Article:
Mulvey, MR orcid.org/0000-0002-6357-3848, Boland, E, Bouhassira, D et al. (6 more authors) (2017) Neuropathic pain in patients with cancer: performance of screening tools and analysis of symptom profiles. British Journal of Anaesthesia, 119 (4). pp. 765-774. ISSN 0007-0912

https://doi.org/10.1093/bja/aex175

OXFORD UNIVERSITY PRESS | BJA British Journal of Anaesthesia

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Journal:	*British Journal of Anaesthesia*
Manuscript ID	BJA-2017-00063-HH055.R1
Manuscript Type:	Review article
Date Submitted by the Author:	n/a
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Mesh keywords:	Cancer pain, Neuropathic pain, Screening tool performance

Neuropathic pain in patients with cancer: performance of screening tools and analysis of symptom profiles

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Abstract

Background: The objectives of this study were to [1] evaluate the methodological quality of included studies, [2] determine the performance of screening tools for identifying neuropathic pain in patients with cancer. **Methods**: Systematic literature search identified studies reporting use of LANSS, DN4 or painDETECT in cancer patients with a clinical diagnosis of neuropathic or not neuropathic pain. Individual patient data was requested to examine descriptor item profiles. **Results**: Six studies recruited a total of 2301 cancer patients of which 1564 (68%) reported pain. Overall accuracy of screening tools ranged from 73%-94%. There was variation in description and rigor of clinical assessment, particularly related to the rigour of clinical judgement of pain as the "referent standard". Individual data from 1351 patients showed large variation in the selection of neuropathic pain descriptor items by cancer patients with neuropathic pain. LANSS and DN4 items characterised a significantly different neuropathic pain symptom profile from non-neuropathic pain in both tumour- and treatment-related cancer pain aetiologies. **Conclusion**: We identified concordance between the clinician diagnosis and screening tool outcomes for LANSS, DN4 and PDQ in patients with cancer pain. Shortcomings in relation to standardised clinician assessment are likely to account for variation in screening tool sensitivity, which should include the use of the neuropathic pain grading system. Further research is needed to standardise and improve clinical assessment in patients with cancer pain. Until the standardisation of clinical diagnosis for neuropathic cancer pain has been validated, screening tools offer practical approach to identify potential cases of neuropathic cancer pain.

Key words

Cancer pain, neuropathic pain, screening tool performance, symptom profile

Introduction

Neuropathic pain affects up to 40% of cancer patients and is associated with increased pain intensity and analgesic consumption and decreased quality of life.[3 15 21 31] While the majority of neuropathic pain in cancer patients arises as a direct result of tissue destruction by tumour, a growing proportion is caused by cancer treatments such as surgery or chemotherapy.[3 12]

Rigorous pain assessment is needed to identify the presence of neuropathic pain in order to direct specific treatment strategies.[11 22] In clinical practice inadequate assessment rigour leads to increased heterogeneity of clinical samples with adverse impact on treatment outcomes for patients.[3] In clinical trials, inadequate assessment rigour (and subsequent inclusion of heterogeneous sample populations) has been associated with the increasing number of neuropathic pain studies which fail to meet their primary efficacy end point.[13 14] The recently updated grading system for neuropathic pain[17] offers a standardised set of assessment criteria for identifying possible, probable and definite cases of neuropathic pain in clinical and research settings. The criteria are (1) history of a relevant neurological lesion or disease of the somatosensory nervous system and pain in a plausible neuroanatomical distribution, (2) on examination pain is associated with sensory signs in the same plausible neuroanatomical distribution, (3) confirmatory diagnostic tests indicate the presence of a lesion or disease of the somatosensory nervous system explaining the pain.[17] Satisfying the three criteria in turn raises the certainty of neuropathic pain from possible, to probable, to definite. However, neither the revised grading system for neuropathic pain,[25] or the original grading system,[32] has been widely applied and evaluated in cancer patients. Nevertheless, studies adhering to this grading system were found to have significantly lower estimates of

neuropathic pain prevalence than non-rigorous studies.[27] Nevertheless the neuropathic pain grading system has yet to be widely adopted because the reliability (inter-rater and test-retest) and applicability of the grading system in clinical practice or research remain unclear. In the recent update of the grading system[17] the authors acknowledged that it cannot yet be used as a "gold standard". In this regard, to date there is a lack of a gold standard for identifying neuropathic pain and validated screening tools represent the best alternative.

Although screening tools cannot be used alone to identify neuropathic pain, the discriminatory value of neuropathic pain descriptors and the role of screening tools to identify possible cases of neuropathic pain has been highlighted in the updated grading system for neuropathic pain.[17] The most widely used neuropathic pain screening tools are the Leeds Assessment of Neuropathic Symptoms and Signs (LANSS)[2], the Douleur Neuropathique 4 (DN4)[6], and painDETECT (PDQ).[18] The LANSS comprises five symptom descriptor times and two sensory examination items; the DN4 comprises seven symptom items and three clinical examination items; the PDQ comprises nine self-reported symptom items.[26]

These screening tools are recommended by Neuropathic Pain Special Interest Group (NeuPSIG) of the International Association for the Study of Pain (IASP) for screening but not for diagnosis.[22] These tools have been validated in a wide range of pain populations, as well as translated into many languages, to discriminate between pain that is predominantly neuropathic and pain that is predominately nociceptive.[26] However, some reports of their

use in cancer populations have suggested that their ability to identify cases of neuropathic pain might be lower than in non-cancer populations in which they were developed.[25 31]

The objectives of our current study were: [1] to evaluate the methodological quality of included studies, [2] determine the performance of screening tools for neuropathic pain in cancer patients against clinician assessment of pain type.

Methods

Search Methods

We undertook a systematic literature search for all studies that reported use of LANSS, DN4 or painDETECT in cancer patients. Electronic database searches were conducted from inception to August 2015 in MEDLINE, EMBASE, CINAHL (searches were updated in March 2017). A search strategy was developed for MEDLINE and altered accordingly for each electronic database (Appendix 4). Names and abbreviations of neuropathic pain screening tools were combined with terms for cancer, pain, neuropathic, neuropathy.

Studies were eligible for inclusion if they included:

- Clinical population of patients with pain from cancer or cancer treatment.
- A clinical diagnosis of pain type from a healthcare professional (but not necessarily a pain specialist).
- A classification of pain using one or more of the following screening tools for neuropathic pain: LANSS[2], DN4[6], PDQ[18].

- Sufficient data for sensitivity and specificity values to be extracted or to be calculated by hand.

All articles were assessed for eligibility by first screening title and abstract and then by full text by two independent assessors. Grey literature search was conducted by reviewing the references lists of included articles and by contacting the authors of the original validation studies for LANSS, DN4 and PDQ to request as yet unpublished reports meeting the eligibility criteria.

Data extraction

We extracted data on clinical setting, pain aetiology: tumour related or cancer treatment related (e.g. chemotherapy, radiotherapy, surgery), cancer diagnosis, exposure to oncology treatment, number of patients with clinical impression of pain type (neuropathic, not neuropathic, unsure), type of clinician who gave clinical impression (e.g. pain specialist, oncologist), type of screening tool used, individual who administer the screening tool, and number of patients with classification of pain from a screening tool (likely neuropathic or unlikely neuropathic).

Evaluating methodological quality of included studies - Assessment of risk of bias in included studies

The impact of the design and execution of included studies on the validity of their findings was evaluated by undertaking an assessment of risk of bias. We used a modified version of

the Cochrane Collaboration's tool for assessing risk of bias.[24] The following criteria were assessed:

Screening tool performance bias: Studies were considered at low risk of bias if the individual administering the screening tool was blinded to clinical judgement or the lack of assessor blinding was unlikely to affect the results (i.e. screening tool was administered prior to clinician making judgement of pain) . Studies were considered at high risk of performance bias if the screening tool assessor had access to or had already made the clinical judgement of pain type prior to administering the screening tool.

Reporting bias: Studies were considered at low risk of reporting bias if they provided a clear description of the methods and person (i.e. pain specialist or palliative care physician) providing the clinical impression of pain type. Studies were considered at high risk of reporting bias if there was no description of the diagnostic or classification process. An unclear risk of reporting bias was assigned if studies reported that pain type was diagnosed or classified but failed to provide a description of the methods used.

Clinician judgement bias: Studies were considered to be at low risk if the individual providing the clinical impression of pain type was blind to the outcome of the screening tool. Studies were considered at high risk if the individual providing the clinical impression of pain type had access to the screening tool outcome. The risk of detection bias was considered unclear if the blinding of the clinician could not be determined from the study report.

Attrition bias due to incomplete reporting of outcome data: studies were considered to be at low risk if they reported complete data for clinical judgement of pain type and reported

sufficient data for the screening tool performance values to be extracted or calculated by hand.

Selection bias in the form of random allocation and allocation concealment was not part of the assessment of risk of bias as allocation to study arms in a clinical trial setting was not considered to affect the outcomes.

Determining the performance of neuropathic pain screening tools

To determine the performance of screening tools data were extracted on sensitivity and specificity values, positive and negative predictive values, and overall performance from the included studies. Where these values were not reported, screening tool performance was calculated by hand if sufficient patient level data were reported.

In addition to extracting screening tool performance from the original reports we contacted authors of included studies. We requested sharing of datasets of anonymised patient data for secondary analysis. Patients were excluded from secondary analysis if the clinical impression of pain was “no pain” or “unsure”, or data on pain type were missing. Patients were also excluded if they had missing screening tool items. Patients were dichotomised into one of two pain groups (neuropathic or not neuropathic) based on clinician impression of pain. The following analyses were undertaken:

1. Patient characteristics (age and sex), pain aetiology, clinician assessed pain group (neuropathic, not neuropathic) and screening tool classification (likely neuropathic, unlikely neuropathic) were summarised descriptively for each dataset and overall.

Chi squared test and Kruskal-Wallis rank test were used as appropriate to test for differences in patient characteristics.

2. Screening tool performance was assessed by calculating sensitivity, specificity, positive and negative predictive values and overall performance. It was intended that these values would be reported only if they differed from the values extracted from the original articles.
3. Screening tool item data were pooled across studies using the same tool and median scale scores were calculated for each screening tool. Differences in median scale scores between the clinician assessed pain groups were analysed using a Wilcoxon rank sum equality test for unmatched data.
4. Using pooled data the frequency of positive item responses between the clinician assessed pain groups was summarised. For each screening tool the differences in the frequency of item selection between the clinician assessed pain groups were analysed using univariable and multivariable logistic regression models (adjusted for age and sex). In each model the "not neuropathic" pain group was the referent group. Data are presented as odds ratios (OR) with 95% confidence intervals (95%CI), and the level of significance was set at $p<0.01$.

Sensitivity analysis

A sensitivity analysis was undertaken to investigate the impact of pain aetiology (tumour-related pain or treatment-related pain) on the performance of neuropathic screening tools. Patients were dichotomised into one of two cancer pain aetiology groups: tumour-related pain or treatment-related pain based on the information provided in the original articles. For one study, dichotomising patients based on aetiology was not possible from the

report.[23] Personal communication with the lead study author indicated that recruitment of patients was from palliative care services and the majority were therefore likely due to tumour related pain (Hardy J, personal communication, 2015). Using the pooled dataset for each screening tool the frequencies of screening tool item selection were summarised by cancer pain aetiology (tumour-related or treatment-related) and the pain groups (neuropathic or not neuropathic). For each screening tool univariable and multivariable logistic regression models were applied to the data to quantify the relationship between screening tool items and being in the neuropathic pain group (“not neuropathic” was the referent group). Each model was stratified by cancer pain aetiology (tumour-related pain or treatment-related pain). For each model data are presented as odds ratios and 95% confidence intervals, $p<0.01$.

All data analysis was performed using STATA IC 13 (StataCorp. 2013. Stata Statistical Software: Release 13. USA).

Results

Results of search and description of studies

A total of 92 unique records were identified through electronic literature database searches and grey literature searches. Screening titles and abstracts excluded 80 records (Figure 1). Full text articles were assessed for eligibility of which six met the inclusion criteria.[7 23 25 28 29 31] The reasons for excluding full text articles were incomplete data summary,[4 10 19 21] duplicated data[20] and lack clinician impression of pain type.[1]

The six included studies recruited a total of 2301 cancer patients of which 1564 (68%) reported pain. There was marked variation in descriptions of cancer type, stage of disease and clinical setting (Table 1). Studies included a heterogeneous population of cancer patients in terms of pain aetiology (e.g. treatment-related, tumour-related or mixed aetiology) as well as clinical impression of pain (neuropathic, not neuropathic, mixed or unclassified). Studies were conducted in a variety of settings including secondary care outpatient services, secondary care inpatient services and palliative care units. Five studies used one screening tool to classify cancer pain[7 23 25 29 31] and one study used three screening tools.[28] Four studies reported data on LANSS, two studies reported data on DN4 and two studies reported data on PDQ (Table 1).

Evaluation of methodological quality - Assessment of risk of bias

The assessment of risk of bias is presented in Appendix 2

of supplementary materials online and summarised here. Overall there was a low risk of bias associated with the administration of screening tools and reporting of screening tool performance values.

Screening tool performance bias: Screening tools were administered by an assessor blinded to clinical impression of pain type[23 25 28] or prior to specialist clinician giving impression of pain type.[7 29 31]

Reporting bias: There was a low to moderate risk of bias associated with the description of criteria or processes used by specialist clinicians to reach an impression of pain type. None of the included studies cited the neuropathic pain grading system,[17 32] despite four of them being published since 2008.[7 23 28 31] Two studies lacked a detailed description of how a

clinical judgment of pain type was reached,[25 31] although they did refer to previously published assessment criteria.[16 30]

Clinician judgement bias: There was variation in the risk of bias associated with clinician assessment of pain type. One study was at high risk of bias because "there was no formal procedure to blind clinicians to LANSS score".[23] In three studies it was unclear whether or not the clinician providing the impression of pain type was blinded to the outcome of the screening tool.[7 25 28] One study explicitly reported clinician blinding[29] and in another study the clinicians were unable to see the patient responses on a tablet computer, therefore clinical blinding is assumed.[31] It should be noted here that two of the included studies were not intended to be validations studies, therefore clinician blinding was not part of the protocols.[7 31]

Attrition bias due to incomplete reporting of outcome data: The risk of bias associated with description of incomplete data was low. In five of the six included studies sufficient data were reported for screening tool performance vales to be extracted or calculated by hand.

Performance of screening tools

The sensitivity values reported in Table 1 varied considerably for all three screening tools. For LANSS and PDQ sensitivity values were lower than reported in development studies (commonly around 80%[2 18]). In contrast specificity values were high for all tools (range 77-100%). DN4 sensitivity and specificity values reported by Perez[28] and Bouhassira[7] were similar to those reported in the original validation paper.[6] Data reported by Perez[28] from patients undergoing chemotherapy within a population who had completed the LANSS, DN4 and PDQ indicated that DN4 was more sensitive than LANSS and PDQ; however, overall

performance was of LANSS and DN4 were similar (87% and 88% respectively, Table 1). The overall performance of all three screening tools reported in Table 1 ranged from 73%-94%.

Secondary analysis of screening tool performance

After contacting the authors of included studies, five datasets were available for secondary analysis: four datasets included data on one screening tool[7 23 25 31] and one dataset included data on two screening tools administered to the same patients.[28] The PDQ data published by Perez et al[28] were not available for secondary analysis. A total of 2249 cancer patients were represented across all five datasets. Across the five datasets 364 patients were excluded due to clinical diagnosis of no pain, 253 excluded due to missing clinical diagnosis, 177 excluded because the clinical diagnosis was "unsure", and 104 exclude due to missing screening tool items. After excluding patients, data were available on 1351 (62%) cancer patients for secondary analysis. See Appendix 1 in supplementary material online for details on excluded patients by individual datasets.

Patient characteristics as well as clinical diagnosis and screening tool classifications are summarised in Table 2. The median age of patients included in the secondary analysis was 63 years (IQR 31-94). There were significant differences in the ages of included patients with the study by Mercadante et al[25] recruiting significantly older patients. Just over half of all patients were female (55%). The combined prevalence of clinically diagnosed tumour-related pain was 70%; the prevalence of treatment-related pain was 20%; the remaining 10% was a combination of mixed treatment/tumour-related pain, comorbid pain and unclear pain aetiology. The combined proportion of patients with a clinical impression of

neuropathic pain was 28%, however this varied significantly across the included datasets from 17.1% [31] to 59%[25]. The combined prevalence of likely neuropathic pain classified by screening tool was 30.6% and did not differ significantly across the included datasets (Table 2). Independently calculated sensitivity and specificity values, positive and negative predictive values and overall performance did not differ from those reported in Table 1 and, therefore, are not reported again in Table 2.

Median (interquartile range) scores were calculated for pooled LANSS and DN4 data and summarised for PDQ data. For each tool median (IQR) scale scores were significantly different between the neuropathic and not neuropathic pain groups: LANSS 12.5 (6-17) and 3 (0-7) respectively ($z= -10.65$ $p<0.000$); DN4 4 (3-5) and 1 (0-2) respectively ($z= -13.58$ $p<0.000$); PDQ 13 (8-18) and 8 (4-12) respectively ($z= -5.43$ $p<0.000$).

Characterising descriptor item selection frequencies

Using the pooled data for LANSS and DN4 data, and the data for PDQ, the frequency of screening tool item selection was summarised by the clinician assessed pain groups (neuropathic or not neuropathic). Across the three screening tools there was large variation in frequency of item selection by cancer patients with clinician assessed neuropathic pain (Figure 2). For LANSS the frequency of item selection in the neuropathic pain group varied between 13.3%-71.5%; for DN4 between 38.5%-61.5%; and for PDQ between 17.2%-49.5%; for PDQ all items were selected by less than 50% of neuropathic pain patients (Figure 2). Univariable logistic regression models found all items on LANSS and DN4 were associated with significantly increased odds of being in the neuropathic pain group compared to the

not neuropathic pain group (Table 3). Univariable logistic regression models for PDQ items found pins and needles, electric shocks, burning, pain evoked by light touch and numbness were associated with significantly increased odds of being in the neuropathic pain group compared to the not neuropathic pain group (Table 3).

Three multivariable logistic regression models were fitted to the data on LANSS, DN4 and PDQ items respectively all predicting the odds of being in the neuropathic pain group compared to the not neuropathic pain group (Table 3). For LANSS data, pins and needles, pain evoked by light touch and altered pinprick threshold remained independent predictors. For DN4 data, tingling, electric shocks, burning, dynamic mechanical allodynia and tactile hypoesthesia were all independent predictors. For PDQ data, burning and numbness were independent predictors.

Sensitivity analysis on neuropathic pain aetiology

Using the pooled data for LANSS and DN4 we investigated differences in descriptor profiles between the clinician diagnosed pain groups (neuropathic or not neuropathic) stratified by tumour-related and treatment-related pain. Sensitivity analysis for PDQ was not possible as there were no data available on treatment-related cancer pain. LANSS and DN4 items distinguished between neuropathic and not neuropathic pain groups within tumour-related and treatment-related aetiological pain groups. In a series of univariable logistic regression models, all LANSS and DN4 items were associated with significantly increased odds of being in the neuropathic pain group versus the not neuropathic pain group for both tumour and

treatment-related pain groups (except LANSS electric shocks in treatment-related cancer pain and DN4 pins and needles and itching in tumour-related cancer pain).

In a multivariable logistic regression model of pooled LANSS items predicting tumour-related neuropathic cancer pain, pins and needles, mottled skin and evoked pain remained significant independent predictors (Table 4). In a similar multivariable model predicting treatment-related neuropathic pain, LANSS items for pins and needles, dynamic mechanical allodynia and altered pin prick threshold remained significant independent predictors (Table 4).

In a multivariable logistic regression model of pooled DN4 items predicting tumour-related neuropathic cancer pain, electric shocks, tingling, numbness and dynamic mechanical allodynia remained significant independent predictors (Table 4). In a similar multivariable model predicting treatment-related neuropathic pain, DN4 items electric shock, tingling, tactile hypoesthesia, pinprick hypoesthesia and dynamic mechanical allodynia remained significant independent predictors (Table 4).

Discussion

Main findings

The data from included studies demonstrate concordance between the clinician diagnosed pain groups and the screening tool results for LANSS, DN4 and PDQ in patients with cancer pain. These finding are supported by our secondary analyses of the data indicating significant differences in median scores between pain groups across all three screening

tools, and overall classification rates of 73-94%. We have shown that neuropathic cancer pain symptom profiles are significantly distinct from non-neuropathic symptom profiles in both tumour-related and treatment-related cancer pain aetiologies (Figure 2 and Table 4).

However, we did find large variation in sensitivity across the screening tools. Furthermore, the median scores for patients with clinically diagnosed neuropathic pain were at the cut-off point for 'likely neuropathic pain' for LANSS and DN4 and below the cut-off point for PDQ. This suggests that many neuropathic pain patients might be incorrectly classified and could explain the large variation in sensitivity and the high level of specificity observed across the included studies (Table 1).

We have shown that all screening tool items (with the exception of items 'pressure', 'time course' and 'radiating' on PDQ) can significantly discriminate between the clinically diagnosed pain groups in cancer patients (Table 3). However, overall the frequency of screening tool item selection by the clinically diagnosed neuropathic cancer pain group was lower when compared with earlier reports in non-cancer populations.[2 6] This finding could account for varying sensitivity reported in Table 1. We further investigated the discriminant ability of LANSS and DN4 items within clinician diagnosed treatment-related and tumour-related pain contexts and found the discriminant ability of individual items persisted (Table 4 and Appendix 3 in Supplementary Materials online).

Underlying neuropathic mechanisms in tumour-related pain may be no different than in other disease aetiologies but the phenotype may be altered by the frequent co-existence of

nociceptive and inflammatory mechanisms; cancer pain is often regarded as a mixed mechanism pain.[5] It is clinically more challenging to distinguish predominantly neuropathic pain from predominantly nociceptive pain within a mixed pain context, particularly for clinicians with little or no training in pain assessment and management. Wrongly attributing pain type (for example, lack of rigour leading to over-diagnosis of neuropathic pain as we have demonstrated in previous analyses[27]) could account for our finding of lower frequency of screening tool items in tumour-related pain. The updated neuropathic pain grading systems for neuropathic pain indicates the importance of identifying pain associated with sensory abnormalities in conjunction with diagnostic tests to confirm a lesion or disease of the somatosensory system.[17] However, the grading system was not designed to identify neuropathic pain within mixed pain syndromes, therefore its ability to identify neuropathic cancer pain, which is often dominated by mixed pain mechanisms, remains unclear and raises doubts about its suitability as a gold standard.

Quality of the evidence

We identified important sources of bias and methodological weakness of included studies. These include considerable variation in description and rigor of clinical assessment, the skills of the clinician (pain expert, oncologist, or palliative care physician), and the reporting of blinding of study personnel responsible for collecting pain outcome data.

Overall there was variation in the risks of bias, particularly related to the rigour of clinical judgement of pain as the “gold standard”. A critical source of bias was non-blinding of the clinicians who gave the impression of pain type. In three of six included studies we were

unable to determine if clinicians were blinded to the outcome of the screening tools (Table2). Consequently this raises concerns about the confidence we could place in the findings of these studies. It is plausible that the variation in screening tool performance reported in Table 1 could result from weaknesses in the screening tools or from inadequate clinical assessment. However, given the low risk of bias associated with screening tool administration and the consistent discriminant validity we found in screening tools (Table 2), as well as their individual items, within studies and when pooled (Tables 5 and 6), we argue that methodological issues regarding clinical assessment is the most likely source of bias.

Strengths and limitations of the review process

We were able to identify studies undertaken in cancer patients from a number of different countries which enables our findings to have international relevance. The included studies varied in terms of cancer type, stage of disease and pain types (Table 1). However, these differences were clearly reported by included studies. We were able to obtain and analyse data from 1351 patients which provides considerable reliability for assessing screening tool performance and in determining item frequencies in this context.

Nevertheless our study has limitations. The data were derived from patients with a range of cancer related pains including tumour-related and treatment-related pains. While tumour-related pains are considered mixed mechanism pains, treatment-related neuropathic pains are more similar in character to classic peripheral neuropathic pains from non-cancer aetiologies. For this reason, we undertook sensitivity analysis to highlight important differences within this heterogeneous sample. For four of the five datasets it was possible to

delineate between different cancer pain types. For data reported by Hardy et el.[23] pain aetiology was not recorded as part of the study protocol. However, as all referrals into the trial were made from palliative care services we classified all the patients as tumour related pain rather than treatment related pain. We recognise that a small minority of patients are likely to have been misclassified. We acknowledge that the heterogeneity inherent in pooling data from tumour and treatment related pains. However, our primary aim, reflected in our title, was to examine the performance of screening tools in identifying neuropathic pain in patients with cancer, rather than in neuropathic cancer pain (tumour pain). It was our intention to determine how useful or not these screening tools were in supporting clinicians to identify neuropathic mechanisms in patients with cancer that have pain. This heterogeneity can be considered to be a methodological strength in terms of generalisability from our data into routine clinical care.

There were significant differences across the studies in the proportion of patients clinically diagnosed with neuropathic or not neuropathic pain (though there were no significant differences in the proportions classified by screening tools as likely or unlikely neuropathic pain). These differences might lead to bias in terms of estimating screening tool performance: the greater the proportion of non-neuropathic patients included in each study, the more accurate the tools will appear because non-selection of items (insensitivity) favours the “unlikely neuropathic pain” classification.

Finally, we acknowledge that our interpretations regarding the PDQ questionnaire are limited as only one dataset was available for secondary analysis. Therefore our ability to comment on the overall performance of the PDQ is constrained.

Implications for practice and research

Our study shows that overall LANSS and DN4 screening tools (and individual items on both tools) are generally able to distinguish between pain clinically diagnosed as neuropathic or not neuropathic in cancer patients. However, this finding should be viewed with caution as methodological shortcomings remain, particularly in relation to standardised clinician assessment of cancer pain. Further research is needed to standardise and improve clinical assessment in patients with cancer pain, which should include evaluating the use of the adapted grading system for neuropathic pain[8 9 17 27] which might enhance discrimination and more accurately phenotype pain in cancer patients. Until the standardisation of clinical diagnosis for neuropathic cancer pain has been validated for both clinical practice and research, screening tools represent a practical approach to identify potential cases of neuropathic cancer pain and informing further diagnostic evaluation. This is particularly relevant for non-specialists, where the neuropathic pain screening tools have their chief strength in clinical practice.

Acknowledgements

The primary author (Matthew Mulvey) is supported by an NIHR Health Technology Assessment Project Grant (reference: HTA_12_188). All other authors declare no conflicts of interest with this manuscript and its content.

Author Contributions

Matthew R. Mulvey – conceived the project, designed the project, extract and analysed data, drafted manuscript and approved final manuscript.

Elaine G. Boland - designed the project, drafted manuscript and approved final manuscript.

Didier Bouhassira - designed the project, drafted manuscript and approved final manuscript.

Rainer Freynhagen - designed the project, drafted manuscript and approved final manuscript.

Janet Hardy - designed the project, drafted manuscript and approved final manuscript.

Marianne J. Hjermstad - designed the project, drafted manuscript and approved final manuscript.

Sebastiano Mercadante - designed the project, drafted manuscript and approved final manuscript.

Concepción Pérez - designed the project, drafted manuscript and approved final manuscript.

Michael. I Bennett - conceived, designed, extract and analysed data, drafted and approved final manuscript.

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Figure and Table legends

Figure 1 – Flow diagram of literature search results

Figure 1 legend:

Flow diagram of systematic literature search results. † The primary reasons for excluding records were (1) review article, (2) incomplete data summary reported on either clinician assessment of pain type or neuropathic pain screening tool outcome, (3) analgesic effectiveness trial not designed to evaluate the performance of screening tools with clinician judgement of pain type.

Figure 2 – LANSS and DN4 item selection frequency by pain groups.

Figure 2 legend

Frequencies of patients reporting screening tool items by clinician diagnosed pain groups (neuropathic or not neuropathic) for LANSS, DN4 and PDQ.

DN4 = Douleur Neuropathique en 4 questions. LANSS = Leeds Assessment of Neuropathic Symptoms and Signs. PDQ = painDETECT.

All items significantly discriminated between the pain groups (Chi^2 $p<0.001$).

APT= Altered Pin-prick Threshold.

DMA = Dynamic Mechanical Allodynia

Table 1 – Search results

Study	Patient population and pain aetiology (tumour-related, treatment-related or mixed pain)	Setting	Patients with cancer pain	Who gave clinical impression of pain?	Screening tool	Sensitivity (%)	Specificity (%)	Positive predictor value (%)	Negative predictor value (%)	Overall performance (%)
Potter3[29]	N=125 head and neck cancer patients N=25 (20%) with tumour-related pain Most common sites: floor of mouth, tongue Stage: N=24/25 not recurrent disease	Cancer out-patients, UK	N=11 Not NP N=13 mixed N=1 NeuP	Pain specialist	LANSS	79	100	100†	84†	88†
Mercadante[25]	N=167 tumour-related pain patients Most common sites: genitourinary, gastrointestinal, breast and lung Stage: not reported	Acute pain relief and supportive care units, Italy	N=60 definite NeuP N=36 possible NeuP N=71 unlikely NeuP	Expert oncology physician experienced in neurological examination	LANSS	29.5	91.4	*	*	*
Rayment[31]**	N=1051 incurable cancer N=670 (64%) with tumour-related pain Most common sites: gastrointestinal, respiratory, breast and urological. Stage: N= 17 locally advanced disease, N=96 metastatic disease	Oncology inpatients and outpatients	N=534 Not NP N=113 NeuP N=23 unclassified	Experienced palliative care clinicians	PDQ	53	77	89	33	73†
Hardy[23]	N=114 patients with tumour or treatment	Hospital or hospice in-	N=49 Not NP N=28 mixed	Experienced palliative care	LANSS	86	100	100	91	94

Study	Patient population and pain aetiology (tumour-related, treatment-related or mixed pain)	Setting	Patients with cancer pain	Who gave clinical impression of pain?	Screening tool	Sensitivity (%)	Specificity (%)	Positive predictor value (%)	Negative predictor value (%)	Overall performance (%)
	pain N=112 (97%) with tumour-related pain Most common sites: lung, breast, colorectal, gastrointestinal, pancreas, prostate. Stage: all advanced malignant disease	patients	N=35 NeuP	clinician						
Perez[28]	N=358 patients receiving chemotherapy N=194 (54%) with treatment- related pain Most common sites: not reported Stage: N=229 stage IV advanced or metastatic	Out-patients hospital, Spain	N=121 Not NP N=34 mixed N= 39 NeuP	Pain specialist	LANSS DN4 PDQ	66 87 18	93 88 97	75† 70† 70†	90† 95† 78†	87† 88† 78†
Bouhassira[7]	N=486 cancer patients N=396 with pain (81% with tumour, treatment and mixed pain) Most common sites: breast, colorectal, head/neck, lung, gynaecology, prostate. Stage: all stages of disease, including advanced stages.	Specialists cancer out-patient clinics, France	N=279 Not NP N=117 NeuP	Pain specialist	DN4	82	88	74	92	86

Table 1 legend:

Not NP = not neuropathic pain. NeuP = neuropathic pain. DN4 = Douleur Neuropathique en 4 questions. LANSS = Leeds Assessment of Neuropathic Symptoms and Signs. PDQ = painDETECT.

*value not reported and unable to calculate by hand - patient level data not reported.

** n=670 patients reported pain, n=570 completed both clinical assessment & painDETECT questionnaire therefore screening tool performance values based on n=570.

†value calculated by hand.

Table 2 - Patient characteristics, pain aetiology and screening tool classification for all datasets

Variable	All datasets Screening tool n=1351	Mercadante[25] LANSS n=166 (12.3)	Bouhassira[7] DN4 n=396 (29.3)	Rayment[31] PD-Q n=545 (40.3)	Hardy[23] LANSS n=84 (6.2	Perez[28] DN4 & LANSS n=160 (11.8)	p-Value
Age	63 (31-94)	68 (35-90)	64 (32-94)	63 (26-90)	66 (20-89)	60 (34-83)	<0.001†
Sex							
Male	611 (45.2)	103 (62.1)	123 (31.1)	266 (48.8)	45 (53.6)	74 (46.3)	<0.001‡
Female	738 (54.6)	63 (37.9)	273 (68.9)	279 (51.2)	39 (46.4)	86 (53.7)	
Pain aetiology							
Tumour related	946 (70)	166 (100)	151 (38.1)	545 (100)	84 (100)		
Treatment related	272 (20.1)		112 (28.3)			160 (100)	
Both	20 (1.5)		20 (5.1)				
Neither (comorbid pain)	108 (8)		108 (27.3)				
Unclear	5 (0.4)		5 (1.3)				
Clinician impression of pain							
Not neuropathic	969 (71.1)	68 (41)	279 (70.5)	452 (82.9)	49 (58.3)	121 (75.6)	<0.001‡
Neuropathic	382 (28.3)	98 (59)	117 (29.5)	93 (17.1)	35 (41.7)	39 (24.4)	
Screening tool classification							
Unlikely neuropathic	937 (69.4)	113 (68.1)	266 (67.2)	392 (71.9)	54 (64.3)	112 (70)	0.44‡
Likely neuropathic	414 (30.6)	53 (31.9)	130 (32.8)	153 (28.1)	30 (35.7)	48 (30)	

Table 2 legend:

Data for age are presented as medians (IQR). Data for all other variables are presented as n(%). DN4 = Douleur Neuropathique en 4 questions.

LANSS = Leeds Assessment of Neuropathic Symptoms and Signs. PDQ = painDETECT.

[‡]Chi^2 and [†]K-Wallis tests excludes 'All' column. Test of difference not performed for variable Pain type due to difference in response options between datasets..

Table 3 – Univariable and multivariable logistic regression models quantifying the relationship between screening tool item selection and clinician diagnosed pain groups (neuropathic pain compared with not neuropathic).

	LANSS n=410		DN4 n=556		PDQ n=545	
Screening tool items	**Univariable**[§]	**Multivariable**	**Univariable**[§]	**Multivariable**	**Univariable**	**Multivariable**
Symptom items						
Pricking, pins and needles	5.1 (3.3-7.8)	2.8 (1.7-4.5)[†]	2.1 (1.4-3.1)	0.6 (0.3-1.2)	2.8 (1.7-4.7)[‡]	1.3 (0.7-2.4)
Tingling			6.1 (4-9.2)	2.8 (1.6-5)[†]		
Electric shocks	2.5 (1.7-3.8)	1.5 (0.9-2.5)	5.9 (3.9-8.9)	3.5 (2-6.3)[‡]	2.3 (1.4-3.8)[†]	1.8 (0.9-3.1)
Hot, burning	2.8 (1.8-4.4)	1.4 (0.8-2.4)	3.1 (2.1-4.7)	2.1 (1.2-3.7)[†]	3.4 (2.1-5.5)[‡]	2.5 (1.4-4.2)[†]
Numbness			4.7 (3.2-7.1)	1.8 (1-3.2)	3.4 (2.1-5.6)[‡]	2.4 (1.3-4.2)[†]
Pain evoked by light touch	5.7 (3.6-9.1)	2.2 (1.2-3.8)[‡]			2.1 (1.2-3.8)[†]	1.3 (0.6-2.5)
Painful cold*			6 (3.3-10.9)	1.7 (0.7-4.2)	2.1 (1.1-3.9)	0.7 (0.3-1.6)
Itching			2.6 (1.6-4.2)	1.2 (0.5-2.7)		
Time course					0.9 (0.6-1.6)	0.8 (0.4-1.3)
Pressure					1.1 (0.7-1.8)	0.8 (0.5-1.5)
Radiating					1.6 (0.9-2.5)	1.1 (0.7-1.9)
Mottled skin	5 (3-8.4)	1.9 (1-3.5)				
Clinical Signs						
Dynamic brush allodynia	5.7 (3.4-9.9)	2 (1-3.8)	8.2 (5.1-13.2)	3.8 (2-7.1)[‡]		
Tactile hypoesthesia			16 (9.6-26.7)	6 (3-12)[‡]		
Altered pinprick threshold	6.1 (3.7-10)	2.2 (1.2-4.1)[†]	17.2 (9.2-32.1)	2.6 (1.1-6.1)		
Pseudo R2		0.23		0.42		0.1

Table 3 legend:

Data are presented as odds ratio (95% CI). The not neuropathic pain group was the referent group for all models.

DN4 = Douleur Neuropathique en 4 questions. LANSS = Leeds Assessment of Neuropathic Symptoms and Signs. PDQ = painDETECT.

[§] $p<0.001$ in all univariable models for LANSS and DN4 screening tool items. [†] $p<0.01$. [‡] $p<0.000$.

*on PDQ = thermal item

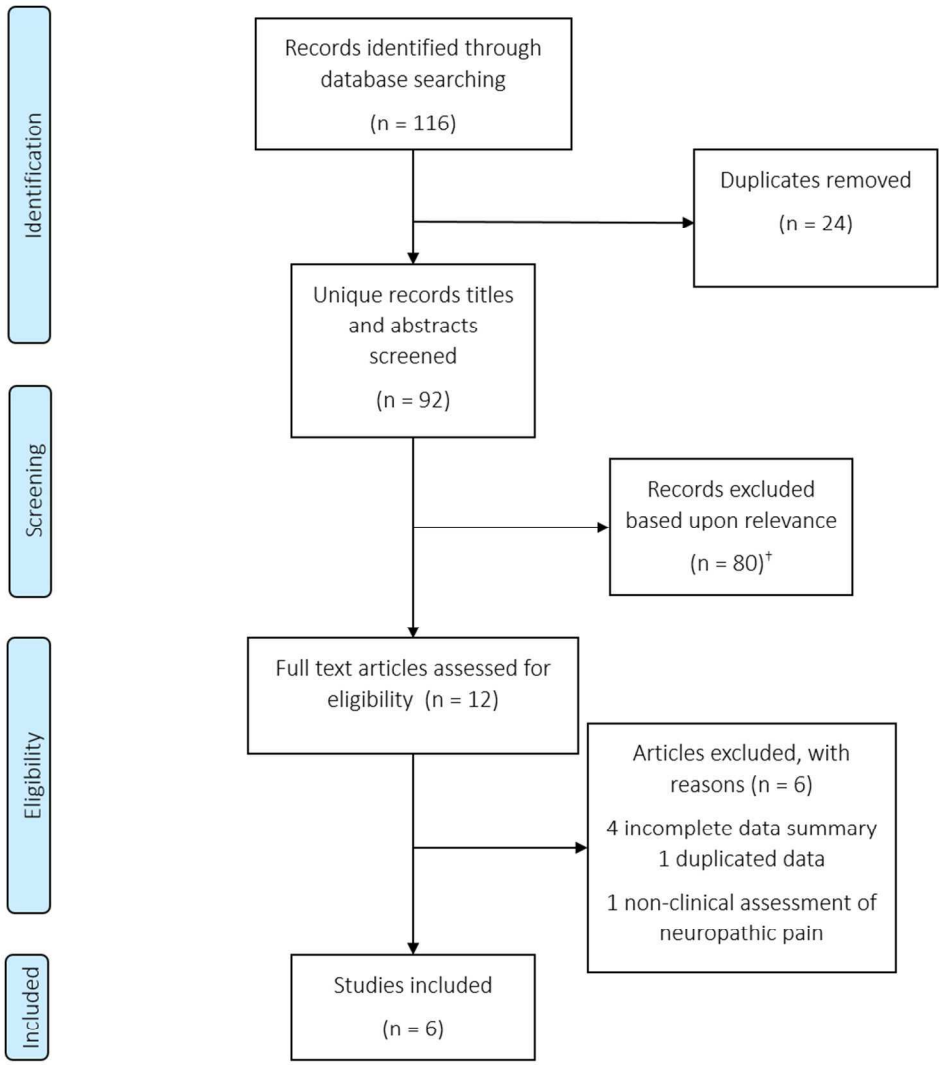
Table 4 – Comparison of screening tool item selection between tumour-related and treatment-related pain

	Tumour pain n=250		Treatment pain n=160	
LANSS items	**Not NP**	**Neuropathic[§]**	**Not NP**	**Neuropathic[§]**
Pin and needles	Referent	3.3 (1.8-6.1)[‡]	Referent	6 (1.3-28.1)[†]
Mottled skin		2.2 (1-4.9)[†]		2.6 (0.5-12.3)
Evoked pain		2.4 (1.2-4.9)[†]		1.7 (0.4-7.4)
Electric shock		1.7 (0.9-3.2)		0.2 (0.03-0.9)
Burning		1.2 (0.7-2.3)		2.1 (0.5-9.4)
DMA		1 (0.5-2.5)		6.4 (1.1-37.9)[†]
Altered pinprick threshold		0.8 (0.4-1.9)		36.2 (8.6-153.1)[‡]
	Tumour pain n=151		**Treatment pain n=112**	
DN4 items	**Not NP**	**Neuropathic[§]**	**Not NP**	**Neuropathic[§]**
Burning	Referent	1.7 (0.5-6.4)	Referent	2.1 (0.7-6)
Painful cold		2.3 (0.3-16.9)		2.5 (0.6-10.2)
Electric shock		9.6 (2.6-35.4)[‡]		2.9 (1.1-7.6)[†]
Tingling		7.9 (1.7-35.9)[‡]		3.2 (1.2-8.6)[†]
Pin and needles		0.04 (0.005-0.3)		1.3 (0.5-3.2)
Numbness		8.4 (1.6-45.1)[†]		1.4 (0.5-3.7)
Itching		0.9 (0.1-6.1)		1.9 (0.5-7.6)
Tactile hypoesthesia		2.8 (0.6-12.6)		7.7 (2.7-22.6)[‡]
Pinprick hypoesthesia		11 (0.8-158.3)		4.7 (1.5-15)[‡]
DMA		7.9 (1.8-34.5)[‡]		5.6 (2-15.6)[‡]

Table 4 legend:

Not NP = Not neuropathic pain. DMA = Dynamic Mechanical Allodynia. [§]Odds ratios (95%CI) are derived from multivariable logistic regression models, not neuropathic pain group was the referent group in all models.

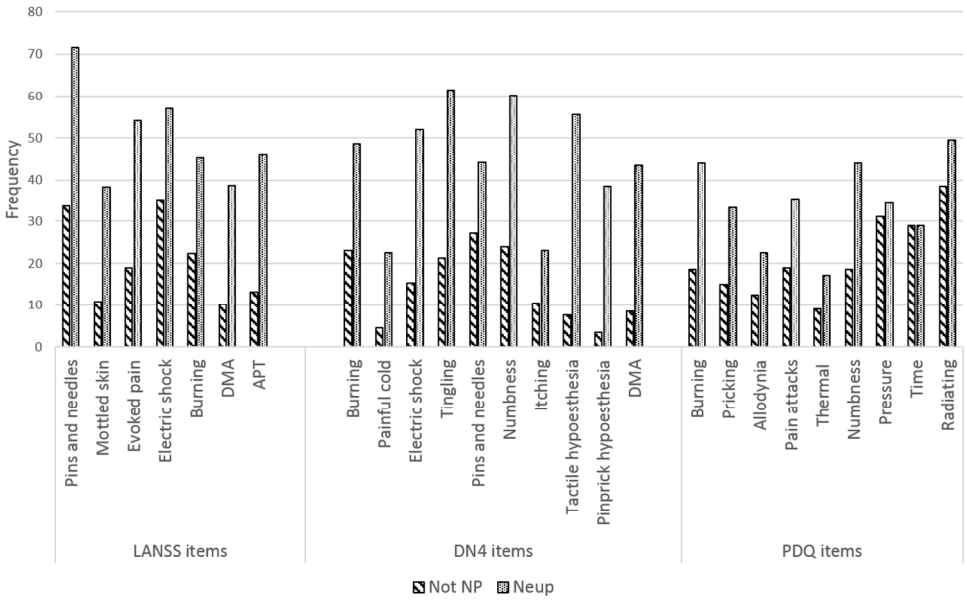
[†]$p<0.01$. [‡]$p<0.001$.



Flow diagram of systematic literature search results. † The primary reasons for excluding records were (1) review article, (2) incomplete data summary reported on either clinician assessment of pain type or neuropathic pain screening tool outcome, (3) analgesic effectiveness trial not designed to evaluate the performance of screening tools with clinician judgement of pain type

Figure 1

174x210mm (150 x 150 DPI)



Frequencies of patients reporting screening tool items by clinician diagnosed pain groups (neuropathic or not neuropathic) for LANSS, DN4 and PDQ. DN4 = Douleur Neuropathique en 4 questions. LANSS = Leeds Assessment of Neuropathic Symptoms and Signs. PDQ = painDETECT. All items significantly discriminated between the pain groups (Chi2 $p<0.001$). APT= Altered Pin-prick Threshold. DMA = Dynamic Mechanical Allodynia

Figure 2

224x139mm (150 x 150 DPI)