite neuropathic pain [2,10,12,13,19], in 2 as probable neuropathic pain [7,21], and in 2 as possible neuropathic pain [1,20] (Table 2).

Pain assessments before and after intervention involved measures of pain intensity (visual analogue scale or numerical rating scale) in all studies, neurological examination in 2 [10,13], specific sensory tests in 2 [2,19], notes about pain episodes in one [1], and paraclinical findings in one study [2] (Table 2).

4. Discussion

Although neuropathic pain is prevalent, severe, and difficult to treat in cancer, the number of RCTs regarding pharmacological interventions is small. The feasibility of RCTs in cancer patients may be hampered by poor patient recruitment. Attrition due to deterioration or death – potentially leading to bias – is likely to occur in studies of patients with advanced cancer. Furthermore, the heterogeneity of different cancer diagnoses and stages included in studies are additional challenges for conducting trials in this area. The scope of RCTs is to provide important evidence to an area characterized by weak and frail patients with no clear inception cohort, pronounced comorbidities, and no "gold standard" for assessment. Aiming at stringency by using the RCT, one may easily pay the price of reduced participation and completeness of data. Thus, in order to obtain best possible data, a pragmatic scientific approach including ethical and practical considerations must often be applied [27]. Another explanation for the limited number of RCTs investigating different drugs for neuropathic pain in advanced cancer may be the high prevalence of mixed nociceptive and neuropathic pain conditions, making pure neuropathic pain syndromes difficult to find [9]. Moreover, the dynamic change of the disease with time may also influence the neuropathic pain component considerably. Thus, RCTs investigating drugs for neuropathic pain customarily assess drug efficacy in patients with a better definable aetiology, for example, painful diabetic polyneuropathy or postherpetic neuralgia. Due to the barriers for conducting RCTs in the cancer population suffering from neuropathic pain, evidence from RCTs in noncancer neuropathic pain conditions are routinely extrapolated to cancer patients.

There have been attempts to classify neuropathic pain based on mechanisms; however, the complexity involving different mechanisms and the varied individual responses make it a difficult task [17,30,31]. Although some aetiologic categories of neuropathic pain may predominate, none of them are aetiologic specific. Therefore, patients suffering from identical diseases may present with heterogeneous symptoms and signs. The diagnostic set-up should therefore aim at detecting specific sensory profiles through clinical examination, questionnaires specified for neuropathic pain, and laboratory tools. Defining precise sensory profiles is mandatory

for successful management of neuropathic pain, because they probably arise through different underlying mechanisms and thus probably respond differently to treatments [3,4].

In the present review, 9 RCTs were selected, and based on their methodological characteristics, all studies reached evidence level 2b and grade B of recommendation. However, regarding definitions and classification of neuropathic pain, the studies differed substantially. Eight studies delivered an operational definition of neuropathic pain, although the definitions varied extensively, probably due to the age of studies. Applying the grading system proposed by Treede et al. [29] to the studies, 4 studies fulfilled the criteria for being definite cases, whereas 5 were probable or possible. Regarding sensory loss, aesthesia, hypersensitivity, pain descriptors, sensory motor dysfunction, and other symptoms and signs, the findings were scattered among the studies (Table 1). In only 4 of 9 studies, neuropathic pain was evaluated by sensory and paraclinical examinations before and after the interventions [2,10,13,19].

A number of specific questionnaires for neuropathic pain has recently been developed and introduced primarily in noncancer neuropathic pain conditions, for example, the Neuropathic Pain Assessment Scale [15], the Leeds Assessment of Neuropathic Pain [5], the Neuropathic Pain Symptom Inventory [6], the Pain Quality Assessment Scale [18], and painDETECT [14]. None of the 9 RCTs of the present review used specific neuropathic pain questionnaires. It seems to be warranted in future studies to implement and validate specific neuropathic pain assessment scales in cancer patients.

The findings of this systematic review should increase awareness of the need to improve assessment and classification of cancer-related neuropathic pain in future RCTs in order to enhance targeted treatment outcomes. Due to the barriers and difficulties in performing these trials in the cancer population, multicenter collaboration to support larger accruals and standardized clinical trials should be a major strategic priority. Specific cancer diagnoses, well-defined disease stages, and neuropathic pain syndromes may be feasible to study in a multicenter collaboration. Although the range of therapies currently available in drug trials for cancer-related neuropathic pain confirms that there is no shortage of potential targets, the systematic assessment of new pharmacological interventions will require concerted and well-designed trials using assessment methods that are standardized, validated, and robust enough to be used across many sites with a minimal training of research staff. The diagnostic assessment of cancer-related neuropathic pain in clinical research must also be convenient, reliable, and practical for patients, who are the most reliable source of information on the efficacy and safety of any new pharmacological intervention.

The 9 RCTs of this review may not, due to lack of consistency, specifically assess neuropathic pain in cancer. If one considers Treede et al. [29] criteria for assessing neuropathic pain as the current "gold standard," there is room for improvement in future RCTs.

Conflict of interest statement

There are no conflicts of interest to report.

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