Improving diagnosis and treatment of neuropathic pain in patients with cancer:
The quality of national guidelines in Europe
The studies presented in this thesis have been performed at the department of Anesthesiology, Pain and Palliative Medicine and the department of Primary and Community Care of the Radboud Nijmegen University Medical Centre. Both departments are part of the Nijmegen Centre for Evidence Based Practice (NCEBP), one of the research institutes of the Radboud University and the Netherlands School of Primary Care Research (CaRe), acknowledged by the Royal Dutch Academy of Science (KNAW). This thesis was also performed at the department of Pain and Palliative Care, at the Clinical Neurosciences Department of the Nice Sophia-Antipolis University, at the University Hospital Centre of Nice and the Centre for the Study and Treatment of Pain, La Timone, Assistance Publique des Hôpitaux de Marseille, in France.

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Graphic design by Ulysse Martel©: Cairn. Kerns are ballistic points to help travelers to find their way in the mountains when the conditions are uncertain. In the same way, the clinical practice guidelines are documents to guide the practitioners in case of difficulties. Nijmegen, 2013 ©Copyright 2013 ISBN 978-94-91024-05-4

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Improving diagnosis and treatment of neuropathic pain in patients with cancer: The quality of national guidelines in Europe

Proefschrift

ter verkrijging van de graad van doctor aan de Radboud Universiteit Nijmegen op gezag van de rector magnificus prof. mr. S.C.J.J. Kortmann, volgens besluit van het college van decanen in het openbaar te verdedigen op dinsdag 29 oktober 2013 om 12.30 uur precies

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Doctoral Thesis

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according to the decision of the Council of Deans
to be defended in public on Tuesday, October 29, 2013
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To Jeanne Piano, Henriette Faivre-Duboz, Lucien Blanc, Alain Hainaut and Jean-Paul Lautié

« Nous trouverons un chemin... ou nous en créerons un. »

Hannibal. Traversée des Alpes.
PROLOGUE

Read in a French forum in September 2009 at this address [http://www.cancerdusein.org](http://www.cancerdusein.org), a forum for patients with breast cancer.

Vero: “Hello to all the fairies, I have it again [breast cancer] for the 2nd time, and I began a new protocol of chemo. Everything goes well except for these pains which arrive especially in the evening and which radiate to the entire body as electric shocks, the pain goes away after one hour or two with painkiller. I do not think that it is due to this chemo, because I had them before. My oncologist told me that it was neuropathic pain; neither more details, nor does he treat it. Does anybody know this problem? Thank you in advance. Vero”

Naia: “Frankly I don’t know too much, I have had big pains but after surgery, it was as electric shocks but somebody told me it was normal and I have no more now. Kisses, Naia”

Mathilde: “Hello Vero. I do not know either about what it is, but I also had pains such as you describe them: a sensation of small electric shocks but especially in my legs since the beginning of my treatment under taxotere. I do not know if it is the same thing. But it was also stronger at night and it prevented me from sleeping. In any case, to delete these effects, I took a painkiller that worked very well: topalgic [tramadol] 100mg. Good luck Véro!!”
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## Abbreviation

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>AEDs</td>
<td>Anti-Epileptic Drugs</td>
</tr>
<tr>
<td>CIPN</td>
<td>Chemotherapy-Induced Peripheral Neuropathy</td>
</tr>
<tr>
<td>CPGs</td>
<td>Clinical practice guidelines</td>
</tr>
<tr>
<td>DN4</td>
<td>Douleur Neuropathique en 4 questions</td>
</tr>
<tr>
<td>EBM</td>
<td>Evidence-Based Medicine</td>
</tr>
<tr>
<td>EFIC</td>
<td>European Federation of IASP Chapters</td>
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<tr>
<td>EMG</td>
<td>Electromyogramme</td>
</tr>
<tr>
<td>ESS</td>
<td>Edmonton Staging System</td>
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<tr>
<td>GP</td>
<td>General Practitioner</td>
</tr>
<tr>
<td>IASP</td>
<td>International Association for the Study of the Pain</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic Resonance Imaging</td>
</tr>
<tr>
<td>NeuPSIG</td>
<td>Special Interest Group on Neuropathic Pain (in IASP)</td>
</tr>
<tr>
<td>NNT</td>
<td>Number Needed to Treat</td>
</tr>
<tr>
<td>NPQ</td>
<td>Neuropathic Pain Questionnaire</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>Non Steroid Anti-Inflammatory Drugs</td>
</tr>
<tr>
<td>PDN</td>
<td>Painful Diabetic Neuropathy</td>
</tr>
<tr>
<td>PHN</td>
<td>Post Herpetic Neuralgia</td>
</tr>
<tr>
<td>QST</td>
<td>Quantitative Sensory Test</td>
</tr>
<tr>
<td>SEP</td>
<td>Somatosensitive Evoked Potentials</td>
</tr>
<tr>
<td>SIGN</td>
<td>Scottish Intercollegiate Guidelines Network</td>
</tr>
<tr>
<td>TADs</td>
<td>Tricyclic Antidepressant Drugs</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
</tr>
</tbody>
</table>
Neuropathic pain in patients with cancer in Europe

1) Cancer in Europe and in France

Cancer is the first cause of death in Europe and its prevalence increased in the past 30 years because of the ageing population, earlier diagnosis and more treatment options which lengthened survival and decreased mortality. (1) In 2008 about 3.2 million persons got cancer in Europe, with a mortality of 1.7 million and a 5-year prevalence of 8.4 million of patients. Considering France, in 2008 the incidence of cancer in men was the highest of all European countries and women were in the 10th position. (2)

Cancer is responsible for a high impairment in quality of life and especially social life. This impairment can be a direct consequence of cancer itself but also a consequence of its treatment. Cancer causes several problems of which the most common encountered are in decreasing frequency pain, dyspnoea, and tiredness. (3) This thesis will study pain in cancer because it is the most common symptom associated with cancer namely pain due to cancer and more specifically neuropathic pain in cancer.

2) Pain in cancer

a. Epidemiology

Pain in cancer is quite common: 40% to 60% of patients with cancer experience moderate or severe pain at least monthly. (4, 5) In France, like in Europe, the incidence of cancer has increased in the past 10 years but the mortality rate remained the same, which means that the number of patients who recover from their cancer but have chronic cancer pain has increased and will even further increase. (6,
7) Pain has a high impact on the patient’s quality of life: 43% of cancer patients with pain think that their pain is a burden, 67% describe it as causing stress, 36% as an intolerable aspect of their cancer and 32% would like to die because of their pain. (4) Pain is often the first symptom of the disease and when pain occurs, many patients fear that the cancer is getting worse or, in case of remission, is coming back. In 2007, a systematic review showed that 33% of the patients had pain after curative treatment, 59% during cancer treatment, 64% in advanced or metastatic stages of the disease and in 53% in total (when all stages are put together). (8) This symptom seems to be an indefatigable fellow traveler, difficult to leave for the patient but also for his family and his professional caregivers. It is obvious that the pain of so many patients with cancer should be relieved appropriately. However, this seems to be very difficult. (8)

b. Pain definition in cancer

Pain is “an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage”. (9) In 2007, Loeser and Treede proposed a revision of the terminology of pain. (10) Cancer pain can have nociceptive and neuropathic components. Nociceptive pain is defined as “an actually or potentially tissue-damaging event transduced and encoded by nociceptors.” (9) Neuropathic pain is a “pain arising as a direct consequence of a lesion or disease affecting the somatosensory system”. (11) These two types of pain can occur, often mixed. (12, 13) Besides, they occur in a dynamic process where emotional impairment of the pain, sleep disorders and quality of life evaluation will be an important clue to manage the pain. (12, 13) The biopsychosocial model will influence pain management as presented in figure 1. (13) In fact, the initial lesion defined as nociceptive is a small part of the chronic pain. The fact that pain duration is over 3
months will develop a suffering for the patients and if this condition persists, a noxious pain behavior will develop creating a chronic pain syndrome. The direct consequence is the high need for a multidisciplinary approach and treatment: drugs for the pain but also psychological support, cognitive and behavioral therapy, physiotherapy and other techniques like hypnosis. (13) In cancer, pain can be a direct lesion of the cancer or due to its treatment (surgery, chemotherapy or radiotherapy). Neuropathic pain should be differentiating from nociceptive pain because the treatment is not the same. In this thesis, we will focus mainly on the pharmacological treatment advocated by national guidelines on cancer pain.

**Figure 1.** Pain model from Loeser in his book definition of pain. (13)

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**c. Pain in patients with cancer: a separate entity?**

To help practitioners, in 1987, the World Health Organization (WHO) proposed a guideline to treat cancer pain: the WHO analgesic pain
ladder. (14) It recommends treating cancer pain by the following three steps. For slight to moderate pain, step I with paracetamol is proposed. For moderate pain, step II with weak opioids is recommended and for severe pain, step III, strong opioids should be prescribed. If this pain ladder is followed correctly, 80% of the patients with cancer can be treated effectively. (15) But there are still 20% of patients for whom this guideline does not work: one of the causes of this inefficacy is the presence of neuropathic pain components. (8, 15)

Pain in patients with cancer is complex because it is a combination of different pain mechanisms. In 1999, Caraceni was the first to map cancer pain: 25% of the patients presented at least two types of pain. About 90% of the pain was caused by the cancer itself and 21% of the patients had pain consecutive to the treatment of the cancer. (16) Pain was considered to be nociceptive in 72% of the patients, neuropathic in 40% and visceral in 35%; about 40% of patients suffered from a combination of pain types. (16) Thus, neuropathic pain in cancer is difficult to diagnose.

3) Neuropathic pain in patients with cancer

a. Epidemiology of an under-diagnosed type of pain

Neuropathic pain can be caused by the tumor itself and/or by the treatment of cancer such as neurotoxic chemotherapy, invasive surgery or radiotherapy. (17) In patients suffering from cancer pain, between 19 and 39% also suffer from neuropathic pain. (18) Little information exists about this population of patients. Only few studies all with a small number of patients studied the treatment of neuropathic pain in patients with cancer. (19, 20) Conclusions were irrevocable: neuropathic pain appears hard to treat, and strong opioids are not always the first choice. (4, 21) In a recent
international study comparing patients with cancer having neuropathic pain and those having only nociceptive pain, the quality of life measured with the EORTC QLQ-C30 was worse in cancer patients with neuropathic pain than in cancer patients with only nociceptive pain concerning physical, cognitive and social functions. (5)

b. Neuropathic pain signs and symptoms

Signs of neuropathic pain can be: the sensation of burning, dysesthesia or paresthesia (like pins and needles), pruritus, electric shocks or cold pain. Symptoms can be associated with hyperesthesia (increased pain sensitivity) or allodynia (pain in response to a non-nociceptive stimulus) in the same body location. (10) In cancer, this type of pain can occur in the legs or in the fingers after chemotherapy, around the scar of a surgery or in the area of previous radiotherapy.

c. Management of neuropathic pain in non-cancer conditions

Neuropathic pain was initially described in non-cancer conditions. Its diagnosis is challenging. Until now, no gold standard for the diagnosis of neuropathic pain has been accepted, although several screening instruments exist, like the McGill Pain Questionnaire, S-LANSS, Neuropathic Pain Questionnaire, DN4, PainDETECT and StEP. (22-26)

These instruments are presented in table 1.
Table 1. The 6 questionnaire to screen neuropathic pain.

<table>
<thead>
<tr>
<th>Instrument</th>
<th>Author</th>
<th>Year</th>
<th>Population included</th>
</tr>
</thead>
<tbody>
<tr>
<td>DN4</td>
<td>Bouhassira</td>
<td>2005</td>
<td>Chronic pain</td>
</tr>
<tr>
<td>McGill Questionnaire</td>
<td>Melzack</td>
<td>1975</td>
<td>Chronic pain</td>
</tr>
<tr>
<td>NPQ</td>
<td>Krause</td>
<td>2003</td>
<td>Chronic pain</td>
</tr>
<tr>
<td>Pain DETECT</td>
<td>Freynhagen</td>
<td>2006</td>
<td>Low back pain</td>
</tr>
<tr>
<td>S-LANSS</td>
<td>Bennett</td>
<td>2005</td>
<td>Chronic pain</td>
</tr>
<tr>
<td>STeP</td>
<td>Scholz</td>
<td>2009</td>
<td>Low back pain</td>
</tr>
</tbody>
</table>

In 2011, an algorithm was created to help physicians and researchers to make a proper diagnosis of neuropathic pain. (Figure 2) (28)

Figure 2. Algorithm of the neuropathic pain diagnosis adapted from the IASP (28)

Pain distribution is plausible and history suggests relevant lesion or disease

Confirmatory tests:

1) Negative or positive sensory signs in the innervation territory of the lesioned nervous structure
2) Diagnosing test confirming the lesion or disease explaining pain

Both 1+2 → Definite neuropathic pain
One 1 or 2 → Probable neuropathic pain
Neither 1 nor 2 → Unconfirmed as neuropathic pain
Up to now, there is also no consensus about the treatment of neuropathic pain in patients with cancer: Hall et al. found 951 different treatment regimens prescribed as an initial therapy in this patient group. (29) Generally, neuropathic pain is treated with adjuvants like tricyclic antidepressants or anticonvulsants. (30) The evidence for these types of drugs, based on number needed to treat (NNT 1.2-3.6) and number needed to harm (NNH 6-28) was mainly derived from research performed in patients with painful diabetic neuropathy (PDN) or post herpetic neuralgia (PHN). (31, 32)

**d. Management of neuropathic pain in patients with cancer**

In 1989, Bruera et al. proposed a new classification for cancer pain, named the Edmonton Staging System (ESS), which was validated in 1995. One of the assessed domains of this score was the mechanism of pain which considered visceral pain, bone-soft tissue, neuropathic pain, mixed pain or unknown. (33, 34) Neuropathic pain was defined as a “pain located in the region where the nerve or nerve root has been damaged”. In 2005, Fainsigner proposed to use the revised Edmonton Staging System (rESS) because the ESS is not efficient to detect neuropathic pain from nociceptive pain. (35) This tool was validated for clinical practice and research with the same definition of neuropathic pain, which did not exclude other kind of pains. The term “neuropathic pain components” was used to underline the fact that it is not a unique physiopathology but more an association of specific symptoms. In 2008, a study demonstrated that by following the WHO guidelines the treatment of neuropathic pain was effective using specific co-analgesics such as amitriptyline, gabapentine and dexamethasone in 53% of the patients. (36) In another study, 20% of the patients were not relieved by the treatments proposed in the WHO guideline of which the majority had neuropathic pain. (16) Concerning the treatment of neuropathic pain in patients with
cancer, amitriptyline only had little efficacy and important side effects although it is recommended in first line in CPGs. (20) In contrast, Caraceni proposed gabapentine because of better benefit risk ratio. (19) No studies compared tricyclic antidepressants drugs and anticonvulsants drugs in cancer. Other randomized controlled trials were rare. Possibly, it explains the lack of consensus on the treatment of neuropathic pain in cancer.

A specific sub-category of neuropathic pain is chemotherapy-induced peripheral neuropathy (CIPN). Hausheer proposed the Patient Neurotoxicity Questionnaire to evaluate the risk to develop CIPN. (37) However, this tool was not appropriate to assess neuropathic pain components. (38) Cavaletti et al. proposed and validated a tool to evaluate CIPN using the Total Neuropathy Score with a questionnaire on quality of life (EORTC QLQ-CIPN20) and a simple pain intensity assessment. (39, 40) Yet, such a tool takes time and seems not specific for neuropathic pain components.

**e. Conclusion**

There is no gold standard for the management of neuropathic pain in patients with cancer. In such a case, evidence-based medicine (EBM) can contribute to help professionals. The following chapter will present the definition and describe the interest why making a clinical practice guideline (CPG) in cancer pain is important.
Developing clinical practice guidelines

1) Definition and interest of a clinical practice guideline (CPG)

Clinical Practice Guidelines (CPGs) have been developed to help practitioners to give the best available care (efficacy and safety) to their patients. (41) They are ‘statements that promote or advocate a particular course of action in clinical care’. (42) Also regarding neuropathic pain in cancer, CPGs can guide practitioners through a structured diagnosis and treatment process. (28, 41) CPGs should be based on a systematic literature review and should give recommendations as a response to specific questions, in a specific patient population for a specific practitioner population. (43) The principles of EBM changed the methodology of guideline development, with a more rigorous selection of references and a higher consensus in the redaction of recommendations. (44) EBM can be classified in four levels with 1 the highest and 4 the lowest level of evidence as presented in table 1. The combination of evidence about a same clinical question can be classified in four grades with grade A as highest grade and grade D as lowest as presented in table 1. When there is no evidence on a question, only a synthesis of experience of the guideline development group can be proposed as “good practice point”. (45) It is important that the quality of a CPG is high, as it aims to influence clinical practice of many practitioners and the care they provide to even more patients. Thus, a good methodology for choosing the evidence is essential.
Table 1. Key to evidence statements and grades of recommendations according SIGN 50

LEVELS OF EVIDENCE

<table>
<thead>
<tr>
<th>Level</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1++</td>
<td>High quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias</td>
</tr>
<tr>
<td>1+</td>
<td>Well-conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias</td>
</tr>
<tr>
<td>1-</td>
<td>Meta-analyses, systematic reviews, or RCTs with a high risk of bias</td>
</tr>
<tr>
<td>2++</td>
<td>High quality systematic reviews of case control or cohort or studies High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal</td>
</tr>
<tr>
<td>2+</td>
<td>Well-conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal</td>
</tr>
<tr>
<td>2-</td>
<td>Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal</td>
</tr>
<tr>
<td>3</td>
<td>Non-analytic studies, e.g. case reports, case series</td>
</tr>
<tr>
<td>4</td>
<td>Expert opinion</td>
</tr>
</tbody>
</table>

GRADES OF RECOMMENDATIONS

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade A</td>
<td>At least one meta-analysis, systematic review, or RCT rated as 1++, and directly applicable to the target population; or A body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results</td>
</tr>
<tr>
<td>Grade B</td>
<td>A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 1++ or 1+</td>
</tr>
<tr>
<td>Grade C</td>
<td>A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 2++</td>
</tr>
<tr>
<td>Grade D</td>
<td>Evidence level 3 or 4; or Extrapolated evidence from studies rated as 2+</td>
</tr>
<tr>
<td>Good practice points</td>
<td>Recommended best practice based on the clinical experience of the guideline development group</td>
</tr>
</tbody>
</table>

RCT randomized controlled trial. Extracted from the SIGN website on 31-Jui-2012 in this URL: http://www.sign.ac.uk/guidelines/fulltext/50/annexb.html (44).
2) Development methodology for a CPG

In Europe, several institutes are specialized in the development of guidelines. The Dutch College of General Practitioners was the first to start guideline development, with the publication in 1989 of its guideline ‘diabetes mellitus’. In 1979, the Dutch Institute for Healthcare Improvement (CBO) was founded by the Dutch Association of Chief Medical Officers. This independent national organization focused in 1999 on the organizational aspects of the quality of care with the development of national guidelines. In 1993, the Scottish Intercollegiate Guidelines Network (SIGN) was created to improve quality of care in Scotland, by the development and dissemination of national CPGs based on current EBM. In 1999, the National Institute for Health and Clinical Excellence (NICE) in the United-Kingdom was developed to reduce the variation of the availability and quality of treatment and care. The same year, the Agence Nationale de Développement de l’Evaluation Médicale (ANDEM) was founded and proposed a specific methodology to create CPGs. More recently, in 2004, the Institute for Quality and Efficiency in Health Care (IQWIK) was created in Germany. Other developers can be proposed as national societies, for example, the French pain society in France or the Palliative Care Society of the Netherlands.

Specific groups of guideline developers are often composed of only methodologists as is the case in the NICE guidelines but these developers are mostly not clinical experts. Consequently, the clinical expertise is lacking to make clinical relevant recommendations. Other developer groups are composed of clinicians and experts of the clinical question(s) but they have usually no training in the methodology of making guidelines. The advantage is that their clinical experience and their practice can help to built clinical
applicable recommendations. However, experts have often financial conflicts of interests (COI) with pharmaceutical industries and they should not take part to the decisions for some questions of the CPG in relation with their COI. (45) These COI should be written in the CPG in details. (45) The best would be combining expertise and knowledge of these two domains: methodological and clinical experiences. This was done in the Netherlands. A national scientific society started the process of making a guideline and invited several national recognized clinical experts together with the national institute of guideline development for the methodological support and guidance.

The described situation raises the question how to develop a high quality CPG. How can we evaluate the rigor of development of a CPG and its applicability in practice?

3) Evaluation of the quality of a CPG

It is important to evaluate the quality of a guideline because it will be used by numerous physicians and other health care professionals as a guide reference to diagnose and treat numerous patients. The first tool to assess guidelines was the Appraisal of Guidelines, Research and Evaluation (AGREE) instrument. It was developed by an international methodologist group in 2003: the AGREE collaboration. (43) Its aim was to assess the methods used to develop a CPG and to know whether the resulting recommendations are sufficiently based on evidence. (43) This 23-item instrument consists of six domains: (1) scope and purpose (overall aim of the guideline and target groups, 3 items); (2) stakeholder involvement (stakeholders involved in guideline development and views of its intended users, 3 items); (3) rigor of development (selection of the evidence and the method to create recommendations, 8 items); (4) clarity and presentation (structure and format of the guideline, 3 items); (5) applicability
facilitators and potential barriers for guideline implementation, 4 items); and (6) editorial independence (biases concerning conflicts of interest, 2 items) and one overall assessment item judging if the CPG is recommended for its use in clinical practice. (43) The ratings of the quality domains showed to be good predictors of outcomes associated with implementation of guidelines, very useful and easy to use. (43) The original AGREE Instrument has been refined to improve the original tool’s usability and its validity and reliability. (43) Thus, in 2008 the AGREE II instrument, a revision of the AGREE instrument, was developed by the AGREE collaboration. (46) Revision was done because the four-point response scale of the AGREE instrument was not reliable enough. (47, 48) The seven-point response scale seemed more relevant, and the new user’s manual clear. (46) Yet, there is no abridged version of this time-consuming instrument (at least 90 minutes per guideline), it appears not efficient for use in developing countries and finally is difficult to evaluate in case of multiple morbidities which means multiple CPGs. (49-51) However, the AGREE II instrument appeared valid to assess the quality of development of a CPG on cancer. (52) Table 2 presents the AGREE and AGREE II instruments.

In conclusion, developing a CPG should follow a rigorous methodology, especially because it will be used by all health care providers and their patients (in fact the target population of the CPG).
### Table 2: Comparison of the original AGREE and the AGREE II items. (43-46)

<table>
<thead>
<tr>
<th>Original AGREE Item</th>
<th>AGREE II Item</th>
</tr>
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<tbody>
<tr>
<td><strong>Domain 1. Scope and Purpose</strong></td>
<td></td>
</tr>
<tr>
<td>1. The overall objective(s) of the guideline is (are) specifically described.</td>
<td>No change</td>
</tr>
<tr>
<td>2. The clinical question(s) covered by the guideline is (are) specifically described.</td>
<td>The health question(s) covered by the guideline is (are) specifically described.</td>
</tr>
<tr>
<td>3. The patients to whom the guideline is meant to apply are specifically described.</td>
<td>The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.</td>
</tr>
<tr>
<td><strong>Domain 2. Stakeholder Involvement</strong></td>
<td></td>
</tr>
<tr>
<td>4. The guideline development group includes individuals from all the relevant professional groups.</td>
<td>No change</td>
</tr>
<tr>
<td>5. The patients’ views and preferences have been sought.</td>
<td>The views and preferences of the target population (patients, public, etc.) have been sought.</td>
</tr>
<tr>
<td>6. The target users of the guideline are clearly defined.</td>
<td>No change</td>
</tr>
<tr>
<td>7. The guideline has been piloted among end users.</td>
<td>Delete item. Incorporated into user guide description of item 19.</td>
</tr>
<tr>
<td><strong>Domain 3. Rigour of Development</strong></td>
<td></td>
</tr>
<tr>
<td>8. Systematic methods were used to search for evidence.</td>
<td>No change in item. Renumber to 7.</td>
</tr>
<tr>
<td>9. The criteria for selecting the evidence are clearly described.</td>
<td>No change in item. Renumber to 8.</td>
</tr>
<tr>
<td><strong>NEW</strong> Item 9. The strengths and limitations of the body of evidence are clearly described.</td>
<td>No change in item. Renumber to 8.</td>
</tr>
<tr>
<td>10. The methods for formulating the recommendations are clearly described.</td>
<td>No change</td>
</tr>
</tbody>
</table>
## Original AGREE Item

<table>
<thead>
<tr>
<th>Original AGREE Item</th>
<th>AGREE II Item</th>
</tr>
</thead>
<tbody>
<tr>
<td>11. The health benefits, side effects, and risks have been considered in formulating the recommendations.</td>
<td>No change</td>
</tr>
<tr>
<td>12. There is an explicit link between the recommendations and the supporting evidence.</td>
<td>No change</td>
</tr>
<tr>
<td>13. The guideline has been externally reviewed by experts prior to its publication.</td>
<td>No change</td>
</tr>
<tr>
<td>14. A procedure for updating the guideline is provided.</td>
<td>No change</td>
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</table>

### Domain 4. Clarity of Presentation

<table>
<thead>
<tr>
<th>Original AGREE Item</th>
<th>AGREE II Item</th>
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<tbody>
<tr>
<td>15. The recommendations are specific and unambiguous.</td>
<td>No change</td>
</tr>
<tr>
<td>16. The different options for management of the condition are clearly presented.</td>
<td>The different options for management of the condition or health issue are clearly presented.</td>
</tr>
<tr>
<td>17. Key recommendations are easily identifiable.</td>
<td>No change</td>
</tr>
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</table>

### Domain 5. Applicability

<table>
<thead>
<tr>
<th>Original AGREE Item</th>
<th>AGREE II Item</th>
</tr>
</thead>
<tbody>
<tr>
<td>18. The guideline is supported with tools for application.</td>
<td>The guideline provides advice and/or tools on how the recommendations can be put into practice. AND Change in domain (from Clarity of Presentation) AND renumber to 19</td>
</tr>
<tr>
<td>19. The potential organizational barriers in applying the recommendations have been discussed.</td>
<td>The guideline describes facilitators and barriers to its application. AND change in order – renumber to 18</td>
</tr>
<tr>
<td>20. The potential cost implications of applying the recommendations have been considered.</td>
<td>The potential resource implications of applying the recommendations have been considered.</td>
</tr>
<tr>
<td>21. The guideline presents key review criteria for monitoring and/or audit purposes.</td>
<td>The guideline presents monitoring and/or auditing criteria.</td>
</tr>
<tr>
<td>Original AGREE Item</td>
<td>AGREE II Item</td>
</tr>
<tr>
<td>----------------------------------------------------------</td>
<td>-------------------------------------------------------------------------------</td>
</tr>
<tr>
<td><strong>Domain 6. Editorial Independence</strong></td>
<td></td>
</tr>
<tr>
<td>22. The guideline is editorially independent from the funding body.</td>
<td>The views of the funding body have not influenced the content of the guideline.</td>
</tr>
<tr>
<td>23. Conflicts of interest of guideline development members have been recorded.</td>
<td>Competing interests of guideline development group members have been recorded and addressed</td>
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</table>
Changing paradigms in understanding the building of CPGs on neuropathic pain in patients with cancer

1) A CPG on neuropathic pain in patients with cancer?

To develop a high quality CPG there is, next to expertise, a need for funding and time. (53) These financial and human means can be justified for public health problems such as diabetes or cardiovascular disease but the interest in an underestimated symptom as neuropathic pain in patients with cancer is far from obvious. Criteria for selection of topics for CPG are:

- “Areas of medical uncertainty as evidenced by wide variation in practice or outcome,
- Conditions where effective treatment is proven and where mortality or morbidity can be reduced,
- Iatrogenic diseases or interventions carrying significant risks or cost,
- Clinical priority areas for NHS Scotland: presently, coronary heart disease and stroke, cancer and mental health. The strategic aims of the NHS in Scotland are also considered: improving health and tackling inequalities, especially with regard to children and young people, developing primary and community care and reshaping hospital services.” (44)

Thus, neuropathic pain in cancer is an eligible topic for a CPG: no consensus on its diagnosis or treatment, a specific treatment on neuropathic pain can improve the quality of life and inadequate treatment can increase side events in this frail population. Besides, cancer is a clear clinical priority in every European country. However, the development of a CPG with few publications of high quality on a
Improving neuropathic cancer pain in Europe

topic is challenging. Is there any CPG in Europe concerning neuropathic pain in cancer?

2) Application of clinical practice guidelines in the primary care setting

The research of this thesis was performed from 2010 to 2013, a period of changes in the attention for neuropathic pain in patients with cancer: a new definition of neuropathic pain in 2008, a new diagnosis algorithm in 2011, and a specific assessment in patients with cancer in 2012. (11, 28, 40) This was even the object of the clinical update of the journal ‘Pain’ in March 2012. (15) Although these recommendations were published and disseminated to a certain level of pain treating physicians, there was no information on their impact in practice.

Since 2011, according to the World Organization of National Colleges, Academies and Academic Associations of General Practitioners (WONCA) in Europe proposed a new definition of the general practitioner. They are “personal doctors, primarily responsible for the provision of comprehensive and continuing care to every individual seeking medical care irrespective of age, sex and illness.” (54) This definition gave three main missions to the GP. First, he has to treat his patients in their global environment (physical, psychological, social, cultural and existential dimensions); the care he provides should be personalized in a comprehensive approach of the patient and its family. Second, he has to prevent disease in a public health dimension. Third, he also has to give effective and safe patient care according evidence-based medicine in a quality management.

In conclusion, every GP should know the CPGs concerning all diseases involved in primary care, which seems not possible regarding available time. Thus, a CPG should be clear to help the GP in an
effective way. This should be particularly the case for pain management in cancer because usually the GP will support the patient and his family until the end.

Literature illustrates that practitioners use CPGs according to their knowledge, attitude and skills. (55) They also use CPGs only if the level of evidence or expert opinion is high, recommendations are clearly linked to the evidence or levels of evidence or grade of recommendations are explicit. (55, 56) For these reasons, we studied whether CPGs on neuropathic pain in patients with cancer exist, if they have a good quality of development and if there are applicable in daily practice.

The Dutch College of General Practitioner (NHG) provides CPGs and develops tools to improve their adherence. In a recent survey of Lugtenberg, more than 95% of the GPs thought that Dutch CPGs were useful sources of advices and based on sufficient evidence but they do not always use them. (57) Barriers to a good adherence were the lack of applicability of the CPG in general or with respect to individual patients, and this is understandable when we know that the care should be person-centered. (57) Besides, the patients’ ability and behavior as the patients’ preferences can contribute to different care, not always in concordance with the CPG recommendations. (57)

3) What we know about neuropathic cancer pain

Neuropathic pain for patients with cancer is an important public health problem in Europe as it: 1) is difficult to diagnose, 2) is difficult to treat, 3) has a high impairment on the quality of life and 4) has a high prevalence which will even increase. That is why a specific clinical practice guideline on neuropathic pain in patients with cancer can contribute to best care for our patients with neuropathic pain.
Looking to all the discussed material in this introduction, I started this research project with the following research questions.

4) Research questions of this thesis

1. Are there specific guidelines in Europe, describing the diagnosis and management of neuropathic pain in cancer patients?

2. If there are specific guidelines found how many of them meet the criteria of a clinical practice guideline (CPG)?

3. What is the quality of the development process and the content (reporting) of each CPG using an internationally validated instrument (AGREE II instrument)?

4. What is the quality of the methodology and development of each recommendation in the selected CPG guideline that meets a basic level of quality?

5. What are the recommendations regarding diagnosing and treating neuropathic pain in patients with cancer and how do they differ in the selected CPGs?

6. Do French pain specialists adhere to the national guidelines on this topic in their clinical decision making as a clinical test of the implementation level of the national CPG?

Outline of the thesis

Chapter 2 answers the research question number 1 and 2. The first step of this work is to find recommendations on chronic pain, neuropathic pain or cancer pain used in Europe. As most of the guidelines are not written in English and not published in Pubmed, we chose to directly involve physicians in all European countries and finding such guidelines. The European Federation of IASP
Chapter 1 - Introduction

[International Association for the Study of Pain] Chapters (EFIC) is composed of pain specialists, each of them being chair of their national association for pain. They are usually experts in their domains and participate in the development of guidelines on pain in their countries. Additionally, in Europe there are pain clinicians with a special interest in neuropathic pain and registered in the IASP in the special interest group on Neuropathic pain (NeuPSIG). In this chapter, these specialists will also be interrogated to know if guidelines on chronic pain, neuropathic pain and cancer pain exist in their country. This seems to be an interesting method to get the most exhaustive list of guidelines. The second part of the article will be to study the recommendations to know if they meet the definition of a CPG according Field’s definition.

Chapter 3 answers the research question number 3. With the material collected in chapter 2 as a basis, we aimed to select CPGs on neuropathic pain in patients with cancer. They will be assessed with the AGREE II instrument to evaluate their quality of development. Results of this assessment will be compared between CPGs made by professional societies and those created by guidelines development organizations.

Chapter 4 answers the research question 4. References used to make recommendations in these CPGs will be studied in relation to the recommendations and comparisons between the CPGs concerning the diagnosis of neuropathic pain in cancer. The methodology used has already been validated in an article on diabetes and will be used for this article. The aim is to assess the level of quality of the references and the grade of recommendations of the clinical messages. Chapter 5 answers research question 5 and uses the same methodology as chapter 4. It concerns the treatment of neuropathic pain.
Chapter 6 responds to the last research question. French pain specialists will be invited to participate in a case vignette study. It aims to answer if they know and use the recommendations on cancer pain and neuropathic pain, as given in French CPGs.

Chapter 7 discusses the main findings of the thesis, considers the methods and limitations, and proposes specific recommendations to improve the implementation and development of CPGs in daily practice, for policymakers and future research.

References


Improving neuropathic cancer pain in Europe


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50. Dawes M. Co-morbidity: we need a guideline for each patient not a guideline for each disease. Fam Pract 2010; 27: 1–2.


56. The European definition of general practitioner/family physician. WONCA Europe. Extract from internet in January the 14th 2013, URL:

Improving neuropathic cancer pain in Europe
CHAPTER 2 - European Inventory of clinical practice guidelines about pain

Submitted March the 27th 2013 in: Douleur et analgésie

Virginie PIANO, Anne DONNET, Jako BURGERS, Stans VERHAGEN, Hans KRESS, Yechiel HEKSTER, Michel LANTERI-MINET, Yvonne ENGELS, Kris VISSERS
SUMMARY

**Introduction:** Clinical practice guidelines (CPGs) are statements that promote or advocate a particular course of action in clinical care. Chronic pain is a frequent disease and is often associated with co-morbidities, so, CPGs are important to guide the practitioners. Are there specific guidelines in Europe, describing the diagnosis and management of neuropathic pain in cancer patients? **Methods:** A questionnaire was sent by email to the chairs of the IASP chapters of each European country with the support of the European Federation of IASP chapters and to the members specialized in neuropathic pain in Europe (NeuPSIG). Name and topic of each document (pain, cancer pain and neuropathic pain, other) was collected. Each document should meet the definition of a CPG. Statistical analysis was made with SPSS 16.0 for group description (number and frequency). **Results:** Forty-one of the 66 participants (62%) answered the questionnaire, representing 30 of the 38 European countries. With their participation, 54 documents were found and validated within 20 of them were CPGs: 6 on chronic pain, 5 on neuropathic pain, 4 on cancer pain, 2 in geriatrics, 1 in pediatrics and 2 on chronic low back pain. **Conclusion:** An important heterogeneity exists in Europe concerning CPGs on the diagnosis and treatment of pain and cancer pain more specifically. A general European CPG can help to improve the European implementation of the CPG in each country and propose a safe and efficient management of the pain after specific adaptations to the health system of each country including pooling the financial and the human resources.
INTRODUCTION

Acute pain is one of the first symptoms leading the patient to visit his practitioner: a diagnosis is made and a treatment is proposed. It is more difficult when pain is resistant to the specific analgesics which are the case for the diagnosis and treatment of cancer pain and chronic pain.

The prevalence of patients with cancer is increasing. In Europe, the incidence of new cases of cancer was 3.2 million per year in 2008 (1). In this population, 64% suffered from pain among them 19-39% had neuropathic pain (2-5). These pains can occur due to the cancer or its treatment (4, 6-8). Chronic pain represented 30% of the French population with 7% of neuropathic chronic pain (9). In chronic and cancer pain, patients reported a severe diminution of their quality of life (10, 11). Thus, it is an important public health problem in Europe.

To guide health caregivers for an optimal pain management of their patients, clinical practice guidelines (CPGs) were developed. These CPGs are “statements that promote or advocate a particular course of action in clinical care” (12, 13). One of these CPGs was published in 1986 by the World Health Organization and concerned the management of cancer pain in three steps (14). Following these recommendations 80 % of these pains can be relieved in patients with cancer (15). However, it appeared that in the population who did not respond to the analgesic treatment, neuropathic pain was very prevalent (15). Chronic pain, especially in neuropathic pain is also resistant to treatment (10).

Referential and documents exist to help practitioners and are published by an international society as the International Association for the Study of Pain (IASP) of its special group of interest on neuropathic pain (NeuPSIG), by a national organization as the
Scottish Intercollegiate Guidelines Network (SIGN) or a national pain society like the Société Française d’Evaluation et de Traitement de la Douleur (SFETD) in France (16-19). Nevertheless, most of the CPGs are national and not available in international database as Pubmed or Embase, especially when they are not written in English. The objective of this research is to make an inventory of European guidelines on chronic pain, neuropathic pain and cancer pain and to collect them all. Besides, all guidelines will be evaluated to check if they meet the criteria of a CPG.

Methods

Inclusion of participants

Chairmen of the European national pain societies, all member of the European Federation of IASP Chapters (EFIC) and European physicians all member of the special interest group on neuropathic pain of the IASP who published in the last 5 years on pain were invited to participate to the study by email with the support of the president of the EFIC.

Study design

Participants received a questionnaire by email 15 days after presentation of the study. They had to quote available CPGs in their counties according the topic (chronic pain, neuropathic pain and cancer pain). Besides, the questionnaire asked if a website or a person can be contacted to have these documents. A reminder was sent 15 days after. In case of non-response, participants were contacted by phone or by fax. All the documents were collected and sent to the authors to validate the selection of documents.

Translation of the documents
Documents were translated into English with the help of the Google translator software to determine easily if the document corresponds to the definition of a CPG. The authors of this article spoke English, French, Italian, Dutch, German and Norwegian. The documents which meet the inclusion criteria were translated a second time by native speaker and physician according to the language of the CPG.

**Document inclusion**

Translated documents had to meet the definition of a CPG from the Institute of Medicine: CPG should inform according to a systematic review of the literature and evaluate the benefit-risk of alternatives options (14).

**Statistical analysis**

Data collection was analyzed with the software: SPSS 16.0© (IBM, NY, USA) using descriptive what and frequencies.

**Results**

**Population of participants**

From March the 1st to April the 30th 2010, 66 participants were contacted within the 34 EFIC and 32 NeuPSIG members. Response rate was 62% (41/66), representing 30 of the 38 European countries. No member was found for Belorussia, Macedonia and Moldavia. Five countries did not respond to our questionnaire: Iceland, Luxembourg, Montenegro, Poland and Latvia. Participants from Ukraine and Russia respond to the email but could not respond to the questionnaire because they were researchers in fundamental research and did not know their national CPGs.

**Collection of the documents**
From the questionnaire, 71 documents were found. Some of them were quoted twice: once for chronic pain and once for neuropathic pain for example because it was the same document for these two topics (figure 1). After collection, 54 national documents were identified and validated by participants. In our study, 24 countries had a document on chronic pain (80%), 22 on cancer pain (73%) and 20 on neuropathic pain (67%). Documents quoted by Ireland were the same as the United-Kingdom (UK). Five documents were about pain in another domain: 2 in elderly population in France and UK, one in pediatrics in France, 2 concerning low back pain in Denmark and UK. Three countries had no available document on pain: Bosnia Herzegovina, Lithuania and Romania (table 1).

**Collection of CPGs**

On the 54 available documents, 20 meet the definition of a CPG: 6 on chronic pain, 5 on neuropathic pain, 4 in cancer pain, 2 in geriatrics, 1 in paediatrics and 2 on low back pain. Serbia quoted the European recommendation from the European Federation of Neurological Societies (EFNS) concerning neuropathic pain (table 1).
**Figure 1.** European collection of documents on chronic pain, neuropathic pain and cancer pain in April 2010.

Legend. CPG clinical practice guideline. EFIC European Federation of IASP Chapter. NeuPSIG: special group of interest on neuropathic pain.
Table 1. Clinical practice guidelines in Europe on chronic pain, neuropathic pain and cancer pain in April 2010.

<table>
<thead>
<tr>
<th>Country</th>
<th>Chronic pain</th>
<th>Neuropathic pain</th>
<th>Cancer pain</th>
<th>Country</th>
<th>Chronic pain</th>
<th>Neuropathic pain</th>
<th>Cancer pain</th>
</tr>
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<tbody>
<tr>
<td>Albania</td>
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<td>Italia</td>
<td>+ CPG</td>
<td>+ CPG</td>
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<td>United-Kingdom</td>
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**Legend.** + quoted as present by participants, - quoted as absent by the participants, CPG clinical practice guideline according to the definition of the Institute of Medicine. 2 CPG on low back pain (UK and Denmark), 2 in geriatrics (UK and France) and 1 in paediatrics (France). a CPG quoted in Ireland were the British ones. b Serbia quoted the recommendation from EFNS.
Discussion

On the 66 contacted participants, 41 answered our questionnaire with a satisfied response rate of 62%, representing 30 of the 38 European countries. Seventy-one documents were quoted in questionnaires. After duplicates removed, 54 documents were collected and validated by the participants. On these documents, 20 were CPGs: 6 on chronic pain, 5 on neuropathic pain, 4 on cancer pain, 2 in geriatrics, 2 for low back pain and 1 in paediatrics. This is the first study which made an inventory of all European guidelines on management of pain, including non-English documents. The existence of a CPG in a country can be an example of a quality indicator for the health system because the presence or absence of a CPG is decisive for an optimal (efficient, safe and updated) management of the disease (20). Few countries used pre-existing recommendations except Ireland and Serbia. Knowing that the development of a CPG is expensive, it is surprising that European countries did not use a translation of existing guidelines, to reduce the financial cost and to guarantee an optimal quality of care, at the condition that the specific guideline should be adapted to the national health care system of the specific country, but together this GCP should be available for all European health caregivers (20).

Strengths and limitations

The proposed methodology facilitates to identification of CPGs which are rarely referenced in international database. This study is a quasi-exhaustive overview of the European production of CPG in 2010. Besides, collected documents were validated by the participants. Nevertheless, it is possible that some CPGs were not quoted and thus, not at our disposition. A country without a national pain society did not give appropriate information. Concerning the translation of
the national guidelines, the authors translated the CPG with a good knowledge of the language but translation errors may occur even if it did not change the comprehension and the evaluation of the document as a CPG. Besides, in Switzerland or in Italy, where the health care system is organized by region, we received local CPGs which cannot give a national view. Finally, this study concerned only Europe because we had the opportunity to be supported by the EFIC.

**Recommendations and perspectives**

It would be interesting repeat this study within two years to observe whether the number of high quality CPGs increases in Europe: this increase can be used as a good quality indicator about pain management in Europe. The other perspective would be to assess their quality of development with a specific tool the Appraisal Guidelines for Research and Evaluation version II (AGREE II) (21). This instrument assesses the quality of development of a CPG using 6 domains and can be a quality indicator to follow regularly. This work was already done for CPGs about neuropathic cancer pain (22-24). It is concluded that even if a topic was common in several CPGs, references used were different between recommendations and that the quality of development of these CPGs should be improved concerning editorial independence and applicability. European CPGs with a satisfied level of quality could be proposed internationally and translated in each country, according their healthcare system. Human and financial means could be pooled for the best management. A tool exists for that: ADAPTE which was translated in French (25). These new methodologies would be interesting to develop in the domain of pain.
Acknowledgements

The authors want to thank the 66 participants who participated in the study.


References


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18. SIGN. Control of Pain in Adults with Cancer. Edinburgh: Scottish Intercollegiate Guidelines Network publication. 2008


Improving neuropathic cancer pain in Europe
CHAPTER 3 - Guidelines for Neuropathic Pain Management in Patients with Cancer: A European Survey and Comparison


Virginie PIANO, Annelies SCHALKWIJK, Jako BURGERS, Stans VERHAGEN, Hans KRESS, Yechiel HEKSTER, Michel LANTERI-MINET, Yvonne ENGELS, Kris VISSERS
Abstract:

Between 19% and 39% of patients with cancer pain suffer from neuropathic pain. Its diagnosis and treatment is still challenging. Yet, national clinical practice guidelines (CPGs) have been developed in several European countries to assist practitioners in managing these patients safely and legally. The aim of this study was to assess the quality of the development and reporting of these CPGs. **Methods:** In collaboration with the European Federation of IASP Chapters, a European inventory of CPGs was conducted. Inclusion criteria were at least one paragraph dedicated to the treatment of neuropathic pain in cancer. Using the Appraisal of Guidelines, Research and Evaluation II instrument, 2 appraisers independently assessed the quality of the development process of the included CPGs in 6 quality domains. Besides, CPGs developed by governmental organization were compared with those developed by professional societies using t-tests. **Results:** Mean scores of the domains “scope and purpose” (80%) and “clarity of presentation” (61%) were satisfactory, “stakeholder involvement” (58%), “rigor of development” (57%), and “editorial independence” (53%) were acceptable, and “applicability” was insufficient (39%). Governmental guidelines had higher quality scores than professional society guidelines for domain “stakeholder involvement” and “editorial independence” (P < 0.01). **Conclusions:** The quality of the development process of the 9 included CPGs varied widely. CPGs should be developed within a structured guideline program, including methodological support. As developing a CPG is expensive and time-consuming, we recommend more international cooperation to increase quality and lower the development costs.
INTRODUCTION

Pain is a common symptom in cancer patients. In Europe, 56% of cancer patients suffer from moderate to severe pain and consequently report difficulties in their daily activities and high impairment of their quality of life. (1) For adequate treatment of pain, it is important that both nociceptive and neuropathic pain is diagnosed, as they need different treatments.

In 1986, the World Health Organization (WHO) published the “WHO analgesic ladder”, a tool for a stepwise pharmacological approach for the treatment of nociceptive pain in cancer patients. (2) This 3-step approach can be effective in approximately 80% of cancer patients. (3) Despite the introduction of this pain ladder and new analgesic pain therapies, the prevalence of pain in cancer patients remained around 50% during the past 40 years. (4) One of the possible reasons for incomplete pain relief may be the presence of neuropathic pain, because 40% of patients with cancer on opioid therapy referred to a specialized pain clinic appeared to have neuropathic pain alone or in combination with nociceptive or visceral pain. (5) No evidence-based algorithm for the treatment of neuropathic pain in cancer exists. In clinical practice, neuropathic pain is often treated with adjuvants like tricyclic antidepressants (amitriptyline or nortriptyline) or anticonvulsants (gabapentin or pregabalin). (6) The evidence for these types of drugs, based on number needed to treat (NNT 1.2–3.6) and number needed to harm (NNH 6–28), is mainly derived from research performed in patients with painful diabetic neuropathy or postherpetic neuralgia (PHN). (7–9) Little scientifically sound data are available to determine these figures for cancer patients with neuropathic pain. (10) Hence, the benefit vs. risk ratio for cancer patients might be worse for these antineuropathic drugs. Additionally, adjuvant drugs for the treatment of neuropathic pain
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are frequently prescribed in combination with opioids, which can increase side effects. (6) Lastly, the mechanisms of neuropathic pain in patients with DPN or PHN are most likely more localized than in patients with cancer, which also may decrease the chance that these patients will benefit from the same symptomatic approach. (11) Clinical practice guidelines (CPGs) can contribute to effective and safe prescription. (12) Systematically developed guidelines can support the practitioner in making appropriate decisions. (13)

Therefore, in this study, we assessed the quality of the development process of national CPGs, developed in European countries, which contain at least one section about neuropathic pain treatment in patients with cancer. While professional societies of medical specialists should be better informed about clinical aspects, organizations specialized in guideline development should be better equipped to guide the process of guideline development. We also studied whether such differences have consequences for the guideline development quality.

METHODS

Collection and Selection of Guidelines

Guideline collection was conducted in 2 steps: (1) a review of the literature and (2) an email with a questionnaire to European pain experts. This second step was needed, as most of the guidelines are non-English and not published in scientific papers, and thus, a review in usual databases would not be sufficient to obtain all guidelines.

For the review, we searched CPGs in MEDLINE in Europe containing at least one chapter on the management of neuropathic pain in patients with cancer. A literature search of the English and non-English literature indexed in Ovid-Medline, Pubmed, Embase, Cinahl,
and the National Guideline Clearinghouse database in April 2010 was conducted using the following search strategy: “Practice Guideline” [Publication Type] or “Guideline” [Publication Type] or “Guidelines as Topic” [Mesh], “Neuralgia” [Mesh], or “neuropathic pain” [All Fields] and “Neoplasms” [Mesh] or “cancer” [All Fields]. Exclusion criteria were studies on guidelines about children or the elderly, guidelines from non-European countries, and international guidelines (when at least 2 countries are represented in the development of the guideline). All articles about clinical practice guideline (CPG) on cancer pain or neuropathic cancer pain were included. Selection was carried out by titles, then by abstracts and finally by reading full text.

For step 2, an invitation for collaboration with the European Federation of IASP Chapters (EFIC) was accepted by as well the past and the current president. The official EFIC (n = 34), and representatives of the NeuPSIG (Neuropathic Pain Special Interest Group of the IASP), all pain specialists (n = 32), were invited by email in March 2010 to mention and send current guidelines in their country that contain information about neuropathic pain treatment in cancer patients. In a second mail, they were invited to validate the collected documents.

**Inclusion and Exclusion Criteria**

Inclusion criteria for further analyses of the collected guidelines were (1) fulfillment of the definition of the Institute of Medicine for practice clinical guidelines and (2) having at least one paragraph dedicated to the treatment of neuropathic pain in cancer. (14) The search period was from January 2007 to March 2010. A CPG was excluded if (1) it was restricted to specific groups, for example, children or frail elderly; (2) it did not include systematically collected literature to support the recommendations; or (3) if it was published
after our inclusion time (March 2010). Each collected CPG was sent to the participant to check and validate our collection.

Translation Process

Each non-English included CPG was translated with the help of a translator toolkit and checked by the authors. All authors were fluent in English. VP, MLM, and KV are French-speaking and able to translate the French guidelines; AS, SV, JB, YE, YH are Dutch, YH is also fluent in Norwegian, and HK, fluent in German. Additional native speakers were contacted for CPGs in other languages.

Assessment Tool: The AGREE II Instrument

At least 2 authors independently scored included CPGs according to the Appraisal of Guidelines, Research and Evaluation II (AGREE II) instrument. (15,16) The AGREE II instrument is widely used to assess the quality of development and reporting of CPGs. It provides an appraisal of the predicted validity of a CPG, that is, the likelihood of a CPG to achieve its intended outcome. This internationally validated 23-item instrument consists of 6 domains divided in items: (1) scope and purpose, which covers the overall aim of the guideline and target groups for whom the guideline is intended (3 items); (2) stakeholder involvement, which evaluates the appropriate stakeholders involved in guideline development and the views of its intended users (3 items); (3) rigor of development, which assesses the selection of the evidence and the method to create recommendations (8 items); (4) clarity and presentation, which evaluates the structure and the format of the guideline (3 items); (5) applicability, which assesses facilitators and potential barriers for guideline implementation (4 items); and (6) editorial independence, which covers biases concerning conflicts of interest (2 items) and one overall assessment item, judging whether the guideline ought to be recommended for its
use in clinical practice. Each item was rated by using a 7-point Likert scale (from 1 “strongly disagree” to 7 “strongly agree”). All CPGs were integrally assessed.

**Appraisers**

According to the AGREE protocol, 2 appraisers (VP and AS) independently assessed each guideline with AGREE II. They were trained in using the AGREE II instrument. Each item score needed to be explained by specific comments. Differences on items scores of more than 1 point on the Likert scale were discussed until consensus was obtained. If no consensus was reached on a specific item, a third appraiser (YE) assessed it independently, and the same procedure of consensus with 3 appraisers was carried out.

**Data Collection**

An item rating < 4 was considered low, ≥ 4 acceptable, and ≥ 6 high. Domain scores per CPG were calculated by summing up the AGREE II item scores and standardizing them as a percentage of the maximum possible domain score, according to the instructions within the instrument with this formula: \([(\text{score obtained}-\text{minimum score possible})/(\text{maximum score possible}-\text{minimum score possible})]\) x 100. A domain score < 60 % was considered as low, ≥ 60% as acceptable, and ≥ 80% as high.

**Statistical Analysis**

All data were collected and analyzed with SPSS 16.0 (NY, USA) using descriptive statistics. Median item and domain scores were calculated. Finally, median domain scores of CPGs developed by organizations specialized in guideline development and CPGs
developed by professional bodies were calculated and compared using t-test.

RESULTS

Literature Review

Selection on Title. The Embase search yielded 177 articles, of which 8 were selected (Figure 1). Of the Medline search, another 16 of 203 retrieved articles were selected. The Cinahl database contained 2 articles, none being selected. A Pubmed search found 35 articles, of which 4 were selected. The National Clearing House search yielded 467 articles, of which 20 were selected.

Selection of Abstract. Of the 48 articles selected by titles, 6 were selected by the abstract, and 2 were duplicates. On this selection, only 1 was included: the SIGN 2008 guideline from the National Clearing House database. (17)

CPG Collection via EFIC

Sixty-two percent of the EFIC and NeuPSIG members responded. Fifty-four documents about pain (including pain in children and pain in elderly), neuropathic pain, and cancer pain were collected. Of these, 17 contained at least one section about neuropathic pain treatment in patients with cancer and were validated by the participants. Nine of these fulfilled the definition of a clinical practice guideline (CPG) and thus met all inclusion criteria (Figure 2). (17–25) Only one included guideline was in English. The other included guidelines were translated into English by the authors for the French and the Dutch guidelines. The Norwegian guidelines were translated into English with the help of the translator toolkit and checked by YH.
The Italian and Spanish guideline translations were checked by native speakers who are also fluent in English.

For each item, consensus in rating was reached between the 2 appraisers. Domain scores for the 9 CPGs are presented in Table 1. The overall median scores were 81% for “scope and purpose”, 58% for “stakeholder involvement”, 57% for “rigor of development”, 61% for “clarity and prescription”, 39% for “applicability”, and 53% for “editorial independence”.
Figure 1. Review of clinical practice guidelines (CPGs) concerning the treatment of neuropathic pain in cancer patients in Europe.

Identification

<table>
<thead>
<tr>
<th>Database</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Embase</td>
<td>177</td>
</tr>
<tr>
<td>Medline</td>
<td>203</td>
</tr>
<tr>
<td>Cinahl</td>
<td>2</td>
</tr>
<tr>
<td>Pubmed</td>
<td>35</td>
</tr>
<tr>
<td>National Clearing House</td>
<td>467</td>
</tr>
<tr>
<td>Total</td>
<td>884</td>
</tr>
</tbody>
</table>

Screening

- Embase (n=8)
- Medline (n=16)
- Cinahl (n=0)
- Pubmed (n=4)
- National Clearing House (n=20)

Total n=48

Records excluded on abstract (n=42)

Eligibility

Documents assessed for eligibility (n=6)

Documents excluded on article (n=5)

Inclusion

CPGs included: (n=1)
SIGN 2008 guideline
Figure 2. Flow chart: collection of European national Clinical Practice Guidelines (CPGs) from March to April 2010.

Webmail inquiry to 34 EFIC and 32 NeuPSIG representatives in 38 European countries (March-April 2010) (n= 71 documents, 41 responders, 30 countries)

Records after duplicates removed (n=54)

Records screened (n=54)

Records excluded: no chapter on neuropathic cancer pain (n=37)

Documents assessed for eligibility (n=17)

Documents excluded: did not fulfill the Field's definition of a CPG (n=8)

CPGs included: (n=9)
Improving neuropathic cancer pain in Europe

Table 1. Assessment of the Quality of the 9 Clinical Practice Guidelines About Neuropathic Cancer Pain Treatment with AGREE II Instrument Between 2005 and 2010

<table>
<thead>
<tr>
<th>Guidelines</th>
<th>Scope and purpose</th>
<th>Stakeholder involvement</th>
<th>Rigor of development</th>
<th>Clarity and presentation</th>
<th>Applicability</th>
<th>Editorial independence</th>
</tr>
</thead>
<tbody>
<tr>
<td>All guidelines</td>
<td>81</td>
<td>58</td>
<td>57</td>
<td>61</td>
<td>39</td>
<td>53</td>
</tr>
<tr>
<td>Netherlands 2008-1</td>
<td>Diagnosis and treatment of pain in patients with cancer *</td>
<td>95</td>
<td>95</td>
<td>96</td>
<td>75</td>
<td>43</td>
</tr>
<tr>
<td>Norway 2009</td>
<td>Pain treatment</td>
<td>86</td>
<td>86</td>
<td>61</td>
<td>61</td>
<td>79</td>
</tr>
<tr>
<td>United Kingdom 2008</td>
<td>Control of pain in adults with cancer *</td>
<td>91</td>
<td>81</td>
<td>70</td>
<td>64</td>
<td>48</td>
</tr>
<tr>
<td>France 2010</td>
<td>Chronic neuropathic pain</td>
<td>86</td>
<td>48</td>
<td>80</td>
<td>71</td>
<td>29</td>
</tr>
<tr>
<td>Spain 2008</td>
<td>Palliative care *</td>
<td>86</td>
<td>67</td>
<td>52</td>
<td>64</td>
<td>25</td>
</tr>
<tr>
<td>Netherlands 2008-II</td>
<td>Pain in palliative care</td>
<td>95</td>
<td>57</td>
<td>32</td>
<td>64</td>
<td>39</td>
</tr>
<tr>
<td>Italy 2008</td>
<td>Pain management in cancer</td>
<td>81</td>
<td>24</td>
<td>52</td>
<td>54</td>
<td>21</td>
</tr>
<tr>
<td>Norway 2007</td>
<td>Palliative care *</td>
<td>67</td>
<td>33</td>
<td>41</td>
<td>29</td>
<td>29</td>
</tr>
<tr>
<td>Italy 2006</td>
<td>Control of cancer pain **</td>
<td>41</td>
<td>29</td>
<td>32</td>
<td>64</td>
<td>39</td>
</tr>
</tbody>
</table>

*Guideline development group ** Local initiative of guideline development; A domain score <60% was considered as low, ≥ 60% as acceptable and ≥ 80% as high (in bold).
The 4 CPGs developed by a guideline development organization (17,20,22,23) had higher domain scores than the 5 CPGs developed by a medical society. (18,19,21,24,25) The difference was significant (P < 0.05) for the domains “stakeholder involvement” and “editorial independence” (Table 2).

<table>
<thead>
<tr>
<th>Origin</th>
<th>Professional society</th>
<th>Guideline development organization</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Scope and purpose</strong></td>
<td>74</td>
<td>89</td>
<td>0.20</td>
</tr>
<tr>
<td>Stakeholder involvement</td>
<td>38</td>
<td>82</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td><strong>Rigor of development</strong></td>
<td>48</td>
<td>70</td>
<td>0.14</td>
</tr>
<tr>
<td><strong>Clarity and presentation</strong></td>
<td>56</td>
<td>66</td>
<td>0.32</td>
</tr>
<tr>
<td><strong>Applicability</strong></td>
<td>31</td>
<td>49</td>
<td>0.15</td>
</tr>
<tr>
<td>Editorial independence</td>
<td>29</td>
<td>84</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>
All items in the domain “scope and purpose” as well as in the domain “clarity and presentation” had a median score of 6 or higher (Table 3). In the domain “stakeholder involvement”, all CPGs included a clear definition of the target users (item 6); other items within this domain received lower median scores. In the domain “rigor of development”, the “formulation of health benefits and safety” (item 11) was the only item with no scores < 4. The domain “applicability” received the lowest median scores, with 3 of 4 items lower than 3 for all CPGs except Norway 2009.

In total, for all guidelines, all items of the domain “scope and purpose” and “clarity and presentation” had high median scores. Three of the 4 items included in the domain “applicability” had median scores < 4.
### Table 3. Median AGREE II item scores of included 9 CPGs

<table>
<thead>
<tr>
<th>Item</th>
<th>Median</th>
<th>Range</th>
<th>CI (95%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Scope and purpose</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall objective(s) of the guideline is (are) specifically described</td>
<td>6</td>
<td>3</td>
<td>4.9-6.74</td>
</tr>
<tr>
<td>Health question(s) covered by the guideline is (are) specifically described</td>
<td>7</td>
<td>3</td>
<td>4.7-7.1</td>
</tr>
<tr>
<td>The population to whom the guideline is meant to apply is specifically described</td>
<td>6</td>
<td>2</td>
<td>4.1-6.4</td>
</tr>
<tr>
<td><strong>Stakeholder involvement</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Guideline development group included individuals from all the relevant professional groups</td>
<td>5</td>
<td>2</td>
<td>3.4-6.4</td>
</tr>
<tr>
<td><strong>Views and preferences of the target population have been sought</strong></td>
<td>1</td>
<td>1</td>
<td>0.7-4.2</td>
</tr>
<tr>
<td>Target users of the guideline are clearly defined</td>
<td>6</td>
<td>2</td>
<td>3.2-6.4</td>
</tr>
<tr>
<td><strong>Rigor of development</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systematic methods were used to search for evidence</td>
<td>2</td>
<td>1</td>
<td>1.4-5.5</td>
</tr>
<tr>
<td>Criteria for selecting the evidence are clearly described</td>
<td>4</td>
<td>1</td>
<td>1.9-5.2</td>
</tr>
<tr>
<td>Strengths and limitations of the body of evidence are clearly described</td>
<td>5</td>
<td>1</td>
<td>2.9-6.1</td>
</tr>
<tr>
<td>Methods used for formulating the recommendations are clearly described</td>
<td>5</td>
<td>2</td>
<td>3.1-5.6</td>
</tr>
<tr>
<td>Health benefits, side effects and risks have been considered in formulating the recommendations</td>
<td>6</td>
<td>4</td>
<td>4.9-6.2</td>
</tr>
<tr>
<td>Explicit link between recommendations and supporting evidence</td>
<td>3.5</td>
<td>1</td>
<td>2.0-5.2</td>
</tr>
<tr>
<td><strong>Guideline has been externally reviewed by experts prior to its publication</strong></td>
<td>2</td>
<td>1</td>
<td>1.2-4.6</td>
</tr>
<tr>
<td>Procedure for updating is provided</td>
<td>5</td>
<td>1</td>
<td>2.2-6.2</td>
</tr>
<tr>
<td><strong>Clarity and presentation</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recommendations are specific and unambiguous</td>
<td>6</td>
<td>2</td>
<td>4.6-7.0</td>
</tr>
<tr>
<td>Different options for management of the condition are clearly presented</td>
<td>6</td>
<td>4</td>
<td>5.1-6.7</td>
</tr>
<tr>
<td>Key recommendations are easily identifiable</td>
<td>6</td>
<td>2</td>
<td>4.1-6.6</td>
</tr>
</tbody>
</table>
Improving neuropathic cancer pain in Europe

<table>
<thead>
<tr>
<th>Item</th>
<th>Median</th>
<th>Range</th>
<th>CI (95%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Applicability</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Guideline described facilitators and barriers to its application</td>
<td>2</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Guideline provides advice and/or tools on how the recommendations can be put into practice</td>
<td>4</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>Potential cost implications of applying the recommendations have been considered</td>
<td>1</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Guideline presents monitoring and/or auditing criteria</td>
<td>2</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Editorial independence</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>The views of the funding body have not influenced the content of the guideline</td>
<td>5</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td>Competing interests of guideline development group members have been recorded and addressed</td>
<td>4</td>
<td>1</td>
<td>7</td>
</tr>
</tbody>
</table>

AGREE, Appraisal of Guidelines, Research and Evaluation II instrument; CPG, clinical practice guidelines, Item scores below or equal to 3: insufficient quality of development. CI confidence interval.
DISCUSSION

Main Findings

This is the first study that systematically assessed the quality of CPGs developed in European countries about the treatment of neuropathic pain in cancer patients. There was much variation in quality between the CPGs.

High-scoring domains were “scope and purpose” and “clarity of presentation”, which is consistent with findings from other studies. (26–28) Applicability of the guideline was low in 8 CPGs, implying that anticipating on implementation needs more emphasis in CPGs to increase practitioners’ use. This confirms the findings from a recent qualitative study among general practitioners about barriers to use guidelines. (29)

One of the factors that could explain differences between CPGs may be the organization responsible for the CPG. In our study, 2 of the CPGs with the highest AGREE II scores were developed by institutes specialized in guideline development. Both the Scottish Intercollegiate Guidelines Network and the Dutch Institute for Healthcare Improvement (CBO, the Netherlands) used a development process that was based on the original AGREE instrument. (17,23) Burgers et al., who assessed the quality of 86 European and Canadian guidelines with the AGREE instrument, concluded that the quality of the development process of CPGs developed in a guideline program and by government agencies was higher than that of CPGs from other organizations. (12) A recent systematic review of Alonso-Coello et al. (26) analyzed studies assessing guidelines published between 1980 and 2007 with the AGREE instrument and found a higher development quality in
recently developed guidelines. In our assessment with AGREE II, we found higher median scores mainly on the purpose and clarity domains. Guideline developers became more aware of the importance and methods of a systematic development process, maybe partly by publications on this topic and the availability of the AGREE and AGREE II instrument. (28)

Most CPGs gave no information about views and preferences of the target patient population and their influence on the development of the recommendations; only 3 CPGs had patients’ representatives in their workgroup (Netherlands 2008-I, U.K. 2008 and Norway 2009). Probably, more guidance is needed on how to involve patients in the guideline development process. (30) Furthermore; most CPGs gave no attention to the applicability and implementation, while this is very important for clinicians to use them. (31)

**Strengths and Limitations**

With the help of EFIC and NeuPSIG collaboration, we were able to obtain an extensive overview of guidelines that contain information about neuropathic pain in cancer patients, and it was possible to overcome the obstacles of gray literature. We used AGREE II, the updated version of the AGREE instrument. AGREE II, which uses a 7-point Likert scale (instead of the 4-point Likert scale in the AGREE instrument), improves the reliability of the item and domain scores. (15, 16) This instrument was used recently for the assessment of guidelines for migraine and gave a good overview of the development of guidelines in pain. (32)

Although neuropathic pain in cancer patients is a worldwide problem, we only assessed European CPGs. The main reason for this restriction was the opportunity to collaborate with the EFIC and NeuPSIG, which
helped us to collect information from 30 of the 38 European countries. Second, we did not find a CPG merely dedicated to the treatment of neuropathic pain in cancer patients. Third, in contrast to other studies, we also included guidelines that were not written in the native language of the researchers. With the translator toolkit, we were able to assess also these 5 CPGs after validation of the translation by native or fluent speakers.

Finally, results of the AGREE II assessment should be interpreted with caution. Using information only available in the CPG may limit the validity of the scores. Besides, AGREE II focuses on the methods and reporting of the guideline, but does not assess the validity of the diagnosis, medical content, and clinical recommendations. (33) In perspective, the comparison of the content of the guidelines could be very interesting for our knowledge about neuropathic pain in patients with cancer and its management in Europe.

CONCLUSIONS AND RECOMMENDATIONS

The quality of CPGs on neuropathic cancer pain is modest. All domains and items showed room for improvement in most CPGs. Yet, 3 items need specific attention in future guideline development about this topic: incorporating the patients’ views, describing the systematic review process, and giving recommendations about the implementation of the CPG. We did not find a CPG merely dedicated to the treatment of neuropathic pain in cancer patients. Yet, this clinical problem in this specific patient group concerns an area of medical uncertainty, iatrogenic complications, and interventions carrying significant risks and costs, and therefore fits into the criteria for creating an independent CPG. (14) It implies that (1) CPG developers should emphasize that the scientific evidence is weak and
should be interpreted with caution and (2) there is a need for more research on neuropathic cancer pain patients to provide evidence for more reliable CPGs. As developing guidelines is time-consuming and expensive, international cooperation in CPG development could be a solution to increase quality and reduce costs. (34)

ACKNOWLEDGMENTS

The authors want to thank the participants of the investigation from EFIC and European NeuPSIG members. We would like to thank Professor Hervé Maisonneuve for his advice about the quality of guidelines. We sincerely thank Dr Cecilia Condello for checking the English translation of the Italian guidelines and Dr Cathy Francino for checking the Spanish guideline.

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AUTHOR CONTRIBUTIONS

VP and AS conceived and designed the experiments and analyzed the data. They also wrote the manuscript with YE and SV. JB contributed to the method, the interpretation of the results, and the discussion regarding the AGREE II instrument. YK contributed to the introduction and discussion. YE, SV, and MLM supervised the overall execution of the project and contributed to the experimental design with KV. HK provided support from the EFIC. All authors discussed the results and commented on the manuscript and agreed the final version.
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Improving neuropathic cancer pain in Europe


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Improving neuropathic cancer pain in Europe
CHAPTER 4 - Diagnosing Neuropathic Pain in Patients with Cancer: Comparative Analysis of Recommendations in National Guidelines from European Countries


Virginie PIANO, Stans VERHAGEN, Annelies SCHALKWIJK, Jako BURGERS, Hans KRESS, Rolf-Detlef TREEDE, Yechiel HEKSTER, Michel LANTERI-MINET, Yvonne ENGELS, Kris VISSERS
Abstract

Background: Neuropathic pain is a prevalent symptom in patients with cancer, which needs a more specific algorithm than nociceptive pain or neuropathic pain from other origin. Clinical practice guidelines (CPGs) can be helpful in optimizing the diagnosis of neuropathic pain in patients with cancer. Methods: In this study, 9 national CPGs in Europe on the diagnosis of neuropathic pain in patients with cancer were included. Recommendations with their grade (according SIGN 55 classification) and supporting literature (first author, patients’ population, year, and type of publication) were compared between CPGs. Results: Nine CPGs including recommendations on neuropathic pain could be selected and were assessed. In total, they used 149 references of which 72 (48%) were about cancer conditions, 39 (26%) about neuropathic pain, and only 3 about neuropathic pain in patients with cancer (2%). Only 28 (19%) references were shared between 2 or more guidelines. There was only one shared reference specifically related to cancer neuropathic pain. Recommendations and their evidence grading strongly differ between CPGs. Conclusion: This work demonstrates an important heterogeneity between European recommendations on diagnosis and assessment of neuropathic pain in patients with cancer. The main weaknesses are the low level of evidence and the absence of specific data focusing on neuropathic pain in patients with cancer. We recommend that physicians dealing with neuropathic pain in patients with cancer should be specially trained, that a specific methodology to develop CPGs should followed, and that specific research should be developed on the diagnosis of neuropathic pain in patients with cancer.
Chapter 4 – Diagnosing neuropathic cancer pain

INTRODUCTION

In Europe, about 56% of patients with cancer suffer at least monthly from moderate to severe pain, causing difficulties in their daily activities. (1,2) In this context, pain is frequently neuropathic (19–39%) with 3 etiologies: cancer-related neuropathic pain, cancer-therapy induced neuropathic pain, and cancer-associated neuropathic pain. (3–6) Like neuropathic pain in general, neuropathic pain in patients with cancer proves to be difficult to treat and is more distressing than nociceptive pain. (3,7) Therefore, neuropathic pain is a considerable problem for patients with cancer, and its prevalence will increase as the global prevalence and incidence of cancer increase. (8) The diagnosis of neuropathic pain in patients with cancer is essential to (1) possibly detect the cause of cancer in an early state, (2) avoid or diminish neurotoxic events after oncological treatment; especially when chemotherapy is given, and (3) facilitate a mechanistically based approach, and (4) propose the optimal pain treatment. (6,9,10) Until now, no gold standard for the diagnosis of neuropathic pain has been accepted. The neuropathic nature of a pain complaint is diagnosed clinically with the evidence of a lesion or disease of the somatosensory system, primarily from history and clinical examination. (11,12) Several screening instruments, such as the McGill Pain Questionnaire, S-LANSS, Neuropathic Pain Questionnaire, DN4, Pain-DETECT, ID Pain, and StEP, have not been specifically validated in patients with cancer. (13–19)

To guide practitioners through a structured diagnosis of neuropathic pain in patients with cancer, clinical practice guidelines (CPGs) were created as “statements that include recommendations intended to optimize patient care that are informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options.” (20) The aim of this study is to evaluate and compare
recommendations proposed in national CPGs from Europe concerning the specific diagnosis of neuropathic pain in patients with cancer and their evidence grading.

**METHOD**

**Selection of CPGs**

The description of the selection of the CPGs was published in a recent article. 21 Nine CPGs from France (France 2010), Italy (Italy 2006, Italy 2009), the Netherlands (Netherlands 2008-I, Netherlands 2008-II), United Kingdom (United Kingdom 2008) were included and used for this study. (22-26, 30) Four were developed by national supported organization such as the Scottish Network of Guidelines Network (SIGN), the Dutch Institute for Healthcare Improvement (CBO), the Spanish National Plan (Guias de practica clinica en el SNS, Ministerio de Sanidad y Consumo), and the Norwegian national program for Palliative Care. (25,27,29,30) Five were developed by a professional society (palliative care, oncology, or national pain society),(22,24,26,28,29) and 1 was developed by an Italian regional health organization. (23) All CPGs were on pain or palliative care management in patients with cancer except France 2010, which was related to neuropathic pain management in general and Norway 2009, which was about pain management in general.

**Collection of the data and analysis**

We developed a procedure aimed to extract recommendations regarding the diagnosis and assessment of neuropathic pain in patients with cancer and their related references used as evidence in the CPG. Recommendations were defined as “statements that promote or advocate a particular course of action in clinical care”. (31) This process was performed in each CPG. Recommendations
were collected according to the diagnosis algorithm recommended by NeuPSIG (special interest group on neuropathic pain) and classified in 2 main domains with different sub-domains. (32) The first was the working hypothesis of a possible neuropathic pain if pain distribution is neuroanatomically plausible and history suggests relevant lesion or disease (3 sub-domains: pain intensity assessment; neuropathic pain screening tools use; and etiological context assessment).

The second was the use of confirmatory tests in 4 sub-domains: negative (i.e., hypoesthesia) or positive (i.e., allodynia) sensory signs, confined to the innervations territory of the lesioned nerve, pain drawing for neuroanatomical plausibility, quantitative sensory tests (QST), diagnosis test confirming lesion, or disease explaining neuropathic pain. The final criterion for the diagnosis of neuropathic pain was an incomplete response to opioid treatment. For each domain, we collected the grade of recommendation given by CPGs authors according to the SIGN-50 criteria. (22) (Table 1)

We performed a focused analysis of references related to the selected recommendations. These references were classified in 5 categories: (1) “clinimetric studies” to validate the diagnosis tools according Feinstein’s definition, (2) “clinical studies” to evaluate the use of diagnosis tools in daily clinical practice, (3) “epidemiological studies”, (4) “clinical practice guidelines” (CPGs), and (5) “other studies”. (20, 32-33) Each reference was also classified according to country of the first author and/or of the work group, journal, and year of publication, and reference topic (cancer pain, acute and chronic pain, neuropathic pain, neuropathic cancer pain, and pain impairment). A reference used in at least 2 CGP was called a shared reference.

**Statistical analysis**
Analysis was performed with SPSS 16.0 using descriptives and frequencies.

Table 1a. Key to evidence statements according SIGN 50

**LEVELS OF EVIDENCE**

<table>
<thead>
<tr>
<th>Level</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1++</td>
<td>High quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias</td>
</tr>
<tr>
<td>1+</td>
<td>Well-conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias</td>
</tr>
<tr>
<td>1-</td>
<td>Meta-analyses, systematic reviews, or RCTs with a high risk of bias</td>
</tr>
<tr>
<td>2++</td>
<td>High quality systematic reviews of case control or cohort or studies High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal</td>
</tr>
<tr>
<td>2+</td>
<td>Well-conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal</td>
</tr>
<tr>
<td>2-</td>
<td>Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal</td>
</tr>
<tr>
<td>3</td>
<td>Non-analytic studies, e.g. case reports, case series</td>
</tr>
<tr>
<td>4</td>
<td>Expert opinion</td>
</tr>
</tbody>
</table>

Extracted from the SIGN website on 31-Jui-2012 in this URL: http://www.sign.ac.uk/guidelines/fulltext/50/annexb.html
### Table 1b. Key to grades of recommendations according SIGN 50

<table>
<thead>
<tr>
<th>GRADE</th>
<th>DESCRIPTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>At least one meta-analysis, systematic review, or RCT rated as 1++, and directly applicable to the target population; <em>or</em> A body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results</td>
</tr>
<tr>
<td>B</td>
<td>A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results; <em>or</em> Extrapolated evidence from studies rated as 1++ or 1+</td>
</tr>
<tr>
<td>C</td>
<td>A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; <em>or</em> Extrapolated evidence from studies rated as 2++</td>
</tr>
<tr>
<td>D</td>
<td>Evidence level 3 or 4; <em>or</em> Extrapolated evidence from studies rated as 2+</td>
</tr>
<tr>
<td>GODD PRACTICE POINTS</td>
<td>Recommended best practice based on the clinical experience of the guideline development group</td>
</tr>
</tbody>
</table>

Extracted from the SIGN website on 31-Jui-2012 in this URL: [http://www.sign.ac.uk/guidelines/fulltext/50/annexb.html](http://www.sign.ac.uk/guidelines/fulltext/50/annexb.html)
RESULTS

*Pages specifically dedicated to the diagnosis of neuropathic pain in patients with cancer*

The 9 included CPGs represented 1480 pages with only 76 (5%) pages focused on the diagnosis of neuropathic pain in patients with cancer. This specific part represented <10% of the whole guideline in 8 of 9 included CPGs with a range from 1/24 pages (0.8%) in Norway 2009 to 39/170 pages (23%) in France 2010.

*Characteristics of the references related to recommendations selected in the “neuropathic pain in patients with cancer” diagnosis and assessment section of CPGs*

Our work collected a total of 149 references related to recommendations selected in the “neuropathic pain in patients with cancer” diagnosis and assessment section of CPGs. Among these, 72 (48%) were about cancer pain, 39 (26%) on acute and chronic pain, 26 (18%) on neuropathic pain, 9 (6%) on pain impairment (emotional impact and quality of life), and only 3 (2%) specifically about neuropathic pain in patients with cancer. Category references were as follows: 46 clinimetric studies (31%), 37 clinical studies (25%), 12 epidemiological studies (8%), 28 CPGs (19%), and 26 others studies (17%). In terms of topic and categories, distribution of references was similar considering each CGP individually (data not shown). Only 28 (19%) of the 149 references were shared between at least two guidelines, 20 shared by two guidelines, 5 by three guidelines, 2 by four guidelines, and 1 by five guidelines. (34) Considering the seven references mentioned in at least three guidelines, 3 were used in a cancer population and 2 in a chronic pain population (one of them in
a neuropathic pain population). (34–40) There was only one shared reference specifically related to neuropathic pain in patients with cancer (Table 2). (41)

The country of the first author of the references according to the origin of the CPG. The proportion of references originating of the same country as the CPG varied from 0 (Spain 2008) to 57% (Norway 2009). Half of the references had a US origin (Table 3).
Table 2. Characteristics of the references related to recommendations selected in the “neuropathic pain in patients with cancer” diagnosis and assessment section of CGP.

<table>
<thead>
<tr>
<th>Reference topic</th>
<th>Number of references</th>
<th>Range of publication year</th>
<th>References categories</th>
<th>Shared references</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Clinimetric studies</td>
<td>Clinical studies</td>
</tr>
<tr>
<td>Cancer pain</td>
<td>72</td>
<td>1980-2009</td>
<td>16</td>
<td>18</td>
</tr>
<tr>
<td>Acute and chronic pain</td>
<td>39</td>
<td>1974-2007</td>
<td>15</td>
<td>14</td>
</tr>
<tr>
<td>Neuropathic pain</td>
<td>26</td>
<td>1990-2010</td>
<td>11</td>
<td>4</td>
</tr>
<tr>
<td>Neuropathic cancer pain</td>
<td>3</td>
<td>2004-2007</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Pain impairment</td>
<td>9</td>
<td>1985-2007</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>149</td>
<td>1974-2010</td>
<td>46</td>
<td>37</td>
</tr>
</tbody>
</table>

Legend: CPG= Clinical Practice Guideline \(^a\) Clinimetrics: to validate diagnosis tool, meeting the Feinstein’s criteria; \(^b\) clinical studies: to evaluate the use of diagnosis tools in daily clinical practice; \(^c\) shared references = number of references which are mentioned in at least 2 guidelines. Other: psychological impairment studies, quality of life studies.
Table 3. The country of the first author of the references according to the origin of the CPG

<table>
<thead>
<tr>
<th>Guidelines</th>
<th>Total</th>
<th>France</th>
<th>Italy</th>
<th>Neth</th>
<th>Norway</th>
<th>Spain</th>
<th>UK</th>
<th>USA</th>
<th>Denmark</th>
<th>Canada</th>
<th>Germany</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>France 2010</td>
<td>54</td>
<td>19 (35)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>5 (9)</td>
<td>23 (43)</td>
<td>3 (6)</td>
<td>-</td>
<td>2 (4)</td>
<td>-</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Italy 2009</td>
<td>23</td>
<td>-</td>
<td>3 (13)</td>
<td>-</td>
<td>-</td>
<td>2 (9)</td>
<td>10 (43)</td>
<td>4 (18)</td>
<td>-</td>
<td>1 (4)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Italy 2006</td>
<td>23</td>
<td>1 (4)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>5 (22)</td>
<td>14 (61)</td>
<td>-</td>
<td>-</td>
<td>2 (9)</td>
<td>1 (4)</td>
<td>-</td>
</tr>
<tr>
<td>Netherlands 2008-I</td>
<td>32</td>
<td>-</td>
<td>5 (16)</td>
<td>3 (9)</td>
<td>1 (3)</td>
<td>2 (6)</td>
<td>12 (38)</td>
<td>1 (3)</td>
<td>2 (6)</td>
<td>1 (4)</td>
<td>1 (4)</td>
<td>-</td>
</tr>
<tr>
<td>Netherlands 2008-II</td>
<td>14</td>
<td>-</td>
<td>2 (14)</td>
<td>-</td>
<td>-</td>
<td>7 (50)</td>
<td>1 (7)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Norway 2009</td>
<td>7</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>4 (57)</td>
<td>-</td>
<td>3 (43)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Norway 2007</td>
<td>7</td>
<td>1 (14)</td>
<td>-</td>
<td>-</td>
<td>1 (14)</td>
<td>2 (29)</td>
<td>-</td>
<td>1 (14)</td>
<td>1 (14)</td>
<td>-</td>
<td>1 (14)</td>
<td>-</td>
</tr>
<tr>
<td>Spain 2008</td>
<td>4</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1 (25)</td>
<td>2 (50)</td>
<td>-</td>
<td>1 (25)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>UK 2008</td>
<td>22</td>
<td>1 (5)</td>
<td>2 (8)</td>
<td>2 (8)</td>
<td>1 (5)</td>
<td>-</td>
<td>2 (9)</td>
<td>9 (41)</td>
<td>-</td>
<td>1 (5)</td>
<td>1 (5)</td>
<td>3 (14)</td>
</tr>
<tr>
<td>Total</td>
<td>149</td>
<td>19 (13)</td>
<td>7 (5)</td>
<td>7 (5)</td>
<td>8 (5)</td>
<td>0</td>
<td>14 (9)</td>
<td>65 (44)</td>
<td>9 (6)</td>
<td>5 (3)</td>
<td>5 (3)</td>
<td>10 (7)</td>
</tr>
</tbody>
</table>

**Legend:** Neth= the Netherlands, UK=United Kingdom, USA=United States of America. "Bold types contain percent of citations of studies from authors of the same country as the origin of the CPG." Other= Australia, China, Finland, Greece, India, Ireland, Japan and Switzerland.
Diagnosis and assessment of neuropathic pain in patients with cancer recommendations and their evidence grading in CPGs

Recommendations on how to perform a pain intensity assessment were mentioned in all CPGs except Norway 2009. The systematic use of neuropathic pain screening tools was recommended in 2 guidelines: the DN4 in the French CGP and the NPQ in the Dutch one (Netherlands 2008-I 1). The assessment of the etiological context (neuropathic pain due to nerve damage, by the cancer itself or related to the surgery, chemotherapy, or radiation) was recommended in all CPGs except the Italian CPG of 2009. The description of the pain with negative signs (i.e., hypoesthesia) or positive signs (i.e., allodynia) was recommended in 4 CPGs: France 2010, Netherlands 2008-I, Netherlands 2008-II, and Norway 2009. Pain drawings were recommended in 3 CPGs (France 2010, Norway 2007, and Norway 2009).

Quantitative sensory testing (QST) was also recommended in 2 CPGs (France 2010 and Norway 2007). Search of a partial response to opioids treatment was recommended in 4 CPGs (Italy 2006, Netherlands 2008-II, Spain, and United Kingdom). The grade of recommendation was mentioned in 6 of the 9 guidelines for the working hypothesis and varied from grade A to grade D. The grade was also proposed in the confirmatory tests in the CPG for France 2010 (grade D) and Netherlands 2008-I (grade B). The grade for the partial response to opioids in neuropathic pain was A for United Kingdom and B for Spain (Table 4).
Table 4a. Diagnosis and assessment of neuropathic pain in patients with cancer recommendations and their evidence grading in CPGs.

<table>
<thead>
<tr>
<th>Guidelines</th>
<th>France 2010</th>
<th>Italy 2009</th>
<th>Italy 2006</th>
<th>Netherlands 2008-I</th>
<th>Netherlands 2008-II</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Elements proposed to make a diagnosis of neuropathic pain</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>1) Working hypothesis:</strong> possible neuropathic pain if pain distribution is neuroanatomically plausible and history suggests relevant lesion or disease.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain intensity assessment</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Neuropathic pain screening tools use</td>
<td>+(DN4)</td>
<td>-</td>
<td>-</td>
<td>+(NPQ)</td>
<td>-</td>
</tr>
<tr>
<td>Etiological context assessment</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Grade of recommendation given by the developers</td>
<td>+(A)</td>
<td>+(A)</td>
<td>+(B)</td>
<td>+(B)</td>
<td>-</td>
</tr>
<tr>
<td><strong>2) Confirmatory tests.</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative or positive sensory signs, confined to innervations territory of the lesioned nervous structure</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Pain drawing for neuroanatomical plausibility</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Quantitative sensory tests</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Diagnosis test confirming lesion or disease explaining neuropathic pain</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+(MRI, EMG)</td>
</tr>
<tr>
<td>Grade of recommendation given by the developers</td>
<td>+(D)</td>
<td>-</td>
<td>-</td>
<td>+(B)</td>
<td>-</td>
</tr>
<tr>
<td><strong>Neuropathic pain diagnosis and treatment response</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neuropathic pain can respond to opioids although the response may be incomplete</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Grade of recommendation given by the developers</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
Improving neuropathic cancer pain in Europe

Table 4b. Diagnosis and assessment of neuropathic pain in patients with cancer recommendations and their evidence grading in CPGs.

<table>
<thead>
<tr>
<th>Guidelines</th>
<th>Norway 2009</th>
<th>Norway 2007*</th>
<th>Spain 2008</th>
<th>United-Kingdom 2008 *</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Elements proposed to make a diagnosis of neuropathic pain</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>1) Working hypothesis:</strong> possible neuropathic pain if pain distribution is neuroanatomically plausible and history suggests relevant lesion or disease.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain intensity assessment</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Neuropathic pain screening tools use</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Etiological context assessment</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Grade of recommendation given by the developers</td>
<td>-</td>
<td>-</td>
<td>+(C)</td>
<td>+(D)</td>
</tr>
<tr>
<td><strong>2) Confirmatory tests.</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative or positive sensory signs, confined to innervations territory of the lesioned nervous structure</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Pain drawing for neuroanatomical plausibility</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Quantitative sensory tests</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Diagnosis test confirming lesion or disease explaining neuropathic pain</td>
<td>-</td>
<td>+(MRI, EMG, SEP)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Grade of recommendation given by the developers</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Neuropathic pain diagnosis and treatment response</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neuropathic pain can respond to opioids although the response may be incomplete</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Grade of recommendation given by the developers</td>
<td>-</td>
<td>-</td>
<td>+ (B)</td>
<td>+ (A)</td>
</tr>
</tbody>
</table>

**Legend:** X: information presented in the guideline. Grade of recommendation according SIGN 50: A (studies with a level of evidence of 1), B (studies with a level of evidence of 2 or extrapolate studies with a level of 1), C (extrapolate studies with a level of evidence of 2) D (studies with a level of 3 or 4). +, information present; -, information absent; QST, Quantitative Sensitive Test; cMRI, cerebral Magnetic Resonance Imaging; EMG, ElectroMyoGramme; SEP, Somatosensitive Evoked Potentials. *The topic of the guideline concerned specifically the treatment of pain in cancer and not the diagnosis.
DISCUSSION

In our previous study, from 54 national guidelines on neuropathic pain in cancer, 9 were selected with an acceptable level of quality. In these 9 national CPGs from Europe, 149 references were collected to argue recommendations on neuropathic pain diagnosis and assessment in patients with cancer. A large majority of references were not specifically related to neuropathic pain in patients with cancer. Hence, recommendations were made according to nonspecific data, extrapolated from references on cancer pain regardless of the neuropathic pain mechanism and references on neuropathic pain regardless on the cancer context. Only 3 (2%) of references used recommendations on neuropathic pain diagnosis and assessment in cancer and focused on neuropathic pain in patients with cancer. Regarding the range of the year of publication, these specific references appear to be more recent than the others. These data are in accordance with the recent interest of neuropathic pain in cancer field. Moreover, our work demonstrates that only 19% of shared references in spite of the open criteria chosen (presence of reference in at least 2 CPGs) to define a shared reference. Such a data is in accordance with the weak level of the “Rigor of development” domain according the AGREE II evaluation of the selected CPGs. The weakness of selected CPGs also concerned the details of proposed recommendations. Considering criteria used in the diagnosis algorithm recommended by NeuPSIG, proposed recommendations of national CPGs in Europe appear too general for a proper diagnosis of neuropathic mechanism in pain occurring in cancer context. Consequently, these findings probably explain the heterogeneity of the evidence grading in these guidelines.
In spite of the limitation of our work detailed, results confirmed the need to consider with caution the recommendations proposed in Europe about the neuropathic pain in patients with cancer diagnosis and assessment. (21) Firstly, practitioners’ specific education should be promoted to develop the capacity to evaluate the evidence level of CPGs and to participate actively in their editorial board with methodologists. Secondly, efforts should be made to ensure that CPGs developers describe the extrapolation process when recommendations are not focused on the target population studies. Thirdly, efforts should also be realized in clinical research to obtain robust data on diagnosis and assessment of neuropathic pain in patients with cancer allowing the development of specific recommendations on this topic. This prospect would best be considered through international cooperation and regular updates.

REFERENCES


Improving neuropathic cancer pain in Europe


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Improving neuropathic cancer pain in Europe


CHAPTER 5 - Treatment for Neuropathic Pain in Patients with Cancer: Comparative Analysis of Recommendations in National Clinical Practice Guidelines from European Countries


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Abstract

Introduction: Neuropathic pain is a common symptom, present in 39% of the patients with cancer pain. Treating this type of pain is challenging, as this patient group is often frail and has comorbidities which increase the risk of side events and hence influences their quality of life. Clinical practice guidelines (CPGs) can be helpful for clinicians, especially when scientific evidence is uncertain or weak. In this study, we focused on the quality of the review of the literature used in treatment recommendations in the selected European CPGs.

Methods: In a previous study, 9 CPGs from European countries that contained at least one paragraph on treatment for neuropathic pain in cancer were included. Recommendations with their grade (according SIGN 55 classification) and supporting literature (first author, patients’ population, year and type of publication) were compared between CPGs.

Results: In all CPGs, amitriptylin was mentioned as the drug of first choice. Six guidelines proposed also gabapentinoids. Only 30 of the 163 citations (18%) were based on studies in patients with cancer. Seven CPGs did not argue the indirect evidence due to extrapolation of study results from non-cancer to patients with cancer.

Conclusion: The majority of guideline development groups extrapolated their results to formulate recommendations from non-cancer publications. Consequently, these guidelines fail to address important issues such as altered kinetics and side effect profiles in these patients. We recommend creating specific recommendations by an international expert group for the treatment for neuropathic pain in patients with cancer supported by targeted research in patients with cancer.
INTRODUCTION

In Europe, the prevalence of moderate to severe pain in patients with cancer is about 56%. (1) Pain in patients with cancer is often related to a combination of nociceptive and neuropathic mechanisms. In a systematic review of Bennett, the prevalence of neuropathic pain in patients with cancer was found to be 19%. The combination of mixed pain (nociceptive pain) was found to be 39.7%. (2) Using the World Health Organization (WHO), analgesic ladder for cancer pain relief resolves the nociceptive component in 80% of the treated patients. However, the neuropathic pain component is often more difficult to treat. (3) Not all drugs are specifically registered for the treatment for neuropathic pain in patients with cancer in European countries. This implies that most specific drugs used for the treatment for neuropathic pain in patients with cancer are used off-label. (4) Most clinical research concerning neuropathic pain treatment is performed in patients with diabetic painful neuropathy (DPN) or post-herpetic neuropathy (PHN) and infrequently in patients with neuropathic cancer pain. Patients with cancer suffering from neuropathic pain should be considered different from patients with neuropathic pain in other context for several reasons. (5) Firstly, approximately 50% of the patients with cancer suffering from neuropathic pain also have nociceptive or visceral pain, in contrast to patients suffering from neuropathic pain in another context. (6) Secondly, they are more fragile with a potential life-threatening disease. Thirdly, in patients with cancer, the effect size of antiepileptic or antidepressant drug, used in addition to the opioids, is less than that seen in patients with non-cancer neuropathic pain. (2)

Clinical practice guidelines (CPGs) were created to improve the treatment for a specific condition and are supposed to be based on the latest evidence. Concerning neuropathic pain in patients with cancer, a recent statement of the International Association for the
Study of the Pain (IASP) emphasized that the extrapolation of data from studies of other neuropathic conditions to patients with cancer-induced neuropathic pain is far from straightforward. (5) In parallel of the evaluation of recommendations on neuropathic pain diagnosis and assessment in patients with cancer, (7) the aim of this study is to compare recommendations proposed in national CPGs from Europe concerning the treatment for neuropathic pain in patients with cancer and their evidence grading.

METHODS

Study Design

The relation between chosen references, their level of evidence, and the recommendations given in CPGs was systematically studied.

Selection of Guidelines

A European inventory of CPGs was performed with the support of the European Federation of the IASP Chapters (EFIC). (7) Nine CPGs were included, and this material was used for this study. All CPGs were published between 2006 and 2009 from France (1), Italy (2), the Netherlands (2), Norway (2), Spain (1), and the United Kingdom (1). (8–16) Four were developed under responsibility of a national organization specialized in guideline development. (9,12,14,15) Five were developed by professional societies (oncology, palliative care, or pain societies). (8,10,11,13,16) One was developed by an Italian regional health organization (Italy 2). (8) None of the guidelines were developed solely or specifically for the treatment for neuropathic pain in patients with cancer.

Collection of the Data and Analysis
We developed a procedure to extract recommendations about how to treat neuropathic pain in patients with cancer. Recommendations were defined as “statements that promote or advocate a particular course of action in clinical care”. (17) These treatment recommendations were extracted together with the related references and used as evidence in each CPG. The references were categorized by study design (meta-analysis and systematic review; randomized controlled trial [RCT] with ≥ 60 patients; RCT with < 60 patients; CPG; other) and topic (neuropathic pain, cancer neuropathic pain, cancer pain, acute and chronic pain, and other). Each reference was also considered according to the country of the first author and/or of the work group, journal, and year of publication. A reference used in at least two CPGs was a shared reference. Recommendations were analyzed considering drugs proposed to treat neuropathic pain in patients with cancer in each CPG. We focused our analysis on three main drugs: amitriptyline; gabapentin; and pregabalin. For each of these three drugs, we collected positioning in therapeutic strategy (first or second line), start and maximum doses, titration scheme, mentioned side effects and contra-indications, the level of evidence, and the grade of the recommendation, according to the Scottish intercollegiate guidelines network (SIGN) 50 criteria.(13)

Statistical Analysis
Analysis was performed with SPSS 16.0 using descriptives and frequencies.

RESULTS
Pages Specifically Dedicated to the Treatment for Neuropathic Pain in Patients with Cancer
The nine included CPGs represented 1,480 pages with only 53.5 (4%) pages focusing on the treatment for neuropathic pain in patients with cancer. The sections about the treatment for neuropathic pain in patients with cancer ranged between half a page (Spain) to 37 pages (France) (0.2% to 22%, mostly below 5%).

**Characteristics of the References Related to Recommendations Selected in the “Neuropathic Pain in Patients with Cancer” Treatment Section of CPG**

Our work collected a total of 163 references related to recommendations selected in the “neuropathic pain in patients with cancer” treatment section of CPGs. Among these, a majority (116/163: 71%) were about neuropathic pain in non-cancer context. Eighteen (11%) references concerned specifically neuropathic pain treatment in patients with cancer (Table 1). A large majority (80%) of references were related to RCTs and meta-analysis, systematic review, or review. According to SIGN-50, 50 references (31%) could be classified as top evidence level (15 systematic reviews and 35 RCTs with a high number of patients).
Table 1. Description of clinical practice guidelines and characteristics of the references mentioned in the section treatment of neuropathic pain in patients with cancer.

<table>
<thead>
<tr>
<th>Reference topic</th>
<th>Number of references</th>
<th>Publication year</th>
<th>Publication type</th>
<th>Shared references</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>SR+R</td>
<td>RCT ≥ 60</td>
</tr>
<tr>
<td>Neuropathic pain</td>
<td>116</td>
<td>1969-2007</td>
<td>20</td>
<td>34</td>
</tr>
<tr>
<td>Cancer neuropathic pain</td>
<td>18</td>
<td>1992-2008</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Cancer pain</td>
<td>14</td>
<td>1980-2007</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Acute and chronic pain</td>
<td>11</td>
<td>1999-2007</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Other</td>
<td>4</td>
<td>2000-2004</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td><strong>163</strong></td>
<td><strong>1969-2008</strong></td>
<td><strong>34</strong></td>
<td><strong>35</strong></td>
</tr>
</tbody>
</table>

**Legend:**
- SR+R: systematic review, meta-analysis and review;
- RCT ≥ 60: randomized controlled trial with 60 or more patients;
- RCT < 60: randomised controlled trial with less than 60 patients;
- CPG: clinical practice guideline;
- Other: cohort study, observational study, case report, local statement;
- Shared references: number of references which are mentioned in at least 2 guidelines.
Table 2. Neuropathic pain treatment in cancer references in nine national CPGs from European countries.

<table>
<thead>
<tr>
<th>Year</th>
<th>Publication type</th>
<th>Title of the reference</th>
<th>First author</th>
<th>Publication</th>
<th>Shared references</th>
</tr>
</thead>
<tbody>
<tr>
<td>2008</td>
<td>RCT, 44&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Amitriptyline in the treatment of chemotherapy-induced neuropathic symptoms.</td>
<td>Kautio</td>
<td>J Pain Symptom Manage</td>
<td>-</td>
</tr>
<tr>
<td>2007</td>
<td>RCT, 36</td>
<td>Tramadol in the treatment of neuropathic cancer pain: a double-blind, placebo-controlled study.</td>
<td>Arbaiza</td>
<td>Clin Drug Investig</td>
<td>-</td>
</tr>
<tr>
<td>2007</td>
<td>Clinical trial, 65</td>
<td>Gabapentin and an opioid combination versus opioid alone for the management of neuropathic cancer pain: a randomized open trial.</td>
<td>Keskinboa</td>
<td>J Pain Symptom Manage</td>
<td>+(2 CPGs)</td>
</tr>
<tr>
<td>2006</td>
<td>Review</td>
<td>How to use antidepressants and anticonvulsants as adjuvant analgesics in the treatment of neuropathic cancer pain.</td>
<td>McDonald</td>
<td>J Support Oncol</td>
<td>-</td>
</tr>
<tr>
<td>2005</td>
<td>Clinical trial, 62</td>
<td>Gabapentin is effective in the treatment of cancer-related neuropathic pain: a prospective, open-label study.</td>
<td>Ross</td>
<td>J Palliat Med</td>
<td>-</td>
</tr>
<tr>
<td>2004</td>
<td>RCT, 121</td>
<td>Gabapentin for neuropathic cancer pain: a randomized controlled trial from the Gabapentin Cancer Pain Study Group.</td>
<td>Caraceni</td>
<td>J Clin Oncol</td>
<td>+ (4 CPGs)</td>
</tr>
<tr>
<td>2004</td>
<td>Review</td>
<td>Adjuvant analgesics in cancer pain management.</td>
<td>Lussier</td>
<td>Oncologist</td>
<td>-</td>
</tr>
<tr>
<td>2003</td>
<td>Systematic review</td>
<td>Ketamine as an adjuvant to opioids for cancer pain.</td>
<td>Bell</td>
<td>J Pain Symptom Manage</td>
<td>-</td>
</tr>
<tr>
<td>2002</td>
<td>RCT, 16</td>
<td>Amitriptyline in neuropathic cancer pain in patients on morphine therapy: a randomized placebo-controlled, double-blind crossover study.</td>
<td>Mercadente</td>
<td>Tumor</td>
<td>+(2 CPGs)</td>
</tr>
</tbody>
</table>
### Chapter 5 – Treating neuropathic cancer pain in Europe

<table>
<thead>
<tr>
<th>Year</th>
<th>Publication type</th>
<th>Title of the reference</th>
<th>First author</th>
<th>Publication</th>
<th>Shared references</th>
</tr>
</thead>
<tbody>
<tr>
<td>2002</td>
<td>RCT, 51</td>
<td>Phase III evaluation of nortriptiline for alleviation of symptoms of cis-platinum induced peripheral neuropathy</td>
<td>Hammack</td>
<td>Pain</td>
<td></td>
</tr>
<tr>
<td>2001</td>
<td>Case report</td>
<td>Gabapentine for pain control in cancer patients ‘wound dressing care</td>
<td>Devulder</td>
<td>J Pain Symptom Manage</td>
<td></td>
</tr>
<tr>
<td>1999</td>
<td>Clinical trial, 593</td>
<td>Assessment and treatment of neuropathic cancer pain following WHO guidelines.</td>
<td>Grond</td>
<td>Pain</td>
<td></td>
</tr>
<tr>
<td>1999</td>
<td>Clinical trial, 22</td>
<td>Gabapentin as an adjuvant to opioid analgesia for neuropathic cancer pain.</td>
<td>Caraceni</td>
<td>J Pain Symptom Manage</td>
<td>+(2 CPGs)</td>
</tr>
<tr>
<td>1997</td>
<td>Review</td>
<td>Neuropathic pain in cancer patients: mechanisms, syndromes, and clinical controversies. (22)</td>
<td>Martin</td>
<td>J Pain Symptom Manage</td>
<td></td>
</tr>
<tr>
<td>1992</td>
<td>RCT, 11</td>
<td>A randomized double blind cross over trial of intravenous lidocaine in the treatment of neuropathic cancer pain</td>
<td>Bruera</td>
<td>Cancer Treat Rep</td>
<td></td>
</tr>
<tr>
<td>1989</td>
<td>RCT, 10</td>
<td>Trial of intravenous lidocaine on painful neuropathy in cancer patients.</td>
<td>Elleman</td>
<td>Clin J Pain</td>
<td></td>
</tr>
</tbody>
</table>

**Legend:** RCT: randomized controlled trial, CPGs: clinical practice guidelines. *a* number of patients included in the trial
Only 30 (18%) of the 163 references were shared between at least two guidelines: 21 shared by two guidelines; four by three guidelines; four by four guidelines; and only one by five guidelines. References specifically related to neuropathic pain in patients with cancer are presented in Table 2. Among these references specifically related to neuropathic pain in patients with cancer, only four were shared by at least two references.

**Treatment for Neuropathic Pain in Patients with Cancer Recommendations and Their Evidence Grading in CPGs**

Drugs recommended in selected CPGs are presented in Table 3. Among these, only three classes were recommended by all CPGs: tricyclic antidepressant drugs; α2δ agonists; and other anticonvulsant drugs. SNRI antidepressant drugs were recommended by four CPGs (France 2010, Italy 2009, Norway 2007, and Spain). Strong opioids, in combination with co-analgesic, were proposed by five CPGs (France 2010, Italy 2009, the Netherlands 2008-I, Norway 2007, and Spain). However, the Netherlands 2008-II recommended not using them, and three CPGs did not mention them (Italy 2006, U.K., and Norway 2009). Capsaicin plaster was recommended by five guidelines (France 2010, the Netherlands 2008-I, Norway 2007, Spain, and U.K.) and not mentioned in the others. Lidocaine 5% plaster was recommended in three guidelines (France 2010, the Netherlands 2008-I, and Spain) not recommended in two guidelines (Norway 2007 and U.K.) and not mentioned in others. Regarding more invasive therapeutic approaches, only ketamine was recommended after indication confirmation by a pain specialist in four CPGs: Italy 2006, the Netherlands 2008-I, Spain, and U.K. Ketamine was not mentioned by the other CPGs, whereas systemic lidocaine was not recommended in four CPGs (France 2010, Italy 2006 and 2009, the Netherlands 2008-I) or not mentioned in other CPGs.
### Table 3. Treatment of neuropathic pain in patients with cancer according to European national clinical practice guidelines.

<table>
<thead>
<tr>
<th>Treatment of neuropathic pain in cancer patients</th>
<th>France</th>
<th>Italy 2009</th>
<th>Italy 2006</th>
<th>Neth. 2008-I</th>
<th>Neth. 2008-II</th>
<th>Norway 2009</th>
<th>Norway 2007&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Spain</th>
<th>UK&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paracetamol, NSAIDs,</td>
<td>-</td>
<td>0</td>
<td>0</td>
<td>-</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Weak opioids (i.e. dextropropoxyphene, tramadol)</td>
<td>+</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>-</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Tricyclic Antidepressant drugs (i.e. amitriptiline, imipramine)</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>SNRI Antidepressant drugs (i.e. venlafaxine, duloxetine)</td>
<td>+</td>
<td>+</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>+</td>
<td>+</td>
<td>0</td>
</tr>
<tr>
<td>α2δ agonists (i.e. gabapentine, prégalbamine)</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Others Anticonvulsant drugs (i.e. carbamazepine, valproate of sodium, phenitoine)</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>-</td>
<td>0</td>
<td>0</td>
<td>-</td>
<td>0</td>
<td>0</td>
<td>+</td>
<td>-</td>
<td>0</td>
</tr>
<tr>
<td>Opioids (i.e. morphine, oxycodone) in combination with coanalgesics</td>
<td>+</td>
<td>+</td>
<td>0</td>
<td>+</td>
<td>-</td>
<td>0</td>
<td>+</td>
<td>+</td>
<td>0</td>
</tr>
<tr>
<td>Lidocaine 5% plaster (only in case of local neuropathic pain)</td>
<td>+</td>
<td>0</td>
<td>0</td>
<td>+</td>
<td>0</td>
<td>0</td>
<td>-&lt;sup&gt;b&lt;/sup&gt;</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Capsaicin plaster (only in case of local neuropathic pain)</td>
<td>+</td>
<td>0</td>
<td>0</td>
<td>+</td>
<td>0</td>
<td>0</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Intravenous ketamine</td>
<td>0</td>
<td>0</td>
<td>+&lt;sup&gt;c&lt;/sup&gt;</td>
<td>+&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>+R</td>
<td>+&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Intravenous lidocaine, mexiletine</td>
<td>-&lt;sup&gt;d&lt;/sup&gt;</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Cannabinoids</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>-</td>
</tr>
</tbody>
</table>

**Legend:**<sup>a</sup> the topic of the guideline concerned specifically the treatment of pain in cancer. <sup>b</sup> no marketing in Norway, <sup>c</sup> consultation with a pain or palliative care specialist (+): should be proposed, (-): should not be proposed, (0): no information. R: refractory neuropathic pain. <sup>d</sup> no marketing concerning mexiletine.
Focused analysis on amitriptyline, pregabalin, and gabapentin is presented in Table 4. For amitriptyline, evidence level for its recommendation varied from 1++ to four according the SIGN 50 criteria. For pregabalin, evidence level for its recommendation varied also from 1++ to 4. For gabapentin, this level varied from 1++ to 2. In accordance level of grading varied in the same way for the three drugs. A large majority of CPGs indicated the use rules of drugs but only three CPGs (France 2010, the Netherlands 2008-II and Norway 2009) detailed systematically the side effects and contra-indications of these drugs.
### Table 4a. Comparison of grade of recommendations and level of evidence proposed for treating neuropathic pain in cancer guidelines.

<table>
<thead>
<tr>
<th></th>
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<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Amitriptyline</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Evidence literature</td>
<td>1</td>
<td>“low”</td>
<td>nm</td>
<td>4</td>
<td>4</td>
<td>1&lt;sup&gt;a&lt;/sup&gt;</td>
<td>nm</td>
<td>1</td>
<td>1++</td>
</tr>
<tr>
<td>Evidence recommendations</td>
<td>A</td>
<td>“weak positive”</td>
<td>A</td>
<td>nm</td>
<td>nm</td>
<td>nm</td>
<td>B</td>
<td>B</td>
<td>A</td>
</tr>
<tr>
<td>Start dose</td>
<td>10-25mg</td>
<td>10-25mg</td>
<td>10mg</td>
<td>10-25mg</td>
<td>10-25mg</td>
<td>10mg 2-4 hours before sleep</td>
<td>nm</td>
<td>10-25mg</td>
<td>nm</td>
</tr>
<tr>
<td>Titration scheme</td>
<td>5-25 mg&lt;sup&gt;b&lt;/sup&gt;</td>
<td>nm</td>
<td>10mg/ 3 days</td>
<td>25mg/week</td>
<td>25mg/ 3-7 days</td>
<td>10mg / 3 days up to 30 mg then 3 weeks stable dose</td>
<td>nm</td>
<td>Slow titration&lt;sup&gt;b&lt;/sup&gt;</td>
<td>nm</td>
</tr>
<tr>
<td>Maximum dose</td>
<td>75-150mg</td>
<td>50-75mg</td>
<td>75mg</td>
<td>50-150mg</td>
<td>75mg</td>
<td>40-50mg</td>
<td>nm</td>
<td>150mg</td>
<td>nm</td>
</tr>
<tr>
<td>Contra-indications&lt;sup&gt;c&lt;/sup&gt;</td>
<td>+</td>
<td>nm</td>
<td>nm</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>nm</td>
<td>nm</td>
<td>nm</td>
</tr>
<tr>
<td>Side-effects&lt;sup&gt;c&lt;/sup&gt;</td>
<td>+</td>
<td>nm</td>
<td>nm</td>
<td>nm</td>
<td>+</td>
<td>+</td>
<td>nm</td>
<td>nm</td>
<td>nm</td>
</tr>
<tr>
<td><strong>Pregabalin</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Evidence literature</td>
<td>1</td>
<td>“low”</td>
<td>No treatment option</td>
<td>4</td>
<td>?</td>
<td>1&lt;sup&gt;a&lt;/sup&gt;</td>
<td>nm</td>
<td>1</td>
<td>1++</td>
</tr>
<tr>
<td>Evidence recommendations</td>
<td>A</td>
<td>“weak positive”</td>
<td>nm</td>
<td>nm</td>
<td>nm</td>
<td>nm</td>
<td>B</td>
<td>B</td>
<td>A</td>
</tr>
<tr>
<td>Start dose</td>
<td>75-150 mg</td>
<td>2 x 25mg</td>
<td>2 x 75mg</td>
<td>2 x 75mg</td>
<td>2x25mg</td>
<td>nm</td>
<td>2 x 25-75mg</td>
<td>nm</td>
<td></td>
</tr>
<tr>
<td>Titration scheme</td>
<td>75mg&lt;sup&gt;b&lt;/sup&gt;</td>
<td>nm</td>
<td>150mg / 2 days</td>
<td>150mg / 2 days</td>
<td>Slowly&lt;sup&gt;b&lt;/sup&gt;</td>
<td>nm</td>
<td>50-150mg/time</td>
<td>nm</td>
<td></td>
</tr>
<tr>
<td>Maximum dose</td>
<td>300-600mg</td>
<td>600mg</td>
<td>2 x 300mg</td>
<td>2 x 300mg</td>
<td>2x300mg</td>
<td>nm</td>
<td>600mg</td>
<td>nm</td>
<td></td>
</tr>
<tr>
<td>Contra-indications&lt;sup&gt;c&lt;/sup&gt;</td>
<td>+</td>
<td>nm</td>
<td>nm</td>
<td>nm</td>
<td>nm</td>
<td>nm</td>
<td>nm</td>
<td>nm</td>
<td></td>
</tr>
<tr>
<td>Side-effects&lt;sup&gt;c&lt;/sup&gt;</td>
<td>+</td>
<td>nm</td>
<td>nm</td>
<td>+</td>
<td>+</td>
<td>nm</td>
<td>nm</td>
<td>nm</td>
<td></td>
</tr>
</tbody>
</table>
### Improving neuropathic cancer pain in Europe

**Table 4b. Comparison of grade of recommendations and level of evidence proposed for treating neuropathic pain in cancer guidelines.**

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Evidence literature</strong></td>
<td>2</td>
<td>“low”</td>
<td>nm</td>
<td>2</td>
<td>2</td>
<td>1&lt;sup&gt;a&lt;/sup&gt;</td>
<td>nm</td>
<td>1+</td>
<td>1++</td>
</tr>
<tr>
<td><strong>Evidence recommendations</strong></td>
<td>A</td>
<td>“weak positive”</td>
<td>A</td>
<td>nm</td>
<td>nm</td>
<td>nm</td>
<td>nm</td>
<td>B</td>
<td>A</td>
</tr>
<tr>
<td><strong>Start dose</strong></td>
<td>1x100-300mg</td>
<td>2x100mg</td>
<td>1x300mg</td>
<td>1x 100-300mg</td>
<td>1x100-300mg</td>
<td>1x300mg</td>
<td>nm</td>
<td>1x300mg</td>
<td>nm</td>
</tr>
<tr>
<td><strong>Titration scheme</strong></td>
<td>100-300mg&lt;sup&gt;b&lt;/sup&gt;</td>
<td>nm</td>
<td>300mg/day</td>
<td>100-300mg/day</td>
<td>100-300mg/day</td>
<td>1x300mg/3 days</td>
<td>nm</td>
<td>1x300mg/3 days</td>
<td>nm</td>
</tr>
<tr>
<td><strong>Maximum dose</strong></td>
<td>1200-3600mg</td>
<td>3600mg</td>
<td>3600mg</td>
<td>3600mg</td>
<td>3600mg</td>
<td>3600mg</td>
<td>nm</td>
<td>3600mg</td>
<td>nm</td>
</tr>
<tr>
<td><strong>Contraindications&lt;sup&gt;c&lt;/sup&gt;</strong></td>
<td>+</td>
<td>nm</td>
<td>+</td>
<td>nm</td>
<td>+</td>
<td>nm</td>
<td>nm</td>
<td>+</td>
<td>nm</td>
</tr>
<tr>
<td><strong>Side-effects&lt;sup&gt;c&lt;/sup&gt;</strong></td>
<td>+</td>
<td>nm</td>
<td>nm</td>
<td>nm</td>
<td>+</td>
<td>+</td>
<td>nm</td>
<td>nm</td>
<td>nm</td>
</tr>
</tbody>
</table>

**Legend:**<sup>a</sup> Non-cancer neuropathy;<sup>b</sup> No further information is given;<sup>c</sup> + = mentioned in the clinical practice guideline (CPG), nm = not mentioned in the CPG.
DISCUSSION

In the nine included CPGs on cancer pain or neuropathic pain with at least one chapter on neuropathic pain in patients with cancer, all developed in European countries, 163 references were used to support the given recommendations on neuropathic pain treatment in patients with cancer. Although the proportion of population-specific references was low (11%), it was higher than our previous study on diagnosis and assessment of neuropathic pain in patients with cancer (3%). (7) Moreover, the mean level of evidence of used references was high (44%). Nevertheless, few references were used in at least two CPGs (18%), and no reference was shared by all the CPGs.

All CPGs recommended the use of antidepressant drugs, α2δ agonists and others anticonvulsant drugs. Proposal of these drugs in first line treatment is not supported by high evidence level. For example, amitriptyline is the oldest anti-neuropathic drug and well investigated in non-cancer populations, (18) but Mercadante et al. (19) demonstrated the analgesic effects on neuropathic pain of 50 mg of amitriptyline were small and associated with side events in patients with cancer. Similar results were found in another study related to treatment for chemotherapy-induced neuropathic symptoms with amitriptyline. (20) We also found diversity in recommendations concerning strong opioids and more invasive approaches such as ketamine. Such second line therapeutic approaches were proposed by some CPGs, whereas they were not mentioned at all in others. This shows a gap between daily practice (wide utilization of ketamine or lidocaine in cancer pain, not only in case of neuropathic pain) and recommendations in part of the CPGs.

Ideally, high quality CPGs should describe adverse events and risks of treatments. In the studied CPGs, these were well described for strong opioids. (7) However, in the majority of the CPGs, adverse events of
antidepressants or anticonvulsants as treatment for neuropathic pain were not mentioned. Up to now, the benefit-risk ratio of these drugs in patients with cancer is unknown. (19,21) Consequently, we recommend that CPGs mention restrictions when study findings in non-cancer populations are extrapolated to patients with cancer. Clinical practice guidelines differ in terms of used references, extrapolation techniques, and assigned levels of evidence. The origin and the composition of the guideline development groups seem to have influenced the clinical recommendations, (22,23) which are based on their clinical experiment and their choice of evidence-based references.

Our results should be interpreted with caution. They are merely based on available information in the CPGs. Only one chapter per CPG concerned neuropathic pain in patients with cancer. These results emphasize the lack of robust references on the treatment for neuropathic pain in cancer conditions. As we limited ourselves to Europe, we were able to develop a detailed study including all European countries. In the future, it would be interesting to include CPGs from other continents.

**Recommendations and Perspective**

The majority of guideline development groups extrapolated results of studies on non-cancer neuropathic pain to recommendations for patients with cancer. Consequently, these CPGs fail to address important issues such as altered kinetics and side effect profiles in these patients. We recommend creating specific recommendations by an international expert group for the treatment for neuropathic pain in patients with cancer supported by targeted research in patients with cancer. For this purpose, there is a need for research protocols with prospective multicenter and multinational studies in
clinical practice comparing different treatment strategies and to publish all studies whether the results reported are positive or negative.

REFERENCES


Improving neuropathic cancer pain in Europe


CHAPTER 6 - A case vignette study to assess the knowledge of pain physicians of neuropathic cancer pain: room for improvement!
Accepted in: Pain physicians in August the 6th 2013

Virginie PIANO, Michel LANTERI-MINET, Kees BESSE, Monique STEEGERS, Anne DONNET, Stans VERHAGEN, Chris van WEEL, Yvonne ENGELS, Kris VISSERS
Abstract

**Background:** From 19 to 39% of patients with cancer suffer from pain that is difficult to diagnose and to treat: neuropathic pain. In France, clinical practice guidelines (CPGs) on this topic exist; but to what extent French pain specialists know and use the recommendations from these CPGs are unknown. **Aim:** The aim was to investigate, with the help of a case vignette, whether pain specialists follow the recommendations in the CPGs in clinical practice on this topic. **Design:** The survey consisted of a case vignette about a patient with pain suffering from an intractable pancreatic cancer with multiple choice questions about diagnosis and treatment of (neuropathic) pain. Percentages of participants who treated the patient as suggested in the CPGs were calculated. **Setting/participants:** An email survey was conducted with the support of the Société Française d’Etude et de Traitement de la Douleur to all pain specialists (primary and secondary care) in France. **Results:** A total of 214 of those invited to participate (921) answered the questionnaire (24%). More than 85% of the respondents declared to know and use these CPGs. Half of the participants diagnosed and treated neuropathic pain components in the case vignette according to the recommendations in the CPGs. **Conclusions:** Although participating pain specialists confirmed to know and to use CPGs on neuropathic pain in cancer patients, half of them did not answer in line with the recommendations. A nationwide program to implement these CPGs is necessary including better education and training of pain specialists in assessing and treating neuropathic pain.
Chapter 6 – Case vignette study

Introduction

In 2002, the 5 year partial cancer prevalence in the French population (the number of cases of people diagnosed with cancer between 1998 and 2002 and still alive at the end of 2002) was 836,000 (1). In 2011, the incidence of cancer was about 365,000 in the French population (2). In patients with cancer, 64% suffer from pain of which between 19% and 39% suffer from neuropathic pain, which seriously reduces their quality of life on a daily basis (3-6). Two reasons for the high prevalence of neuropathic pain in this patient group can be underlined. Firstly, its diagnosis is difficult, particularly in patients with cancer, because of the combination with other comorbidities (7-9). Secondly, these patients are known to be resistant to usual nociceptive pain treatments (10, 11). Uncontrolled neuropathic pain in patients with cancer increases depression and insomnia rates (12, 13). Thus, optimal neuropathic pain diagnosis and treatment are essential.

Clinical practice guidelines (CPGs) for cancer or for neuropathic pain encourage practitioners to detect neuropathic components earlier with screening instruments and physical examination and to treat them with tricyclic antidepressant (TADs) or anticonvulsant drugs (AEDs) in combination with other drugs such as morphine (14-16). Yet previous studies have identified that practitioners do not always follow such CPGs (17-20). It is important to assess whether physicians are familiar with CPGs and use them in their daily practice. Use of a case vignette for this purpose appeared successful regarding a CPG on chronic pain (21-22). A case vignette uses a case study with “text, images or other forms of stimuli to which research participants are asked to respond” (23). This might be a convenient, valid and inexpensive way to evaluate knowledge of the content of the CPGs
on neuropathic cancer pain. To evaluate this method, we chose the population of pain specialists.

In France, advanced training in pain, a two year course, has existed since 1998. Physicians with any medical specialty can follow this training. A majority of these are members of the Société Française d’Etude et de Traitement de la Douleur (SFETD). The practitioners in this group are pain specialists and are expected to have detailed knowledge of the recommendations in pain-related CPGs, but this has not been studied yet. We therefore studied whether French pain specialists know and use the most important recommendations from a practice-based perspective on neuropathic pain in patients with cancer.

**Method**

**Participants**

All 931 physicians who were registered in the SFETD in March 2012 were invited to take part in the survey.

**Survey mailings**

On 31 May 2012, SFETD sent an e-mail to all participants providing a link to an Internet-based survey (Copyright 1999-2012, SurveyMonkey, Palo Alto, CA). Non-responders received a reminder two weeks later. Inclusion finished on 1 July. Questionnaires were analyzed anonymously and only used if informed consent was given.

**The case vignette (Table 1 and annex)**
**Initial case vignette.** The originally Dutch version of the case vignette was developed by two Dutch pain anaesthesiologists, who respectively took part in and chaired the Dutch cancer pain guideline development group in 2008 (KB, KV). The format was based on prior surveys regarding physician knowledge, communication and attitudes with respect to patients with cancer (18, 19). A forward backward translation procedure was used to develop the French version.

**Validation and pre-test.** The French case vignette was approved by the board of the SFETD. It was pilot tested with the help of six pain specialists (an anaesthesiologist, a neurologist, a palliative care specialist, a general practitioner (GP) in a palliative care network at home and a GP in a pain centre) in order to adapt the case vignette to the recommendations in the French CPGs and to the French healthcare system. The results of the pilot were discussed by participants and researchers. Table 1 describes the main components of the French CPG used for the construction of this case vignette: the recommendations for each theme, their justification, their clarity and the referenced question(s) in the case vignette (14-16). (Tables 1a and b) The final questionnaire, translated into English by an English native speaker, is presented in annex 1.

We studied whether the medical specialty influenced adherence to CPGs recommendations. The population of the SFETD included 921 physicians with, among other specialties, 258 anaesthesiologists and 277 general practitioners (GPs). Anaesthesiologists usually focus on the underlying health problem and are trained to perform invasive treatments, whilst GPs focus on the global health problem of the patient and home care. Our hypothesis was that GPs would be more influenced by the context at home, while anaesthesiologists would be more experienced in the diagnosis of the pain. Furthermore, we...
expected the latter to propose invasive treatment earlier in the trajectory.

The case vignette was divided into 5 consecutive parts, in which the disease stage worsened. Part I concerned the occurrence of pain in the diagnosis of an intractable pancreatic cancer pain, in a patient with a good performance status, using the WHO pain analgesic ladder. Part II studied the adaptation of the pain treatment, with the patient still having a good performance status. Part III explored how the participants managed the impairment of the pain: the emotional management for the patient and their family and the care of insomnia. Part IV concerned specifically neuropathic components of the pain: its diagnosis and its treatment in an oncological context. Part V assessed the choice of invasive treatment and the route administration of pain treatment in the patient, in a terminal stage at home.

**Statistical analysis.**

Statistical analysis was performed with SPSS 20.0 (IBM, New York, NY, USA) and consisted of descriptive statistics: proportions, medians and range. For inter-group comparisons of continuous or ordinal variables, t tests or nonparametric Wilcoxon rank sum tests were used. Chi-square tests were used to compare categorical variables. All statistical testing was carried out with a p-value <0.05.
Table 1a. Summary of the French clinical practice guidelines on cancer pain to construct the case vignette.

<table>
<thead>
<tr>
<th>Guidelines</th>
<th>Recommendations</th>
<th>References</th>
<th>Question(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pain diagnosis</strong></td>
<td>Necessary to make a diagnosis of the pain (nociceptive and/or neuropathic pain)</td>
<td>Chapter 2.1.2 p. 37-38</td>
<td>1,3,4</td>
</tr>
<tr>
<td><strong>Pain assessment</strong></td>
<td>One dimensional scale and multidimensional scales</td>
<td>Chapter 2.1.3 p. 39-42</td>
<td>1,4,12</td>
</tr>
<tr>
<td><strong>Neuropathic pain</strong></td>
<td>Tricyclic antidepressant drugs or anticonvulsants</td>
<td>Chapter 4.1.3 p. 66-67</td>
<td>3,13,14</td>
</tr>
<tr>
<td><strong>Paracetamol</strong></td>
<td>In 1st line in mild pain</td>
<td>Chapter 3.1.1 p. 58</td>
<td>2,5</td>
</tr>
<tr>
<td><strong>NSAIDs</strong></td>
<td>For inflammatory pain or bone pains</td>
<td>Chapter 3.1 p. 58</td>
<td>2,5</td>
</tr>
<tr>
<td><strong>Corticosteroids</strong></td>
<td>Elevated intra cranial pressure, medullar compression, peripheral nervous compression, bones metastasis</td>
<td>Chapter 4.1 p. 63-66</td>
<td>14,16</td>
</tr>
<tr>
<td><strong>Weak opioids</strong></td>
<td>For moderate pain, precaution with tramadol if epilepsy or association with antidepressants, no association with dextropropoxyphen and carbamazepin</td>
<td>Chapter 3.2 p. 59</td>
<td>2,5</td>
</tr>
<tr>
<td><strong>Strong opioids</strong></td>
<td>For moderate to severe pain, titration is always necessary</td>
<td>Chapter 1 p. 15-34</td>
<td>2,5</td>
</tr>
<tr>
<td><strong>Opioid route</strong></td>
<td>Oral administration in 1st line, subcutaneous or intravenous in 2nd line</td>
<td>Chapter 1 p. 15, chapter 5.4.1-4 p. 86-87</td>
<td>14</td>
</tr>
<tr>
<td><strong>Opioid rotation</strong></td>
<td>In case of intractable side effects or phenomenon of opioid resistance defined by no efficacy and no side events despite a rapid and massive increase of the opioid dose</td>
<td>Chapter 2.4.3 p. 73-77</td>
<td>4,6</td>
</tr>
<tr>
<td><strong>Constipation</strong></td>
<td>Prophylactic laxative in case of weak or strong opioids with dietetic rules</td>
<td>Chapter 1.7.1 p. 22-25</td>
<td>6</td>
</tr>
<tr>
<td>Guidelines</td>
<td>Recommendations</td>
<td>References</td>
<td>Question(s)</td>
</tr>
<tr>
<td>------------</td>
<td>-----------------</td>
<td>------------</td>
<td>-------------</td>
</tr>
<tr>
<td><strong>Nausea</strong></td>
<td>Anti-emetic only if nausea occurs</td>
<td>Chapter 1.7.2 p. 26</td>
<td>6</td>
</tr>
<tr>
<td><strong>Sedation</strong></td>
<td>No treatment</td>
<td>Chapter 1.7.3 p. 27</td>
<td>6</td>
</tr>
<tr>
<td><strong>Blocks</strong></td>
<td>Celiac plexus block or splanchnic nerve block for the cancer of the pancreatic corpse</td>
<td>Chapter 5.2.1 p. 78-79</td>
<td>7,12,15</td>
</tr>
<tr>
<td><strong>Spinal route</strong></td>
<td>Specialized consultation in case of intractable pain</td>
<td>Chapter 5.4.5 p. 87</td>
<td>7,12,15</td>
</tr>
<tr>
<td><strong>Insomnia</strong></td>
<td>Amitriptyline is useful in case of insomnia with pain and depression. Benzodiazepine has an interest only in case of acute pain or agitation in patient in late stage. Relaxation and psychological control.</td>
<td>Chapter 4.2 p. 66, Chapter 4.5 p. 68-69, Chapter 5.3.2 p. 82</td>
<td>9, 10</td>
</tr>
<tr>
<td><strong>Psychological evaluation</strong></td>
<td>Systematically at the beginning and if psychiatric troubles and for pain assessment</td>
<td>Chapter 2.1.4 p. 42-43</td>
<td>8, 9</td>
</tr>
<tr>
<td><strong>Depression</strong></td>
<td>Psychologist consultation and antidepressant drugs</td>
<td>Chapter 2.1.2 p. 66</td>
<td>11</td>
</tr>
<tr>
<td><strong>Familial evaluation</strong></td>
<td>By the medical team, contact the family also without the patient</td>
<td>Chapter 2.1.4 p. 43-45</td>
<td>8</td>
</tr>
<tr>
<td><strong>Social assessment</strong></td>
<td>By the medical team and the general practitioner</td>
<td>Chapter 2.1.4 p. 45</td>
<td>8</td>
</tr>
</tbody>
</table>

*Cancer pain clinical practice guidelines of 1995 (12-13)*

*Questions are presented in annex 1 with the answers following the clinical practice guidelines (CPGs)*
Table 1b. Summary of the French clinical practice guidelines on neuropathic in cancer pain to construct the case vignette.

<table>
<thead>
<tr>
<th>Guideline</th>
<th>Recommendations</th>
<th>References</th>
<th>Question(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Neuropathic pain</strong></td>
<td>Diagnostic of neuropathic pain in cancer conditions</td>
<td>Chapter 2.3 table 2.2 p. 68</td>
<td>3,13,14</td>
</tr>
<tr>
<td>Tricyclic antidepressant drugs</td>
<td></td>
<td>Chapter 5.1.1.1 p.: 62-63, table 4.1 p. 123</td>
<td></td>
</tr>
<tr>
<td>Gabapentin</td>
<td></td>
<td>Chapter 5.1.2 table 4.2 p.125</td>
<td></td>
</tr>
<tr>
<td>Tramadol</td>
<td></td>
<td>Chapter 5.1.3.2 table 4.3 p. 127</td>
<td></td>
</tr>
</tbody>
</table>

a Neuropathic pain clinical practice guideline 2010 (14)

b Questions are presented in annex 1 with the answers following the clinical practice guideline (CPGs)

Results

Ten of the 931 mailed surveys were returned unopened, leaving 921 surveys. A total of 214 completed surveys were returned (response rate 24%). Of those, 158 (74%) answered the questionnaire in full.

Demographic data (Table 2)

Median age of the respondents was 51 (range 28-72) years; 54% were women (Table 2). Most of them were GPs (43%) representing
91/277 GPs of the SFETD or anaesthesiologists (30%) representing 65/258 anaesthesiologists of the SFETD (25%). Two thirds of the respondents (63%) had been practicing medicine for at least 20 years. More than half (58%) worked in a state hospital; 57% in pain consultations or a pain centre. Only three participants did not treat patients with cancer. Sixteen percent of the respondents treated fewer than 10 patients with cancer per year, 35% between 10 and 49, 17% between 50 and 100 and 31% more than 100 patients yearly. Almost all of them confirmed that they were aware of the existence of a cancer pain CPG (94%) and a neuropathic pain CPG (97%) and that they used them (88% and 94% respectively). Participants spent 15 minutes on average to complete the questionnaire.

*Pain management in patients with cancer by French pain specialists and comparison to CPGs (Table 3)*

Table 3 illustrates the number and proportion of respondents who answered the case vignette as recommended in the French CPGs.
Table 2. Demographic and Practice Characteristics of Eligible Study Respondents.

<table>
<thead>
<tr>
<th>Characteristics of participants</th>
<th>Respondents</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N0 (N=214)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>116</td>
</tr>
<tr>
<td>Men</td>
<td>98</td>
</tr>
<tr>
<td>Medical specialty</td>
<td></td>
</tr>
<tr>
<td>Anesthesiology</td>
<td>65</td>
</tr>
<tr>
<td><strong>General practice</strong></td>
<td>91</td>
</tr>
<tr>
<td>Geriatric</td>
<td>12</td>
</tr>
<tr>
<td>Neurology</td>
<td>5</td>
</tr>
<tr>
<td>Oncology</td>
<td>11</td>
</tr>
<tr>
<td>Pediatric</td>
<td>6</td>
</tr>
<tr>
<td>Psychiatry</td>
<td>1</td>
</tr>
<tr>
<td>Rehabilitation practice</td>
<td>6</td>
</tr>
<tr>
<td>Rheumatology</td>
<td>6</td>
</tr>
<tr>
<td>Other</td>
<td>11</td>
</tr>
<tr>
<td>Number of years of practice after education</td>
<td></td>
</tr>
<tr>
<td>Less than 5 years</td>
<td>14</td>
</tr>
<tr>
<td>5-10 years</td>
<td>16</td>
</tr>
<tr>
<td>11-20 years</td>
<td>49</td>
</tr>
<tr>
<td>More than 20 years</td>
<td>135</td>
</tr>
<tr>
<td>Location of medical practice</td>
<td></td>
</tr>
<tr>
<td>(multiple response possible)</td>
<td></td>
</tr>
<tr>
<td>In an office</td>
<td>24</td>
</tr>
<tr>
<td>Retiring house</td>
<td>15</td>
</tr>
<tr>
<td><strong>Public hospital</strong></td>
<td>124</td>
</tr>
<tr>
<td>Private hospital</td>
<td>30</td>
</tr>
<tr>
<td>Non-governmental funding</td>
<td>2</td>
</tr>
<tr>
<td>Pain clinic consultations</td>
<td>122</td>
</tr>
<tr>
<td>Oncology</td>
<td>19</td>
</tr>
<tr>
<td>Palliative care unit</td>
<td>31</td>
</tr>
<tr>
<td>Other</td>
<td>21</td>
</tr>
<tr>
<td>Number of patients with cancer followed per year</td>
<td></td>
</tr>
<tr>
<td>No patient</td>
<td>3</td>
</tr>
<tr>
<td>&lt;10 patients</td>
<td>34</td>
</tr>
<tr>
<td><strong>10-49 patients</strong></td>
<td>74</td>
</tr>
<tr>
<td>50-100 patients</td>
<td>37</td>
</tr>
<tr>
<td>&gt; 100 patients</td>
<td>66</td>
</tr>
<tr>
<td>Cancer pain guidelines</td>
<td></td>
</tr>
<tr>
<td>Do you know this guideline? Yes</td>
<td>201</td>
</tr>
<tr>
<td>Do you use this guideline? Yes</td>
<td>190</td>
</tr>
<tr>
<td>Neuropathic pain guideline</td>
<td></td>
</tr>
<tr>
<td>Do you know this guideline? yes</td>
<td>208</td>
</tr>
<tr>
<td>Do you use this guideline? Yes</td>
<td>202</td>
</tr>
</tbody>
</table>
In part I, concerning the management of the initial pain, almost all pain specialists followed the CPG recommendations to assess the pain and made a clear diagnosis (97%). However, only 60% treated the pain in accordance with the CPGs (which used the WHO analgesic ladder). There was no significant difference between the medical specialties.

In part II, more than 70% of the participants adapted the treatment after a pain evaluation and followed the WHO analgesic ladder as recommended in the guidelines. The prevention of side effects was in accordance to the CPGs in slightly more than half of the respondents (56%) and 44% had an early proposal for invasive treatment (celiac plexus block or splanchnic nerve block for cancer of the pancreatic corpse). There was no significant difference between the medical specialties.

In part III, 98% of the respondents proposed a psychologist for the management of depression. Only 24% of the participants proposed a multidimensional assessment of the pain, a consultation with a psychologist and addition of an antidepressant drug for the treatment of depression. There was a significant difference between the percentage of anaesthesiologists who followed the CPGs (37%) and GPs (14%, p=0.007).

In part IV, neuropathic pain was diagnosed and treated by more than 50% of the pain specialists. AEDs were proposed by 30% of them (47/158) and TADs by 9% (15/158) or an increase of opioids by 6% (9/158) as presented in the recommendations. Specific treatment of neuropathic pain without specification was quoted by 6% (10/158). Other treatments of the cancer CPG were proposed: ketamine by 11% (18/158) and lidocaine by 2.5% (4/158). There was no significant difference between medical specialties.
In *part V*, 57% of the participants chose, as recommended, intrathecal infusion of opioids or a specialized consultation for invasive treatment, with no significant difference between medical specialties. More than 80% of the participants correctly proposed the sub-cutaneous or the intravenous administration of the medication. There was no significant difference between medical specialties.

Answers were not related to practice location, number of years of practice, number of cancer patients seen per year, sex or age. The details of each response on the case vignette are described in annex 1.
Table 3. Case vignette: management of pain in patient with a pancreatic cancer by French pain specialists

<table>
<thead>
<tr>
<th>Number and proportion of French pain specialists who followed the cancer and neuropathic pain clinical practice guidelines</th>
<th>Respondents</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number</td>
</tr>
<tr>
<td>Initial pain management (188 respondents)</td>
<td></td>
</tr>
<tr>
<td>Strategy of the pain management (Question 1)</td>
<td>159</td>
</tr>
<tr>
<td>Treatment of the pain (Question 2)</td>
<td>112</td>
</tr>
<tr>
<td>Diagnosis of the pain (Question 3)</td>
<td>182</td>
</tr>
<tr>
<td>Adaptation of pain management (178 respondents)</td>
<td></td>
</tr>
<tr>
<td>Strategy of the pain management (Question 4)</td>
<td>127</td>
</tr>
<tr>
<td>Treatment of the pain (Question 5)</td>
<td>153</td>
</tr>
<tr>
<td>Prevention of side effect with strong opioids (Question 6)</td>
<td>100</td>
</tr>
<tr>
<td>Choice of an invasive treatment (Question 7)</td>
<td>150</td>
</tr>
<tr>
<td>Impairment of the pain: (172 respondents)</td>
<td></td>
</tr>
<tr>
<td>Mourning management (Question 8)</td>
<td>168</td>
</tr>
<tr>
<td>Strategy of the insomnia management (Question 9)</td>
<td>55</td>
</tr>
<tr>
<td>Treatment of insomnia (Question 10)</td>
<td>47</td>
</tr>
<tr>
<td>Strategy of the depression management (Question 11)</td>
<td>42&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Neuropathic pain management (158 respondents)</td>
<td></td>
</tr>
<tr>
<td>Strategy of the pain management (Question 12)</td>
<td>119</td>
</tr>
<tr>
<td>Diagnosis of the neuropathic pain (Question 13)</td>
<td>86</td>
</tr>
<tr>
<td>Treatment of the neuropathic pain (Question 14)</td>
<td>79</td>
</tr>
<tr>
<td>Pain management in end of life (158 respondents)</td>
<td></td>
</tr>
<tr>
<td>Choice of an invasive treatment (Question 15)</td>
<td>91</td>
</tr>
<tr>
<td>Choice of administration route after thrombus at home (Question 16)</td>
<td>135</td>
</tr>
</tbody>
</table>

<sup>a</sup> significant difference between anaesthesiologists (37%) versus general practitioners (14%) to follow CPG concerning depression impairment (p=0.007).
Discussion

This study assessed the knowledge and the use of CPGs among French pain specialists concerning neuropathic pain in a patient with cancer. Although over 85% of the respondents claimed they know and use the CPGs, only some of them followed the recommendations regarding this case vignette. Three important messages can be learned from our survey.

Firstly, the management of nociceptive cancer pain using the WHO analgesic ladder was good with over 75% of the participants following the CPGs. This ladder was published in the eighties and apparently well known by pain specialists (24).

Secondly, there was very little adherence to the CPGs with regard to the management of the impairment caused by the pain such as depression and insomnia. Regarding insomnia, only 26% of the respondents proposed a multidimensional pain assessment. Concerning depression, only 28% of the anaesthesiologists compared with 11% of the GPs proposed antidepressant drugs and a consultation with a psychologist. The lack of precision in the CPGs concerning these two topics can be underlined (table 1). There are several explanations for this low number of GPs who adhered to the CPG regarding the treatment of depression. Antidepressants drugs are not proposed as the first choice in the treatment of depression in the French CPG for GPs. (25) In 2012, a Dutch study revealed that GPs find it difficult to differentiate between normal and abnormal sadness. They did not strictly apply criteria of depressive disorder. They rely on their clinical judgment, strongly consider the patient’s context and background factors, and rarely prescribe antidepressant drugs (26). Furthermore, a meta-analysis demonstrated the importance of the association of psychotherapy and a
pharmacological approach to improve patients with depressive disorders in cancer but without assessing the TADs (27). In these conditions, it is difficult to make a clear recommendation in CPGs.

Thirdly, only half of the respondents followed the CPGs regarding neuropathic pain management. Although this figure can be considered high compared to literature on guideline adhesion, they are quite low in this population of pain specialists with extensive training in neuropathic pain (28). It is probable that these CPGs are not clear enough on neuropathic pain management in patients with cancer (Table 1). In fact, recommendations in CPGs are not sufficiently based on clinical practice and thus not easily applicable (29). Besides, only 2% of the references used in European CPGs on neuropathic pain in cancer concerned patients with cancer (30). There is an urgent need of good randomized controlled trials on this specific population (31). Moreover, no implementation strategies were linked to the publication of the CPGs, although this, together with monitoring its impact, is necessary to improve the use of a CPG (32).

**Strengths and limits**

To our knowledge, this is the first study to investigate the practical knowledge of pain specialists concerning neuropathic pain components in cancer pain. This is also the first vignette study in which practitioners had to deal with pain in patients with cancer. Relevant points for patient care were identified: 1) physicians should realize that they have a responsibility to know and use a CPG and consult the updated CPGs, especially in the case of limited knowledge on a topic, 2) specific training in pain is beneficial to improve the professionals’ knowledge.
Although the response rate was low (24%), it was comparable to other French surveys using case vignettes and seemed to be a good representation of the whole population of the SFETD (33, 34). However, the respondents of the case vignette were probably more involved in cancer pain management, giving the best responses. Finally, they were not familiar with this method of knowledge assessment. Consequently, those who did not complete the questionnaire probably had difficulty using it to use it. This also explains the decline in the number of participants from the beginning to the end of the questionnaire.

The aim of this study was not to validate the case vignette, but to assess the knowledge of pain physicians. Yet, as well the Dutch version of the vignette as the French one were pilot tested.

**Recommendations**

A case vignette seems to be an interesting method for evaluating the knowledge and application of CPGs in pain management. Specific case vignettes should be developed and tested for several aspects of pain education as they are an inexpensive tool, convenient for assessing this implementation in a large group of physicians and are easy to repeat, for example after a training or implementation program (36-39). Structured training and evaluations resulting in a diploma will improve the knowledge of the practicing physicians about specific problems. There is a need to implement the CPG on neuropathic pain in France, probably with specific communication on this subject and a dedicated educational module in the curricula. Case vignettes assessing specific key messages of pain recommendations contained in CPGs could be a way to evaluate the level of the educational module and adapt the training.

**Acknowledgements**
We would like to thank the board of the Société Française d’Etude et de Traitement de la Douleur who supported this study and authorized the use of their listing, in particular Madame Pascaline Lavalade. We also thank the French pain specialists who participated in the survey. We gratefully thank the participants of the pre-test. We thank the two native translators for the case vignette adaptation into French (translation and back translation).

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**Authors contribution**

V. Piano and K. Besse conceived and designed the experiments. K. Besse and K. Vissers developed the case vignette. V. Piano analyzed the data. They created the procedure. They also wrote the manuscript with Y. Engels, M. Lanteri-Minet and S. Verhagen. Y. Engels and K. Vissers supervised the overall execution of the project and contributed to the experimental design. M. Lanteri-Minet provided support from the SFETD. All authors discussed the results and commented on the manuscript and agreed the final version.

**Conflicts of interest:**

Virginie Piano is the president of the Association Française des Jeunes chercheurs en Douleur et Soins Palliatifs. Michel Lanteri-Minet is the president of the SFETD and chaired the French neuropathic pain guideline in 2010. Besse Kees and Kris Vissers respectively took part in and chaired the Dutch cancer pain guideline development group in 2008.
References


Improving neuropathic cancer pain in Europe


22. Bishop A, Foster NE, Thomas E, et al. How does the self-reported clinical management of patients with low back pain relate to the attitudes and beliefs of


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Supplement file. Case vignette questionnaire, responses following the CPGs and responses of the participants

PART I- INITIAL PAIN MANAGEMENT IN CANCER –

Mrs. A is 45 years old. She is married and has got 2 children (12 and 15 years old). After the discovery of a silent icterus (abnormal blood chemistry), a non-operable pancreas cancer is diagnosed. The family is informed that the prognosis is bad. The (bile) excretion was secured with a stent in the bile duct. The patient is in good conditions and had a good appetite. Mrs. A. received chemotherapy on her demand.

Few weeks after leaving the hospital, she consults you because she has pain in the upper abdomen. It is vise like pain with a stabbing component.

1) You decide the following strategy (many possible answers):

A. Pharmacological treatment 170 (90%)
B. Pain measurement with one-dimensional scale 66 (35%)
   (only intensity of the pain)
C. Pain measurement with multidimensional scale 141 (75%)
   (pain intensity and others dimensions as social, psychological or quality of life impairment)
D. Others investigations for diagnosis, precise: 92 (92%)

Answers recommended in CPGs: A in combination with B or C, +/-D

2) The pharmacological treatment included (if you choose an association, cross all boxes you need):

A. Paracetamol 106 (56%)
B. Non Steroid Anti-Inflammatory drug (NSAID) 15 (8%)
C. Corticosteroids in short cure 55 (29%)
D. Weak opioids 65 (35%)
E. Strong opioids 101 (54%)
F. Other, precise: 67 (36%)
Answers recommended in CPGs: A, B, D, E alone or in combination but no C, and no treatment of neuropathic pain components (tricyclic antidepressant or anticonvulsant) in answer E: other.

3) What kind of pain is it?

A. Nociceptive pain 23 (12%)
B. Neuropathic pain 5 (3%)
C. Mixed pain 114 (31%)
D. Visceral pain 40 (21%)
E. Other, precise: 6 (3%)

Answer recommended in CPGs: no B

PART II - ADAPTATION OF PAIN MANAGEMENT IN CANCER -

The pain is acceptable during a few months. After a while, the pain increases. The patient suffers from pain in her upper abdomen; mainly the night and her pain make her wake up early in the morning.

4) You decided the following strategy (many answers possible):

A. Adaptation of the pharmacological treatment 171 (96%)
B. Research for constipation 122 (69%)
C. Pain measurement with one-dimensional scale 61 (34%)
   (only intensity of the pain)
D. Pain measurement with multidimensional scale117 (66%)
   (pain intensity and others dimensions as social, psychological or quality of life impairment)
E. Invasive pain treatment (nerve block) 70 (39%)
F. Others investigations for diagnosis, precise: 39 (22%)

Answers recommended in CPGs: A in combination with B+/-F, in combination with C and/or D, E non obligatory

5) The adaptation of the pharmacological treatment included (if you choose an association, cross all boxes you need):

A. Add or increase paracetamol 33 (19%)
B. Add or increase a Non Steroid Anti-Inflammatory Drug (NSAID) 14 (8%)

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Chapter 6 – Case vignette study

C. Add or increase a short cure of corticosteroids  85  (48%)
D. Add or increase weak opioids  8  (5%)
E. Add or increase strong opioids  167  (94%)

Answers recommended in CPGs: E if mention of a pain assessment in question 4 (answer C and/or D)

6) To treat or avoid possible side effects of strong opioids, you prescribe systematically the following drug (many possible answers):

A. Laxative  171  (96%)
B. Anti-emetic  70  (39%)
C. A treat to avoid sedation  2  (1%)
D. Other, precise:  12  (7%)

Answer recommended in CPGs: A, B accepted only if mention in D “in case of nausea”

7) An invasive pain treatment can be:

A. Chordotomy  1  (1%)
B. Celiac plexus block  146  (82%)
C. Splanchnic nerve block  21  (12%)
D. Hypogastric nerve block  10  (6%)
E. A “lower end” block  0  (0%)
F. Intraspinal administration of opioids  86  (48%)
G. Other, precise:  12  (7%)

Answers recommended in CPGs: B and/or C +/- F. Accepted if no answer but mentioned in G: specialized consultation

PART III - MANAGEMENT OF PATIENT PAIN AND ENVIRONMENT –

8) The patient worries about her children reactions concerning her future death. In addition to a discussion with her general practitioner, you proposed to help her to meet (many answers possible):

A. A psychologist  169  (98%)
B. A social worker  92  (53%)
C. A pastoral assistant  58  (34%)
D. Other, precise:  53  (31%)

Answers recommended in CPGs: A obligatory
9) The pain decreases after your treatment but the problem of sleepiness are still present. You decided (many answers possible):

   A. Adaptation of the pharmacological treatment 138 (80%)
   B. Pain measurement with one-dimensional scale 28 (16%)
       (only intensity of the pain)
   C. Pain measurement with multidimensional scale 75 (44%)
       (pain intensity and others dimensions as social, psychological or quality of life impairment)
   D. Psychological consultation 121 (70%)
   E. Other proposal, precise: 39 (23%)

Answers recommended in CPGs: A in combination with C +/- B and D

10) The adaptation of pharmacological treatment included (many answers possible):

   A. Add a benzodiazepine 137 (80%)
   B. Add antidepressant drug 81 (47%)
   C. Use methylphenidate 1 (1%)
   D. Other, precise: 27 (16%)

Answers recommended in CPGs: B

11) The patient always present insomnia and she feels a lot of fear of suffering. You decided the following strategy (many possible answers):

   A. Discussion about her case in a multidisciplinary team meeting 130 (76%)
   B. Refer the patient to a clinical psychologist 129 (75%)
   C. To meet pastoral assistance 13 (8%)
   D. Refer the patient to the nurse specialized in cancer announcement 19 (11%)
   E. Prescribe an antidepressant drug 42 (24%)
   F. Propose hospitalization at home 56 (33%)
   G. Other, precise: 48 (28%)

Answers recommended in CPGs: B and E obligatory
PART IV - MANAGEMENT OF NEUROPATHIC CANCER PAIN –

Few days after, the pain increases and is located in the whole abdomen. The status of the patient has decreased drastically and the chemotherapy was interrupted because of the progression of the disease.

12) The patient had stabbing pain and paroxysmal pain and permanent burning gastric pain. The viselike pain has increased. She suffers from paresthesia in her legs. You decided the following strategy (many possible answers):

A. Adaptation of the pharmacological treatment 129 (82%)
B. Pain measurement with one-dimensional scale 39 (25%)
   (only intensity of the pain)
C. Pain measurement with multidimensional scale 82 (52%)
   (pain intensity and others dimensions as social, psychological or quality of life impairment)
D. Invasive pain treatment (nerve block) 95 (60%)
E. Others investigations for diagnosis, precise: 43 (27%)

Answers recommended in CPGs: A in combination with C +/- B and D. E non obligatory

13) In your opinion, what kind of pain is it?

A. Nociceptive pain 1 (1%)
B. Neuropathic pain 23 (15%)
C. Mixed pain 116 (73%)
D. Visceral pain 15 (10%)
E. Other, precise: 3 (2%)

Answers recommended in CPGs: B, E if “neuropathic pain components” is mentioned and C if treatment neuropathic pain mentioned in question 14

14) Despite an optimal titration of strong opioids, the pain persists. Which adaptation(s) of the pharmacological treatment can be proposed?

A. Increase opioids dose 9 (6%)
Improving neuropathic cancer pain in Europe

B. Opioids rotation 95 (60%)
C. Intravenous administration of opioids 94 (60%)
D. Adjuvant treatment, precise: 67 (61%)

Answers recommended in CPGs: D (with mention of: neuropathic pain treatment or anticonvulsant or tricyclic antidepressants drugs) and/or (A or B or C)

PART V - MANAGEMENT OF PAIN IN END OF LIFE –

15) An invasive treatment can be:

A. Chordotomy 4 (3%)
B. Celiac plexus block 39 (25%)
C. Splanchnic nerve block 5 (3%)
D. Hypogastric nerve block 5 (3%)
E. A “lower end” block 5 (3%)
F. Intraspinal administration of opioids 87 (55%)
G. Other, precise: 13 (8%)

Answers recommended in CPGs: F or G: specialized consultation

The patient doesn’t want an invasive pain treatment at this moment. The disease is complicated with a venous pelvic thrombosis and the patient has to take acenocoumarol. After a while, the situation of the patient becomes worse and worse. The patient is very tired. She cannot eat, drinking is an effort. The life expectancy is estimated between one and two weeks. The opioids cannot be taken orally and the intensity of the pain is high.

16) You choose the new administration of opioids at home:

A. Intraspinal administration 13 (8%)
B. Sub-cutaneous administration 36 (23%)
C. Transcutaneous administration 10 (6%)
D. Intravenous administration 84 (53%)
E. Other, precise: 15 (10%)

Answers recommended in CPGs: B and/or D
CHAPTER 7 – Discussion

Virginie PIANO
Improving neuropathic cancer pain in Europe
This thesis analysed the quality of all available guidelines on neuropathic pain in patients with cancer in European countries. This chapter discusses the different research questions of this thesis: the quality and limitations of the individual results of the research questions, the main findings, and the conclusions of the chapters. Further, implications for practice, education and future research are considered.

BACKGROUND

Cancer is the first cause of death in Europe. (1) The most inconvenient symptom is pain, present in about 60% of the patients with cancer. (2, 3) Between 19 and 39% of them suffer from neuropathic pain. (4) This type of pain is well known for its pharmacologic resistance and may cause high disability like depression or insomnia. (5, 6) Despite the high prevalence of neuropathic pain in patients with cancer and its high impact on the quality of daily life, there is no consensus in the literature concerning its diagnosis or its treatment. General guidelines to improve the management of neuropathic pain have been published recently: diagnosis and treatment recommendations of the European Federation of Neurological Societies (EFNS) were launched in 2010 and updated in the past two years. Besides, an algorithm for neuropathic pain diagnosis was published in 2011. (7, 8) However, these recommendations were created for non-oncological neuropathic pain; specific guidelines for patients with neuropathic cancer pain in Europe are absent in recent literature.

Another important issue is the quality of the development of a guideline. If guidelines on this topic exist in Europe, the content should be assessed. In fact, clinical practice guidelines (CPGs) are “statements that promote or advocate a particular course of action in clinical care”. (9) These statements should be proposed according to
the recent review of the literature. (10) The lack of specific literature on neuropathic pain in cancer makes the development of specific recommendations challenging or impossible. A specific tool has been developed to assess the quality of development of guidelines: the Appraisal of Guidelines, Research and Evaluation (AGREE) instrument. (10) This internationally validated instrument consists of 6 domains: 1) scope and purpose (overall aim of the guideline and target groups); 2) stakeholder involvement (stakeholders involved in guideline development and views of its intended users); 3) rigor of development (selection of the evidence and the method to create recommendations); 4) clarity and presentation (structure and format of the guideline); 5) applicability (facilitators and potential barriers for guideline implementation); 6) editorial independence (biases concerning conflicts of interest) and one overall assessment item judging if the CPG is recommended for its use in clinical practice. (10) The ratings of the quality domains showed to be good predictors of outcomes associated with implementation of guidelines, very useful and easy to use. (10) The original AGREE instrument has been refined to improve the original tool’s usability and its validity and reliability. (11) Thus, in 2008 the AGREE II instrument, a revision of the AGREE instrument, was developed by the AGREE collaboration. (11) Revision was done because the four-point response scale of the AGREE instrument was not reliable enough. (12, 13) The seven-point response scale seemed relevant, and the new user’s manual clear. (11) Besides, the AGREE II instrument appeared valid to assess the quality of development of a CPG on cancer. (12) For those reasons, we used the AGREE II instrument to assess the quality of development of European guidelines that contain at least one chapter on neuropathic cancer pain.

Assessing the whole quality of a guideline is interesting, but this instrument is not built to evaluate the quality of the
recommendations in a guideline in detail. A systematic review of the references used to create recommendations can be useful to evaluate their robustness as proposed in an article on diabetes. (14) Particularly the diagnosis of neuropathic pain should be studied well: an early diagnosis guarantees a specific treatment and critically improves the quality of life of the patients. The treatment of neuropathic pain in patients with cancer is also an important issue of the thesis: recommendations are mostly based on extrapolation of recommendations in studies about neuropathic pain in a non-cancer population to this type of pain in a cancer population. (15-17)

The number of guidelines has exponentially increased over the past decades and practitioners are supposed to know them and to use them properly. (18, 19) Knowing the numerous recommendations proposed, their application in clinical practice seems not possible without a very clear and short message for each clinical question. There is no consensus on how to evaluate the application of a guideline but the methodology using a case vignette in cancer and in pain seemed promising. (20, 21) A case vignette uses a case study with “text, images or other forms of stimuli to which research participants are asked to respond”. (22) This method, easy to use and inexpensive, showed a good reliability and reproducibility. (21, 23) The applicability of neuropathic cancer pain guidelines can be assessed using a case vignette, and might also give direction to future adaptation of guidelines in Europe.

MAIN FINDINGS

In chapter 2, the aim was to make an inventory of guidelines in Europe concerning neuropathic cancer pain. To be exhaustive, we aimed to check all guidelines concerning pain: guidelines on pain in a non-cancer context, on neuropathic pain, on cancer pain and on neuropathic pain in patients with cancer. As most guidelines are not
published in peer reviewed journals, the inventory was made using an email questionnaire addressed to European physicians with a special interest in neuropathic pain, namely members of the International Association for the Study of Pain (IASP) and of the European Federation of IASP Chapters (EFIC). The response rate was high: 41 of the 66 invited physicians answered the questionnaire (62%), representing thirty of the 38 European countries (79%). With their participation, 54 documents were found, of which 20 were CPGs: 6 on chronic pain, 5 on neuropathic pain, 4 on cancer pain, 2 in geriatrics, 1 in pediatrics and 2 on chronic low back pain. The number of countries with guidelines on pain was higher than we expected and each country used its own guideline. Only Serbia used the EFNS guideline and Ireland used the British CPGs. This framework was the basis for the assessment of 9 of these CPGs, all containing at least one chapter on neuropathic pain in patients with cancer: two Italian, one French, one British, two Dutch, two Norwegian and one Spanish CPG. (24-32)

In chapter 3, the aim was to assess the quality of the development of these 9 guidelines that contained at least a chapter on neuropathic pain in cancer. There was much variation in quality between the CPGs. Scope and purpose of most CPGs was good, as well as the clarity of presentation, which is consistent with findings from other studies. (18, 33-34) Applicability of the CPGs was mostly low, implying that anticipating on implementation needs more emphasis in order to increase practitioners’ use. (35) One of the factors that could explain differences between CPGs may be the organization responsible for the CPG. In our study, two of the CPGs with the highest AGREE II scores were developed by institutes specialized in guideline development. A same result was demonstrated in a study of Burgers. (36) The review of Alonso-Coello et al. found a higher developmental quality in recently developed guidelines. (18) In our
assessment with AGREE II, we found higher median scores on the “purpose” and “clarity” domains in more recent CPGs. Guideline developers became more aware of the importance and methods of a systematic development process, maybe partly by publications on this topic and the availability of the AGREE and AGREE II instrument. (34) Most CPGs gave no information about views and preferences of the target patient population and their influence on the development of the recommendations; only three CPGs had patient’ representatives in their workgroup. (30-32) Probably, more guidance is needed on how to involve patients in this process. (37) Furthermore; most CPGs gave no attention to the applicability and implementation, while this is very important for clinicians. (38)

In chapter 4, the aim was to study to which articles was referred regarding the recommendations on diagnosis of neuropathic pain in patients with cancer. About 149 articles were linked to the recommendations on neuropathic pain diagnosis and assessment in patients with cancer. More than 95% of them were not specifically related to patients with cancer. Only three references used recommendations on neuropathic pain diagnosis and assessment in cancer and focused on this patient population. Regarding the year of publication, these specific references appeared to be more recent than the others, in accordance with the recent interest of neuropathic pain in the cancer field. (39) Moreover, we found that only to 19% of the articles was referred in more than one CPG. These findings are in accordance with the weak rigor of development, as found in the AGREE II evaluation of the CPGs. (15) Concerning the key messages, in all CPGs it was recommended that the diagnosis of neuropathic pain should be done with a clinical examination: a good interrogation of the patient concerning the location of the pain and its components. Only two CPGs recommended using questionnaires to diagnose neuropathic pain, the “Douleur neuropathique en 4
questions (DN4) in the French CPG and the “neuropathic pain questionnaire (NPQ) in the Dutch one. (25, 32) No further investigation was mentioned in the CPGs, except for the Dutch (29) and the Norwegian CPG (26): IRM and EMG were recommended. This difference can be explained recommendations made by the EFNS to confirm the lesion by further tests to make a diagnosis of “certain neuropathic pain” and if the results are negative or not contributive, a diagnosis of “probable neuropathic pain”. (8)

In chapter 5, 163 references were used to support the recommendations on neuropathic pain treatment in patients with cancer. Although the proportion of population-specific references again was low (11%), it was higher than regarding the diagnosis of neuropathic pain in patients with cancer (3%). (16) Moreover, the mean evidence level of the references was higher (44%). Nevertheless, few references were used in at least two CPGs (18%), and no reference was shared by all the CPGs. All CPGs recommended the use of antidepressant drugs, α2δ agonists and others anticonvulsant drugs. Yet, prescribing these drugs in first line treatment is not supported by high evidence level literature. For example, amitriptyline is the oldest anti-neuropathic drug and well investigated in non-cancer populations. (40) However Mercadante et al. demonstrated that the analgesic effects on neuropathic pain of 50 mg of amitriptyline were small and associated with severe side events in patients with cancer. (41) Similar results were found in another study related to treatment for chemotherapy-induced neuropathic symptoms with amitriptyline. (42) In the majority of the CPGs, adverse events of antidepressants or anticonvulsants as treatment for neuropathic pain were not mentioned. Up to now, the benefit-risk ratio of these drugs in patients with cancer is unknown. (41, 43) Consequently, we recommend that CPGs mention restrictions when study findings in non-cancer populations are extrapolated to patients with cancer.
In chapter 6, we assessed the knowledge and the use of CPGs of 214 French pain specialists concerning neuropathic pain in a patient with cancer. Although more than 85% of the respondents declared to know and to use the CPGs, only part of them followed the recommendations regarding this case vignette. About 95% followed recommendations for the management of nociceptive cancer pain, using the WHO analgesic ladder. This ladder was already published in the eighties and apparently well known by pain specialists. (44)

Concerning depression, only 28% of the anaesthesiologists versus 11% of the GPs proposed antidepressant drugs and a consultation together with a psychologist. These results can be explained: antidepressants drugs are not proposed as first choice in the treatment of depression in the French CPG for GPs and literature showed the lack of efficacy of these drugs without frequent psychotherapy. (45-47) In these conditions, it is difficult to make a clear recommendation in CPGs. Only 50% of the respondents followed the CPGs regarding neuropathic pain management. Although this figure can be considered as high in comparison to literature on guideline adhesion, they are quite low in this population of pain specialists with an extensive training in neuropathic pain. (48)

In fact, recommendations in CPGs are not sufficiently based on clinical practice and thus not easily applicable. (15) Moreover, there was no implementation strategy connected to the publication of the CPGs, although this, together with monitoring its impact, is necessary to improve the use of a CPG. (49)

**STRENGTHS AND LIMITATIONS OF THIS THESIS**

This thesis is innovative, as well in the choice of the topic as in the methods used.

*Neuropathic cancer pain in Europe and GPGs*
Lately, neuropathic pain in patients with cancer has started to get more attention from the professional community as confirmed by a recent article in the IASP newsletter. (39) Neuropathic cancer pain was described as difficult to diagnose and to treat. A need for randomized placebo-controlled trials was underlined by the authors. (39) Yet, studies concerning this topic are scarce. In this thesis, literature concerning the management of neuropathic pain in cancer used in CPGs was studied in a structure and detailed way. Diagnosis and treatment were clearly described and the lack of uniformity in the choice of the evidence was underlined. (15-18) Moreover, the choice of a European overview was interesting: most of the studies used only English guidelines and a lot of information was lacking. (18-19) Using this methodology, it was possible to explore different cultures and medical context in Europe, which can differ from Anglo-Saxon literature. Our results emphasized the heterogeneity and the extent of guidelines on pain and especially neuropathic cancer pain CPGs in Europe and their different level of quality. Of the 30 countries, 8 had no CPG on cancer pain, despite the international recommendation of the WHO published in 1986. (44) Ten countries had no CPG on neuropathic pain, despite the EFNS guideline. (7) In conclusion, neuropathic pain in patients with cancer should be scientifically studied and translated to CPGs by a special group of interest in international pain society. Efforts should be made to integrate physicians’ point of view and knowledge to increase the implementation of a CPG. In this aspect, a cultural and economical adaptation of the guideline is needed, to facilitate implementation.

**Method and design of the studies**

**Inventory of CPGs in Europe.** An extensive overview of guidelines that contain information about pain was made with the help of EFIC and the NeuPSIG members. In contrast to other studies, we also included
guidelines that were not written in the native language of the researchers. (18, 19) With the translator toolkit of Google, we were able to assess the non-English CPGs after validation of the translation by native or fluent speakers to improve the quality of the translation. Although neuropathic pain in cancer patients is a worldwide problem, we only assessed European CPGs. The main reason for this restriction was the opportunity to collaborate with the EFIC and NeuPSIG, which helped us to collect information from 30 of the 38 European countries.

The AGREE II instrument. We used AGREE II, the updated version of the AGREE instrument. AGREE II, which uses a 7-point Likert scale (instead of the 4-point Likert scale in the AGREE instrument), improves the reliability of the item and domain scores. (12, 13) This instrument was used recently for the assessment of guidelines for migraine and gave a good overview of the development of guidelines in cancer. (18, 19) However, results of the AGREE II assessment should be interpreted with caution. Using information only available in the CPG may limit the validity of the scores. Besides, AGREE II focuses on the methods and reporting of the guideline, but does not assess the validity of the diagnosis, medical content, and clinical recommendations. (10) For that reason, each reference and clinical messages in these 9 CPGs were studied and analyzed in article 3 and 4.

Levels of evidence and grades of recommendation. In a precedent article on diabetes, the levels of evidence and grades of recommendation were analyzed according the references quoted in CPGs (14). This method was used for the first time in neuropathic cancer pain for the diagnosis and the treatment. (16, 17) Considering criteria used in the diagnosis algorithm recommended by NeuPSIG, proposed recommendations of national CPGs in Europe appeared too
general for a proper diagnosis of neuropathic mechanism in pain occurring in a cancer context. (8) The results emphasized also the lack of robust references on treatment for neuropathic pain in cancer conditions. (17) These findings might be partly explained by the heterogeneity of the evidence grading in these guidelines. Detailed recommendations are available to evaluate the level of evidence of an article and the grade of a recommendation. (50) However, their utilization becomes difficult when there are few references on a clinical topic.

*Case vignette for pain specialists training.* This is the first study that investigated practical knowledge of pain specialists and the first vignette study in which they had to deal with pain in a patient with cancer. Relevant points for patient care were identified: 1) physicians should realize that they have responsibility to know and use a CPG and look at the updated CPGs, especially in case of limited knowledge on a topic, 2) a specific training in pain is interesting to improve the professionals’ knowledge. Although the response rate was low (24%), it was comparable with other French surveys using case vignettes and seemed to be a good representation of all members of the French pain society. (51, 52) Yet, the respondents of the case vignette were probably the ones most involved in cancer pain management, giving the best responses. Pain physicians were not familiar with this method of case vignette, explaining that those who did not complete the questionnaire probably had problems to use it, explaining the number of participants that did not complete the entire questionnaire.

**PERSPECTIVES FOR FUTURE RESEARCH**

There are several reasons why developing a CPG on neuropathic pain in cancer preferably should be done with an international team. The most important reason is to improve the quality of the CPGs for a
better implementation. Besides, it would help to pool costs and time. Up to now there are too few high quality studies to give strong recommendations: in a European or international context studies can be performed with a better power and better methodology than per country. Each participating country will have the opportunity to fine-tune the international guideline to the national health care and cultural situation. A European CPG can be interesting to obtain a high quality CPG on neuropathic pain in patients with cancer. The aim is to have the best review of the literature, an exhaustive experts’ opinion, studies on patients’ view and a good description of the possible barriers and facilitators for guideline application. However, this international guideline can be interesting only if it is adapted to the specificity and culture of each country, its medical obligations and its social environment. The ADAPTE working group developed a procedure to adapt each international guideline for the national context. (53) Proposed in 2006, 7 steps were described, presented in table 1. (53) A global European CPG, not too detailed to have room to adapt it to each specific situation, as a “blueprint” can be interesting. This blueprint document should be a document with the most important information about the specific topic that can be adapted by every professional group according their local standards in implementable material.

A European CPG on neuropathic pain in patients with cancer would facilitate the creation of a high quality CPG with the best experts and the best methodologists, including GPs and patients.

Next, each country can adapt such a European CPG to the national context. For example, in 2009 the IASP proposed the “Recommendations for Pain Treatment Services” which was adapted by each Chapter for their own country. (54) Another example is the adaptation and the translation of the definition and roles of a GP by
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the WONCA Europe. (55) Good quality of care for every patient in combination with saving time and money.

Table 1. The ADAPTE procedure in 7 steps. (54)

<table>
<thead>
<tr>
<th>Step</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Step 1</td>
<td>Definition of the clinical question: healthcare setting and context should be studied.</td>
</tr>
<tr>
<td>Step 2</td>
<td>Literature search: the language should be chosen according to the target population</td>
</tr>
<tr>
<td>Step 3</td>
<td>Assessing clinical content of the source guideline: the target population interest should be clearly studied</td>
</tr>
<tr>
<td>Step 4</td>
<td>Quality and coherence of the source: CPG should be assessed using AGREE II instrument</td>
</tr>
<tr>
<td>Step 5</td>
<td>Adaptations of the recommendations should be done by national experts</td>
</tr>
<tr>
<td>Step 6</td>
<td>External review of the adapted guideline</td>
</tr>
<tr>
<td>Step 7</td>
<td>Adoption, endorsement and implementation of the adapted CPG should be regularly realized and updated</td>
</tr>
</tbody>
</table>

The European collection of the guidelines gave an important amount of data, wealthy in clinical messages and literature on neuropathic pain in patients with cancer. A worldwide overview, using North-American and Australian CPGs could be interesting to complete this topic.

**GENERAL CONCLUSION**

In Europe in 2010, 54 documents on chronic pain, neuropathic pain or cancer pain were available to guide physicians. Among them, only 20 met the criteria of CPGs. It is surprising that European countries did not use available CPGs already present in other pain societies. An international inventory is needed to improve the data collection and
give more guidance on the management of neuropathic pain in patients with cancer.

Concerning CPGs on neuropathic cancer pain in Europe, their quality is modest. All domains and items showed room for improvement in most CPGs, in particular incorporating the patients’ views, describing the systematic review process, and giving recommendations about the implementation of the CPG. The majority of guideline development groups extrapolated results of studies on non-cancer neuropathic pain to recommendations for patients with cancer. Consequently, these CPGs fail to address important issues such as altered kinetics and side effect profiles in these patients. This can be explained by the fact that we did not find a CPG merely dedicated to the treatment of neuropathic pain in cancer patients.

This clinical problem in this specific patient group concerns an area of medical uncertainty, iatrogenic complications, and interventions with significant risks and costs, and therefore fits into the criteria for creating an independent CPG. (9) CPG developers should emphasize that the scientific evidence is weak and should be interpreted with caution. Besides, more research is needed on neuropathic cancer pain patients to provide evidence for more reliable CPGs.

As developing guidelines is time-consuming and expensive; international cooperation in CPG development might be a solution to increase quality and to reduce costs. (56) We advise more international central cooperation (clinicians and methodologists) for the development of a European CPG on neuropathic pain in cancer patients: it would help to pool resources into a high quality guideline module.
A high quality level of the CPG is required but not sufficient. Their applicability is often not evaluated. One of the barriers to use a CPG was its unsuitability in daily practice. (57)

Next step can be the assessment of the knowledge and the application of CPGs in Europe. Specific case vignettes can be developed and tested for several aspects of pain education as they are an inexpensive tool, easy to use to assess this in a large group of physicians, which can easily be repeated, for example after a training or implementation program (58-61). It will help to evaluate the level of the educational module and adapt the training accordingly. Structured education and evaluations resulting in a diploma will improve the knowledge of the practicing physicians.

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Improving neuropathic cancer pain in Europe
Chapter 8 – Summary

Virginie PIANO
Improving neuropathic cancer pain in Europe
Summary

This thesis concerns the quality of clinical practice guidelines (CPGs) from European countries on neuropathic pain in patients with cancer. This work was co-funded by the Netherlands Organisation for Health Research and Development (ZonMw).

Chapter 1. Introduction

Between 19% and 39% of patients with cancer pain suffer from neuropathic pain (NP). Diagnosing and treating NP in this group of patients is difficult and built on weak support in the scientific literature. Yet physicians need guidance on how to screen, to diagnose and to treat. CPGs can be a useful aid. CPGs are ‘systematically developed statements to assist practitioners and patient decisions about appropriate health care for specific circumstances’. However, do CPGs on this topic for this patient group exist in Europe? And if so, what is their quality? Are they based on systematic reviews? Are they applicable in practice? This thesis studied these questions in five articles.

CHAPTER 2. Inventory of clinical practice guidelines in Europe for the treatment of neuropathic pain in patients with cancer

CPGs are ‘systematically developed statements to assist practitioners and patient decisions about appropriate health care for specific circumstances’. Many patients in Europe suffer from chronic pain, often in combination with comorbidities. If available and of good quality, CPGs can guide practitioners in diagnosing and treating pain. Therefore, we studied the number and quality of CPGs in European countries for chronic pain, cancer pain and neuropathic pain.

A questionnaire was sent by email to the European Federation of IASP chapters (EFIC) and IASP members specialised in neuropathic pain in Europe (NeuPSIG). Data on the name and topic (pain, cancer pain and neuropathic pain, other) of each document was collected. The documents had to meet the criteria of a CPG. Frequencies were calculated using SPSS 16. The questionnaire was completed by 41 of the 66 email recipients (62%), representing 30 of the 38 European countries. Together, they mentioned 54
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documents, of which 20 met the CPG criteria: 6 for chronic pain, 5 for neuropathic pain, 4 for cancer pain, 2 in geriatrics, 1 in paediatrics and 2 for chronic lower back pain.

There was significant heterogeneity within Europe concerning the availability, quality and content of CPGs. An international CPG could be helpful in making the management of pain safer and more efficient. Such a blueprint could be adapted for use in each country according to its health system.


Between 19% and 39% of patients with cancer pain suffer from neuropathic pain. Diagnosing and treating NP is challenging. CPGs have been developed in several European countries to assist practitioners in managing NP in these patients safely and legally. The aim of this study was to assess the quality of the development and reporting of these CPGs.

A European inventory of CPGs was conducted in collaboration with the EFIC. The inclusion criterion was that at least one paragraph should be dedicated to the treatment of neuropathic pain in cancer. Using the Appraisal of Guidelines, Research and Evaluation II instrument (AGREEII), two appraisers independently assessed the quality of the development process of the CPGs included with regard to its six domains. Furthermore, t-tests were used to compare CPGs developed by governmental organisations with those developed by professional societies. The mean scores of the domains of ‘scope and purpose’ (80%) and ‘clarity of presentation’ (61%) were satisfactory, ‘stakeholder involvement’ (58%), ‘rigour of development’ (57%), and ‘editorial independence’ (53%) were acceptable, and ‘applicability’ was insufficient (39%). Governmental guidelines had higher scores than professional society guidelines for the domains of ‘stakeholder involvement’ and ‘editorial independence’ (P < 0.01). The quality of the development process of the nine CPGs included varied widely. CPGs should be developed within a structured guideline programme that includes methodological support. As developing a CPG is expensive and time-
consuming, we recommend more international cooperation to increase the quality and lower the developmental costs.

CHAPTER 4. Diagnosing neuropathic pain in patients with cancer: comparative analysis of recommendations in national guidelines in European countries

Neuropathic pain is a prevalent symptom in patients with cancer and it needs a more specific algorithm than nociceptive pain or neuropathic pain originating from a source other than cancer or its treatment. Clinical practice guidelines (CPGs) can be helpful in optimising the diagnosis of neuropathic pain in patients with cancer. In this study, all nine national CPGs in Europe on the diagnosis of neuropathic pain in patients with cancer were examined. A comparison was made between CPGs of the recommendations, the quality (grading) of the supporting literature (according to the SIGN 55 classification) and characteristics of the supporting literature (first author, patients’ population, year and type of publication). In total, 149 references were used in the 9 CPGs, of which 72 (48%) were about cancer conditions, 39 (26%) about neuropathic pain, and only 3 about neuropathic pain in patients with cancer (2%). Only 28 (19%) references were shared between 2 or more guidelines. There was only one shared reference specifically related to neuropathic pain in patients with cancer.

Recommendations and the grading of the supporting evidence differed substantially between the CPGs. This study showed significant heterogeneity in European recommendations on the diagnosis and assessment of neuropathic pain in patients with cancer. The main weaknesses are the low level of the supporting evidence and the absence of specific data focusing on neuropathic pain in patients with cancer. We recommend that physicians dealing with neuropathic pain in patients with cancer should be specially trained for this, that a specific methodology for developing CPGs should be adopted and that high quality research is needed on the diagnosis of neuropathic pain in patients with cancer.
CHAPTER 5. Treatment of neuropathic pain in patients with cancer: comparative analysis of recommendations in national clinical practice guidelines from European countries

Of patients with cancer, 19-39% suffer from neuropathic pain. Treating this type of pain is challenging as this patient group is often frail and has co-morbidities that increase the risk of side-effects and hence affect their quality of life. CPGs can be helpful for clinicians, especially when scientific evidence is uncertain or weak. In this study, we focused on the quality of the review of the literature used to give treatment recommendations in the selected European CPGs. Nine CPGs from European countries that contained at least one paragraph on neuropathic pain in cancer were included. A comparison was made between CPGs of the recommendations, the quality (grading) of the supporting literature (according to the SIGN 55 classification) and characteristics of the supporting literature (first author, patients’ population, year and type of publication). In all the CPGs, amitriptyline was mentioned as the drug of first choice. Six guidelines also proposed gabapentinoids. Only 30 of the 163 citations (18%) were based on studies of patients with cancer. Seven CPGs did not discuss the indirect evidence through the extrapolation of study results from non-cancer patients to patients with cancer. The majority of guideline development groups extrapolated their results to formulate recommendations based on non-cancer publications, without explicitly mentioning this as a limitation. Consequently, these guidelines fail to address important issues such as the different kinetics and side-effect profiles in these patients. We recommend creating specific recommendations by an international expert group for the treatment for neuropathic pain in patients with cancer, supported by targeted research on patients with cancer.

CHAPTER 6. A vignette study to evaluate the practical knowledge of French pain specialists concerning clinical practice guidelines on neuropathic pain in patients with cancer

Between 19% and 39% of patients with cancer suffer from pain that is difficult to diagnose and to treat: neuropathic pain. In France, CPGs on this topic exist, but the extent to which French pain specialists are aware of the
recommendations from these CPGs and use them is unknown. The aim was to investigate, with the help of a case vignette, whether pain specialists follow the recommendations in the CPGs in clinical practice. The survey consisted of a case vignette about a patient with pain suffering from an intractable pancreatic cancer. The vignette included multiple choice questions about the diagnosis and treatment of (neuropathic) pain. An email survey was conducted with the support of the Société Française d’Etude et de Traitement de la Douleur [French society for the study and treatment of pain], with questionnaires being sent to all pain specialists (primary and secondary care) in France. The percentages of respondents who treated the patient as suggested in the CPGs were calculated. A total of 214 (24%) of those invited to participate (921) completed the questionnaire. More than 85% of the respondents said that they were familiar with and used these CPGs. Half of the respondents diagnosed and treated neuropathic pain components in the case vignette in accordance with the recommendations in the CPGs. Although the responding pain specialists stated that they knew and used the CPGs on neuropathic pain in cancer patients, half of them did not give answers that were in line with the recommendations. A nationwide programme to implement these CPGs is necessary, including better education and training of pain specialists in assessing and treating neuropathic pain.

Chapter 7. General discussion

In 2010, we collected 54 documents from European countries with recommendations on diagnosing and treating chronic pain, neuropathic pain or cancer pain. Twenty documents met the clinical practice guideline criteria. Their developmental quality, as determined with the AGREEII instrument, was moderate. Greater efforts need to be made in incorporating patients’ views, describing the systematic review process and giving recommendations on the implementation of the CPG. The majority of guideline development groups extrapolated the results of studies of non-cancer neuropathic pain to arrive at recommendations for patients with cancer.
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NP in patients with cancer is an area where medical knowledge is lacking, where iatrogenic complications are involved and where interventions carry significant risks and costs; it therefore meets the criteria for creating a separate CPG. As the development of guidelines is time-consuming and expensive, international cooperation in CPG development can be a solution that can increase quality and reduce costs. For that reason, we recommend more international and centralised cooperation (involving clinicians, general practitioners and researchers) for the development of a European CPG on neuropathic pain in cancer patients; it would enable the pooling of resources to produce a high quality CPG. Specific case vignettes can be developed and tested for various aspects of pain education as they are an inexpensive tool and easy to use. They can be used to assess the implementation of the CPG among a large group of physicians, and can easily be repeated, for example after a training programme or implementation programme. This will help to evaluate the standard of the educational module and adapt the training programme accordingly.
Chapter 9 – Samenvatting
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Samenvatting

Dit proefschrift gaat over de kwaliteit van klinische praktijk richtlijnen (CPGs) uit Europese landen met betrekking tot neuropathische pijn bij patiënten met kanker. Dit werk werd mede gefinancierd door de Nederlandse organisatie voor gezondheidsonderzoek en zorginnovatie (ZonMw).

Hoofdstuk 1. Introductie

Tussen 19% en 39% van de patiënten met kanker lijdt aan neuropathische pijn (NP). Diagnose en behandeling van NP in deze groep patiënten is moeilijk en is beperkt onderbouwd in de wetenschappelijke literatuur. Toch hebben de artsen aanwijzingen nodig over hoe te screenen, te diagnosticeren en te behandelen. Hiervoor kunnen CPGs een handig hulpmiddel zijn. CPGs zijn 'systematisch ontwikkelde richtlijnen om artsen en patiënten te helpen beslissen over passende zorg in specifieke omstandigheden'. Echter, bestaan er CPGs over dit onderwerp voor deze groep patiënten in Europa? En zo ja, wat is hun kwaliteit? Zijn ze gebaseerd op systematische reviews? Zijn ze toepasbaar in de praktijk? Dit proefschrift bestudeerde deze vragen in vijf artikelen.

HOOFDSTUK 2. Inventarisatie van klinische praktijk richtlijnen in Europa voor de behandeling van neuropathische pijn bij patiënten met kanker

CPGs zijn 'systematisch ontwikkelde richtlijnen om artsen en patiënten te helpen beslissen over passende zorg in specifieke omstandigheden'. Veel patiënten in Europa lijden aan chronische pijn, vaak in combinatie met comorbiditeiten. Indien beschikbaar en van goede kwaliteit, kunnen CPGs artsen begeleiden in het diagnosticeren en behandelen van pijn. Daarom bestudeerden wij het aantal en de kwaliteit van CPGs in Europese landen voor chronische pijn, pijn bij kanker en neuropathische pijn. Een vragenlijst werd toegezonden via e-mail naar de Europese Federatie van IASP afdelingen (EFIC) en IASP leden gespecialiseerd in neuropathische pijn in Europa (NeuPSIG). Gegevens over de naam en het onderwerp (pijn, pijn bij kanker en neuropathische pijn, of andere soorten pijn) werden van elk document verzameld. De documenten moesten aan de criteria van een
CPG voldoen. De frequenties werden berekend met behulp van SPSS 16. De vragenlijst werd ingevuld door 41 van de 66 personen aan wie de e-mail was gestuurd (62 %), wat neerkomt op 30 van de 38 Europese landen. Samen hebben ze 54 documenten genoemd, waarvan er 20 voldeden aan de criteria voor CPGs: 6 voor chronische pijn, 5 voor neuropathische pijn, 4 voor pijn bij kanker, 2 in de geriatrie, 1 in de pediatrie en 2 voor chronische lage rugpijn.

Er was een significante heterogeniteit binnen Europa met betrekking tot de beschikbaarheid, de kwaliteit en de inhoud van CPGs. Een internationale CPG zou nuttig kunnen zijn bij het veiliger en efficiënter behandelen van de pijn. Een dergelijke blauwdruk kan worden aangepast voor gebruik in elk land volgens de daar aanwezige gezondheidszorg.

HOOFDSTUK 3. Richtlijnen voor neuropathische pijn bij patiënten met kanker: een Europees onderzoek en vergelijking

Tussen 19% en 39% van de patiënten met pijn bij kanker hebben last van neuropathische pijn. De diagnose en behandeling van NP zijn een uitdaging. CPGs zijn ontwikkeld in verschillende Europese landen om artsen te helpen bij het veilig en legaal behandelen van NP bij deze patiënten. Het doel van deze studie was de kwaliteit van de ontwikkeling en de rapportage van deze CPGs te beoordelen.

Een Europese inventarisatie van CPGs werd uitgevoerd in samenwerking met de EFIC. Het inclusiecriterium was dat tenminste één paragraaf moest zijn gewijd aan de behandeling van neuropathische pijn bij kanker. Met behulp van het ‘Instrument voor Beoordeling van Richtlijnen’ (AGREE II) hebben twee onderzoekers, onafhankelijk van elkaar, de kwaliteit met betrekking tot de zes domeinen beoordeeld van het ontwikkelingsproces van de CPGs. Verder werden t-toetsen gebruikt om CPGs ontwikkeld door overheidsorganisaties te vergelijken met die ontwikkeld door wetenschappelijke organisaties. De gemiddelde scores van de domeinen van 'onderwerp en doel' (80%) en 'helderheid en presentatie' (61%) waren bevredigend, 'betrokkenheid van belanghebbenden' (58%), 'methodologie’(57%) en 'onafhankelijkheid van de opstellers’ (53%) waren acceptabel, en 'toepassing' was ontevredend (39%). Overheidsrichtlijnen hadden hogere scores dan wetenschappelijke organisatie richtlijnen voor
hoofdstuk 4. diagnose van neuropathische pijn bij patiënten met kanker: vergelijkende analyse van de aanbevelingen in nationale richtlijnen van de Europese landen

Neuropathische pijn is een veel voorkomend symptoom bij patiënten met kanker en het behoeft een meer specifiek algoritme dan nociceptieve pijn of neuropathische pijn die afkomstig is van een andere bron dan kanker of de behandeling er van. Klinische praktijk richtlijnen (CPGs) kunnen behulpzaam zijn bij het optimaliseren van de diagnose van neuropathische pijn bij patiënten met kanker. In deze studie werden alle negen nationale CPGs in Europa op het gebied van neuropathische pijn bij patiënten met kanker onderzocht. Er werd een vergelijking gemaakt tussen CPGs op het gebied van de aanbevelingen, de kwaliteit van de ondersteunende literatuur (volgens de SIGN 55 -classificatie) en de kenmerken van de ondersteunende literatuur (eerste auteur, populatie van patiënten, jaar en soort publicatie). In totaal werden 149 referenties gebruikt in de 9 CPGs, waarvan er 72 (48%) waren over kanker, 39 (26%) over neuropathische pijn, en maar 3 over neuropathische pijn bij patiënten met kanker (2%). Slechts 28 (19%) referenties werden gedeeld tussen 2 of meer richtlijnen. Er was maar één gedeelde verwijzing specifiek gerelateerd aan neuropathische pijn bij patiënten met kanker.

De aanbevelingen en de kwaliteit van het ondersteunende bewijs verschilt wezenlijk tussen de CPGs. Deze studie toont een aanzienlijke heterogeniteit in de Europese aanbevelingen over de diagnose en evaluatie van neuropathische pijn bij patiënten met kanker. De belangrijkste tekortkomingen zijn het lage niveau van het ondersteunend bewijs en het ontbreken van specifieke gegevens gericht op neuropathische pijn bij
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patiënten met kanker. We raden aan dat artsen die omgaan met neuropathische pijn bij patiënten met kanker speciaal worden opgeleid, dat er een specifieke methodologie voor het ontwikkelen van CPGs moet worden aangenomen en dat er meer wetenschappelijk onderzoek van hoge kwaliteit wordt gedaan over de diagnose van neuropathische pijn bij patiënten met kanker.

HOOFDSTUK 5. Behandeling van neuropathische pijn bij patiënten met kanker: vergelijkende analyse van de aanbevelingen in de nationale klinische praktijk richtlijnen uit Europese landen

Van de patiënten met kanker heeft 19-39% last van neuropathische pijn. Het behandelen van dit soort pijn is een uitdaging want deze patiëntengroep is vaak kwetsbaar en heeft comorbiditeiten die het risico op bijwerkingen verhogen en daarmee invloed heeft op hun kwaliteit van leven. CPGs kunnen nuttig voor clinici, vooral wanneer wetenschappelijk bewijs onzeker of zwak is. In deze studie hebben we ons gericht op de kwaliteit van de literatuur die is gebruikt om aanbevelingen voor de behandeling te geven in de geselecteerde Europese CPGs. Negen CPGs uit Europese landen, die tenminste één paragraaf over neuropathische pijn bij kanker bevatten, werden opgenomen. Er werd een vergelijking gemaakt tussen CPGs van de aanbevelingen, de kwaliteit van de ondersteunende literatuur (volgens de SIGN 55 -classificatie) en de kenmerken van de ondersteunende literatuur (eerste auteur, populatie van patiënten, jaar en soort publicatie). In alle CPGs werd amitriptyline genoemd als het middel van eerste keus. Zes richtlijnen stelden ook gabapentinoïden voor. Slechts 30 van de 163 citaties (18%) waren gebaseerd op studies met patiënten met kanker. Zeven CPGs hebben het indirect bewijs door de extrapolatie van de studieresultaten van patiënten met pijn door een niet-oncologische oorzaak naar patiënten met kanker niet bediscussieerd. De meerderheid van de richtlijnontwikkelingsgroepen extrapoleerden hun resultaten om aanbevelingen te formuleren op basis van niet-kanker publicaties, zonder expliciet aan te geven dat dit geldt als een beperking. Daardoor zijn deze richtlijnen niet in staat belangrijke kwesties, zoals de verschillen in de kinetiek en bijwerkingen van bij deze patiënten, aan te geven. Wij raden aan om een internationale groep van deskundigen specifieke aanbevelingen
te laten opstellen voor de behandeling van neuropathische pijn bij patiënten met kanker ondersteund door gericht onderzoek bij patiënten met kanker.

HOOFDSTUK 6. Een case vignette studie naar de praktische kennis van Franse pijn specialisten betreffende klinische praktijk richtlijnen over neuropathische pijn bij patiënten met kanker

Van de patiënten met kanker lijdt tussen de 19% en 39% aan pijn die moeilijk te diagnosticeren en te behandelen is: neuropathische pijn. In Frankrijk bestaan CPGs over dit onderwerp, maar de mate waarin de Franse pijn specialisten zich bewust zijn van de aanbevelingen uit deze CPGs en ze gebruiken is niet bekend. Het doel was om te onderzoeken, met behulp van een case vignette, of pijn specialisten de aanbevelingen uit de CPGs in de klinische praktijk volgen. Het onderzoek bestond uit een case vignette over een patiënt met pijn die lijdt aan onbehandelbare alvleesklierkanker. In de vignette zijn meerkeuzevragen opgenomen over de diagnose en behandeling van (neuropathische) pijn. Een e-mail enquête met vragenlijsten werd in Frankrijk uitgevoerd met de steun van de Société Française d’Etude et de Traitement de la Douleur (Franse vereniging voor de studie en behandeling van pijn). Deze enquête werd aan alle pijn specialisten (primaire en secundaire zorg) verzonden. De percentages van de respondenten die de patiënt behandelden zoals gesuggereerd in de CPGs werden berekend. Een totaal van 214 (24%) van hen die waren uitgenodigd om deel te nemen (921) vulden de vragenlijst in. Meer dan 85% van de respondenten zei dat ze bekend waren met deze CPGs en deze gebruikten. De helft van de respondenten diagnosticeerde en behandelde de neuropathische pijn onderdelen in de case vignette volgens de aanbevelingen in de CPGs. Hoewel de reagerende pijn specialisten verklaarden dat zij de CPGs over neuropathische pijn bij patiënten met kanker kenden en gebruikten, gaf de helft van hen antwoorden die niet in overeenstemming waren met de gegeven aanbevelingen. Een landelijk programma om deze CPGs implementeren is noodzakelijk, inclusief beter onderwijs en training van de pijn specialisten in de beoordeling en behandeling van neuropathische pijn.
Hoofdstuk 7. Algemene discussie

In 2010 hebben we 54 documenten verzameld van Europese landen met aanbevelingen over de diagnose en behandeling van chronische pijn, neuropathische pijn of pijn bij kanker. Twintig documenten voldeden aan de criteria voor een klinische praktijk richtlijn. Hun ontwikkelingskwaliteit, bepaald met het AGREEII instrument, was matig. Grotere inspanningen moeten worden gedaan om de mening en opvattingen van patiënten een plek te geven, het systematisch review proces te beschrijven en het geven van aanbevelingen over de implementatie van de CPG. De meerderheid van de werkgroepen voor richtlijnontwikkeling extrapoleerden de resultaten van studies van niet-kanker neuropathische pijn om te komen tot aanbevelingen voor patiënten met pijn bij kanker.

NP bij patiënten met kanker is een gebied waar medische kennis ontbreekt, waar iatrogene complicaties voorkomen en waar interventies significante risico's en kosten met zich meebrengen. Daarom voldoet het aan de criteria voor het creëren van een aparte CPG. Aangezien de ontwikkeling van richtlijnen tijdrovend is en veel geld kost, kan internationale samenwerking in CPG ontwikkeling een oplossing zijn om de kwaliteit te verhogen en de kosten te verlagen. Om die reden raden we een meer internationale en gecentraliseerde samenwerking aan (waarbij medisch specialisten, huisartsen en onderzoekers zijn betrokken) voor de ontwikkeling van een Europees CPG over neuropathische pijn bij patiënten met kanker. Het bundelen van de middelen maakt het mogelijk om een CPG van hoge kwaliteit te ontwikkelen. Specifieke case vignettes kunnen worden ontwikkeld en getest voor de verschillende aspecten van pijn onderwijs omdat ze een goedkoop hulpmiddel en gemakkelijk in gebruik zijn. Ze kunnen worden gebruikt om de implementatie van de CPG onder een grote groep artsen te beoordelen, en kunnen gemakkelijk worden herhaald, bijvoorbeeld na een training of implementatieprogramma. Dit zal helpen om de kwaliteit van de onderwijsmodule te evalueren en het trainingsprogramma daaraan aan te passen.
Résumé
Improving neuropathic cancer pain in Europe
Cette thèse étudie la qualité des recommandations européennes portant sur la douleur neuropathique des patients souffrant d'un cancer. Ce travail a été financé par l'organisation néerlandaise pour la recherche et le développement en santé (ZonMw).

**Chapitre 1 – L’introduction.**

Dix-neuf à 39% des patients avec des douleurs cancéreuses souffrent de douleur neuropathique. Diagnostiquer et traiter la douleur neuropathique dans ce groupe de patients est difficile et fondé sur des données scientifiques de faible niveau. Or, il est nécessaire de guider les médecins à détecter, diagnostiquer et traiter ces douleurs. Des recommandations de bonne pratique peuvent être utiles. Ce sont des « recommandations systématiquement développées pour aider les praticiens et les décisions des patients sur les soins de santé appropriés dans des circonstances spécifiques ». Or, existe-t-il de telles recommandations en Europe ? Si oui, quelle est leur qualité de développement ? Sur quelle revue de la littérature sont-elles fondées ? Sont-elles applicables ? Cette thèse va répondre à ces questions en 5 articles.

**Chapitre 2 - L’inventaire des recommandations de bonne pratique portant sur la douleur en Europe.**

Les recommandations de pratique clinique (RPC) « recommandations systématiquement développées pour aider les praticiens et les décisions des patients sur les soins de santé appropriés dans des circonstances spécifiques ». Beaucoup de patients en Europe souffrent de douleur chronique, souvent en association avec des comorbidités. Si elles sont disponibles et de bonne qualité, les RPC peuvent guider les praticiens dans le diagnostic et le traitement de la douleur. De ce fait, nous avons étudié le nombre et la qualité des RPC dans les pays européens concernant la douleur chronique, la douleur cancéreuse et la douleur neuropathique.

Un questionnaire envoyé par email aux responsables des sociétés savantes de la douleur et les cliniciens appartenant au groupe des douleurs neuropathiques de l’International Association for the Study of Pain (IASP) en
Europe. Le nom et le thème de chaque document cité (douleur chronique, douleur cancéreuse, douleur neuropathique et autre) a été collecté. Chaque document devait répondre à la définition d’une RPC. L’analyse statistique a été réalisée avec le logiciel SPSS 16.0. Quarante-et-un des 66 participants (62%) ont répondu au questionnaire, représentant 30 des 38 pays européens. Parmi les pays répondants, 54 documents ont été collectés et parmi eux, 20 correspondaient à la définition de RPC : 6 sur la douleur chronique, 5 sur la douleur neuropathique, 4 sur la douleur cancéreuse, 2 sur la prise en charge des douleurs de la personne âgée, 1 pour la pédiatrie et 2 sur la douleur lombaire chronique.

Il existait une importante hétérogénéité en Europe sur la disponibilité, le contenu et la qualité des RPC. La rédaction d’une RPC européenne permettrait de proposer une prise en charge plus sûre et efficace. Celle-ci pourrait ensuite être adaptée dans chaque pays selon son système de santé.

Chapitre 3 - Recommandations pour la prise en charge des douleurs neuropathiques des patients souffrant de cancer: une enquête européenne et comparaison.

Entre 19 et 39% des patients souffrant d’un cancer ont des douleurs neuropathiques. Son diagnostic et son traitement est toujours un défi. En fait, des recommandations de pratique clinique (RPC) nationales ont été développées dans plusieurs pays européens afin d’aider les médecins à gérer ces patients de façon sûre et légale. L’objectif de cette étude était d’évaluer la qualité de développement de ces RPC.

En collaboration avec la fédération européenne des chapitres de l’IASP (EFIC), un inventaire européen de RPC a été élaboré. Les critères d’inclusion étaient d’avoir au moins un chapitre concernant le traitement des douleurs neuropathiques dans le cancer. L’instrument Appraisal of Guidelines, Research and Evaluation II (AGREE II) a été utilisé par deux évaluateurs indépendants afin de mesurer la qualité du processus de développement de ces RPC inclues selon 6 items. De plus, les RPC développées par les organisations gouvernementales ont été comparées à celles développées
par les sociétés savantes en utilisant des tests-t. La moyenne des scores pour le domaine « champ et objectifs » (80%) et « clarté de présentation » (61%) était satisfaisante. La moyenne pour les domaines « participation des groupes concernés » (58%), « rigueur d’élaboration de la RPC » (57%) et « indépendance éditoriale » (53%) était acceptable. La moyenne des scores pour le domaine « applicabilité » était insuffisante (39%). Les recommandations gouvernementales avaient un score de qualité supérieur aux recommandations des sociétés savantes pour les domaines « participation des groupes concernés » et « indépendance éditoriale » (p<0,01). La qualité du processus de développement des 9 RPC inclues était très variable. De ce fait, les RPC devraient être développées sur le modèle d’un programme structuré, incluant un support méthodologique. Comme cela est onéreux et chronophage, nous recommandons une plus grande coopération internationale afin d’améliorer la qualité et de diminuer les coûts.

**Chapitre 4 – Diagnostiquer la douleur neuropathique chez les patients souffrant de cancer : une analyses comparative des recommandations de bonne pratique nationales dans les pays européens.**

La prévalence de la douleur neuropathique est élevée chez les patients souffrant de cancer. Cela requiert un algorithme de diagnostic plus spécifique que lors des études des douleurs non cancéreuses qu’elle soit nociceptive ou neuropathique. Les RPC peuvent aider en optimisant le diagnostic des douleurs neuropathiques dans le cancer. Dans cette étude, 9 RPC nationales en Europe portant sur le diagnostic des douleurs neuropathiques cancéreuses ont été inclues. Les recommandations avec leur grade d’évidence (selon la classification SIGN-50 du *Scottish Intercollegiate Guidelines Network*) et les références utilisées (premier auteurs, population de patients, année et type de publication) ont été comparées entre les RPC. Neuf RPC concernant la douleur neuropathique cancéreuse ont été sélectionnées et analysées. Au total, 149 références ont été citées dont 72 (48%) concernaient le cancer, 39 (26%) concernaient la douleur neuropathique et 3 (2%) concernaient la douleur neuropathique chez les patients souffrant de cancer. Seulement 28 références (19%)
étaint partagées entre 2 RPC ou plus. Seule une référence partagée concernait la douleur neuropathique cancéreuse.

Les recommandations et leur grade d’évidence différaient largement entre les RPC. Cette étude montrait une hétérogénéité importante entre les RPC européennes portant sur le diagnostic et l’évaluation des douleurs neuropathiques chez les patients souffrant de cancer. La principale faiblesse était le niveau faible d’évidence et l’absence de données spécifiques concernant la douleur neuropathique cancéreuse. Nous recommandons que les médecins s’occupant des douleurs neuropathiques chez les patients souffrant de cancer soient formés spécifiquement et que la recherche s’intéresse à ce domaine précis.

Chapitre 5 – Le traitement des douleurs neuropathiques chez les patients souffrant d’un cancer : analyse comparative des recommandations nationales issues des recommandations de pratique clinique en Europe.

Des patients souffrant de cancer, 19 à 39 % souffraient de douleur neuropathique. Traiter ce type de douleur reste un défi parce que ce groupe de patients est souvent fragile et a des comorbidités qui vont augmenter le risque d’événements indésirables et donc influencer sa qualité de vie. Les RPC peuvent aider les médecins, en particulier parce que l’évidence scientifique est incertaine ou faible. Dans cette étude, nous avons étudié en détail la qualité de la revue de la littérature utilisée dans les recommandations portant sur le traitement des RPC européennes sélectionnées. Dans une étude précédente, 9 RPC européennes qui contenaient au moins un paragraphe sur le traitement des douleurs neuropathiques dans le cancer ont été inclues. Les recommandations avec leur grade d’évidence (selon la classification SIGN-50) et les références utilisées (premiers auteurs, population de patients, année et type de publication) ont été comparées entre les RPC. Dans toutes les RPC, l’amitriptyline a été mentionnée comme le traitement de première intention. Six RPC proposaient aussi la gabapentine. Seulement 30 des 163 références (18%) étaient des études portant sur les patients souffrant de cancer. Sept RPC n’argumentaient pas l’extrapolation des résultats des études portant sur des patients sans cancer vers des patients avec un
cancer. La majorité des groupes de développement des RPC extrapolait les résultats des populations en dehors d’un contexte oncologique pour formuler des recommandations sur le cancer. En conséquence, ces RPC échouaient à donner les points principaux concernant la cinétique altérée et les événements indésirables chez ces patients. Nous conseillons de créer des recommandations spécifiques par un groupe international d’experts pour le traitement des douleurs neuropathiques chez les patients souffrant de cancer avec le support d’une recherche ciblée dans cette population spécifique.

Chapitre 6 – Une vignette clinique pour évaluer la connaissance et la pratique des médecins français spécialisés en douleur concernant les recommandations de pratique clinique portant sur la douleur neuropathique cancéreuse.

Entre 19 et 39% des patients ayant un cancer souffrent de douleur neuropathique, celles-ci sont difficiles à diagnostiquer et à traiter. En France, il existe des RPC sur ce sujet mais leur connaissance et leur utilisation par les algologues n’est pas répertoriée. L’objectif de l’étude était d’étudier si les médecins français spécialisés en douleur suivaient ces recommandations en utilisant une vignette clinique d’un patient souffrant de douleur neuropathique cancéreuse dans la cadre d’un cancer du pancréas. Les participants, membres de la SFETD, ont répondu à un questionnaire en ligne. Plusieurs options diagnostiques et thérapeutiques étaient proposées. Le pourcentage de participants qui suivaient les RPC ont été calculés pour chaque question de la vignette clinique. Sur les 921 médecins de la SFETD, 214 (24%) ont répondu au questionnaire. Plus de 85% d’entre eux déclaraient connaitre et utiliser les RPC. La moitié d’entre eux diagnostiquait et traitait la douleur neuropathique dans la vignette clinique en concordance totale avec les RPC. Bien que les médecins spécialisés en douleur connaissent et utilisent les RBP, seulement la moitié d’entre eux les suivent pour prendre en charge la douleur neuropathique. Un programme national d’implémentation de ces RBP sera utile afin d’évaluer les facteurs limitant l’utilisation de ces RBP.

Chapitre 7 – Discussion générale.
En 2010, dans les pays européens, 54 documents sur la douleur chronique, la douleur neuropathique ou la douleur cancéreuse ont été disponibles pour guider les médecins. Vingt documents répondaient à la définition d’une recommandation de pratique clinique (RPC). Leur qualité, définie par l’AGREE II instrument, était modeste concernant les RPC spécifiques de la douleur neuropathique cancéreuse. Des efforts sont encore nécessaires pour faire participer les patients à leur développement, pour décrire le processus de réalisation dans la revue de la littérature ou encore donner des indications sur le moyen d’implémenter ces RPC. La majorité des groupes de développement des RPC extrapolaient les résultats d’études d’une population non cancéreuse pour aboutir à des recommandations pour la population souffrant de cancer.

La douleur neuropathique dans le cancer est un domaine où la connaissance médicale est insuffisante, où les complications iatrogènes sont fréquentes et où les interventions médicales portent un risque et un coût significatif, il s’agit donc de critères justifiant la création d’une recommandation spécifique. Comme développer une RPC est chronophage et onéreuse, une coopération internationale dans le développement d’une RPC pourrait être une solution pour améliorer la qualité des soins et réduire les coûts. Pour cette raison, nous conseillons une plus grande collaboration internationale (avec des méthodologistes et des cliniciens dont les médecins généralistes) pour le développement d’une RPC européenne portant sur la douleur neuropathique cancéreuse : cela aiderait à mutualiser les ressources pour obtenir un bon niveau de qualité. Des vignettes cliniques spécifiques devraient être développées et testées pour plusieurs aspects concernant la formation en douleur parce que ce sont des outils bon marché et faciles à utiliser. Elles pourraient être utilisées pour évaluer l’implémentation des RPC dans un large groupe de médecins, pouvant être facilement répétés dans le temps, après une formation ou pour tester l’implémentation du programme d’une RPC. Cela permettra d’évaluer le module actuel de formation et d’adapter éventuellement l’enseignement des cliniciens en fonction de nouvelles données enregistrées.
Epilogue

Marseille, May the 14th 2013

Dear Vero, Naia and Mathilde,

I am physician, general practitioner, pain specialist and I would like to answer your questions.

Each of you has neuropathic pain: it is a pain caused by a lesion of a nerve. In your case, Naia, I think that it is caused by the surgery. Vero, your neuropathic pain seems related to the chemotherapy you received. And Mathilde, the cancer itself seems responsible for the pain. Indeed, this pain is often described as burning, like pins and needles or electric shocks. Your physician can diagnose it during a physical examination; no other tests will be necessary. And like all three of you experience: this pain is very uncomfortable and needs treatment with other drugs than you are used to take for other kinds of pain. Although it sounds strange, drugs that are also meant to treat epilepsy or a depression are the best options to reduce neuropathic pain. These treatments might help you, but they can have unpleasant side effects, which your physician needs to discuss with you. By starting with a small dose and monitoring the effect and side effects of the drugs, you have the highest change that your pain will be relieved with limited and tolerable side effects. Don’t hesitate to discuss this with your doctor, and to ask him as your partner in improving the quality of your life.

The research on treating neuropathic pain that is related to cancer is still poor. I have been studying it in the past few years, and will continue to study it. I will follow the discussions on this forum, and will keep you up to date if new developments are available. All the best for the three of you!

Yours sincerely,

Virginie Piano, MD
PORT FOLIO

International activities
09-2012 NCEBP PhD Retreat in Wageningen, The Netherlands
05-2012 International Headache Academy, Copenhague, Denmark
03-2011 Nijmegen Centre for Evidence Based Practice (NCEBP, research institute of the Radboud University Nijmegen Medical Centre) introduction course
11-2011 EFIC Pain school in Montescano, Italy: diagnosis of neuropathic pain.
07-2011 Course lecturer for the Erasmus intensive Program of the Network for Primary Health Care in Istanbul, Turkey.

Publications make a distinction between international peer reviewed, national, book chapters


Posters


- Facteurs prédictifs de réponse au traitement par lidocaïne intraveineuse des douleurs neuropathiques irréductibles. Premier auteur. JNLF les 5-6 avril 2012.
- Evaluation de la qualité des recommandations de pratique clinique européennes portant sur la prise en charge des douleurs neuropathiques cancéreuses avec l’instrument AGREE II. Premier auteur. JNLF les 5-6 avril 2012.
- Systematic administration of lidocaïne to relieve intractable neuropathic pain: predictive factor of response. First author. Presentation during the 14th world congress on pain, Milan 2012.
- Diagnosing Neuropathic Pain in Patients with Cancer: Comparative Analysis of Recommendations in European Guidelines with the LinkER Procedure. First author. 13th congress of the European Association for Palliative Care, Trondheim, 2012.
- Analysis of European Recommendations and Evidence Analysis of Treatment of Neuropathic Pain in Cancer Patients with the LinkER Procedure. First author. 13th congress of the European Association for Palliative Care, Trondheim, 2012.
- Comparative analysis of European recommendations and evidence analysis of treatment of neuropathic pain in cancer patients. Second author. 7th congress of the European Federation of IASP Chapters (EFIC).
• Prise en charge de la douleur chronique par le médecin généraliste : étude qualitative. Présentation au congrès de la CNGE, Rouen 2010.
• Evaluation prospective ouverte du traitement des douleurs neuropathiques irréductibles par lidocaïne intraveineuse (Lidodol 2). Présentation à la SFETD Marseille, en novembre 2010.
• Chemin clinique de l’hôpital de jour d’un centre tertiaire de la douleur (Lidodol 1). SFETD Marseille, en novembre 2010.
• Cardiac Safety in Cluster Headache Patients Using Supra-Maximum Dose of Verapamil. Presented at the 14th International Headache Congress (September 10 - 13, 2009, Philadelphia, PA).

Oral presentations

• Valorisation des actes infirmiers pour le cours supérieur des infirmières lors du 13ème congrès annuel de la SFETD, Paris 2013.
• ATS. Codages des hospitalisations complètes et de jour en douleur chronique. SFETD, 2011.
• Pédagogie. Expérimentation d’une « cellule RSCA » au DERMG de Nice. CNGE, 2011.
• NHPC Erasmus Intensive Program Pain management in palliative care Istanbul, 2011.
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**Supervision**

- Direction de thèse en médecine: Mlle Coralie Nevels (mention très honorable avec félicitations du jury) Université de Médecine de Nice, 27/09/2012
- Direction de thèse en médecine: Mlle Claire Hannotel (mention très honorable avec félicitations du jury, proposition au prix de thèse) Université de Médecine de Nice, 27/09/2012
- Direction de mémoire de sage-femme: Mlle Julia Defforge, Ecole de sage-femme, Université de Nice, 04/05/2013, mention bien.

**Actual work**

- Educational program for daily chronic headaches: promotor in CETD, La Timone, AP-HM, Marseille.

**Grants / Awards**

- Communications affichées sélectionnées aux Journées de Neurologie de Langue Française du 3 au 6 avril 2012 le jeudi 5 avril 2012 pour le poster « Facteurs prédictifs de réponse au traitement par lidocaïne intraveineuse des douleurs neuropathiques irréductibles ».
- Poster Award in the 12th congress of the European Association for Palliative Care (EAPC), Lisbon (2011)
- Prix “Bruno Massena”, major of the promotion, Master 2 « Engineer in Health System » (2009)
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Improving neuropathic cancer pain in Europe

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Chapter 10 - Curriculum vitae
CURRICULUM VITAE

Virginie Piano was born in August, the 11th 1982 in Draguignan in the South of France. She is interested in medicine since ever, following her mother who is a general practitioner during her visits and learning anatomy with her father who was an embalmer. Practitioner in 2007, she made her internship in general practice. She became doctor in general practice in 2010. She is the first graduate of the Diplôme d’Études Spécialisées Complémentaires (DESC) Médecine de la Douleur, Médecine Palliative of Nice, a for pain specialization in 2011. She was an assistant specialist in the Department of Pain and Palliative Care of Nice University Hospital Centre from 2010 to 2012. She is hospital practitioner in the Pain Centre of La Timone hospital in the University Medical Centre of Marseille since November 2012. She keeps teaching to medical and nurse students and medical practitioners.

During her last year of internship in medicine, she had a grant from Erasmus with the Socrates program in Nijmegen: she spent three months in the department of anesthesiology, pain and palliative care directed by Professor Kris Vissers and in the department of primary and community care directed by Professor Chris van Weel. It was the start of a beautiful collaboration with the Radboud University Nijmegen Medical Centre. She started her PhD in the Netherlands in the Nijmegen Centre for Evidence Based Practice (NCEBP) in 2010. Her area for research was neuropathic pain in patients with cancer evaluation: the NeuPiVal project.

In 2011 with three friends, she created the Association Française des Jeunes chercheurs en Douleur et Soins Palliatifs to improve the education and the research in pain and palliative care. She is engaged in the EFIC task force for pain education since 2012 and in quality indicator since 2013. She is engaged in the French pain society, the French headache society, the French palliative society and the IASP.

When Virginie is not in her office in Marseille, she is walking with David in the French Alps.
Improving neuropathic cancer pain in Europe
In Europe, from 19 to 39% of the patients with cancer pain suffer from neuropathic pain. This pain is difficult to relieve and needs a specific management. To guide practitioners, clinical practice guidelines (CPGs) can be proposed. The aim of this thesis is 1) to assess the quality of development of these European CPGs, 2) to compare diagnosis and treatment between CPGs with their evidence and 3) to evaluate the applicability of these CPGs in practice.

All European CPGs about the management of neuropathic cancer pain were collected and assessed with AGREE II instrument to evaluate the quality development. Each reference mentioned in CPGs was registered and each recommendation was compared between CPGs. A case vignette on neuropathic cancer pain was proposed to evaluate the applicability of CPGs.

Nine CPGs met the criteria in Europe. Applicability, rigor of development and editorial independence were low. Only 18% of the references collected concerned cancer population. No consensus was found about the diagnosis. Six of the 9 CPGs extrapolated results from non-cancer to cancer patients without reservations. Only 54% of the French pain specialists diagnosed and treated neuropathic pain in a case vignette on cancer.

We advise more international central cooperation (clinicians and methodologists) for the development of a European CPG on neuropathic pain in cancer patients: it would help to pool resources into a high quality guideline module.