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Title:

The use of Quantitative Sensory Testing (QST) in cancer pain assessment: a systematic review

Running header

Use of QST in cancer pain assessment

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Conflict of interest

All authors declare no conflicts of interest with this manuscript and its content

Significance

This systematic review found that pain in cancer patients is associated with abnormal sensory responses to thermal, mechanical and pinprick stimuli. However, these findings are based primarily on studies of chemotherapy-induced peripheral neuropathy and data on tumour-related pain are lacking, warranting further research.

Key words

Cancer, Pain, Quantitative Sensory Testing, QST, Assessment, Systematic Review

Abstract

Objective: To summarises the literature on the use of quantitative sensory testing (QST) in the assessment of pain in people with cancer and to describe which QST parameters consistently demonstrate abnormal sensory processing in patients with cancer pain.

Databases and Data Treatment: Medline, EMBASE, AMED, CINAHL, SCOPUS and CENTRAL were searched for observational or experimental studies using QST in patients with a cancer diagnosis and reporting pain. Search strategies were based on the terms 'quantitative sensory testing', 'cancer', 'pain', 'cancer pain' and 'assessment'. Databases were search from inception to January 2019. Data were extracted and synthesised narratively, structured around the different QST modalities and sub-grouped by cancer pain aetiology (tumour- or treatment-related pain)

Results: Searches identified 286 records of which 18 met the eligibility criteria for inclusion. Three studies included patients with tumour-related pain, and 15 studies included patients with pain from chemotherapy induced peripheral neuropathy (CIPN). Across all studies, 50% (9/18) reported sensory abnormities using thermal detection thresholds (cool and warm), 44% (8/18) reported abnormal mechanical detection thresholds using von-Frey filaments and 39% (7/18) found abnormal pin-prick thresholds. Abnormal vibration and thermal pain (heat/cold) thresholds were each reported in a third of included studies.

Conclusion: This systematic review highlights the lack of published data characterising the sensory phenotype of tumour-related cancer pain. This has implications for our understanding of the underlying pathophysiological mechanisms of cancer pain. Understanding the multiple mechanisms driving cancer pain will help to move towards rational individualised analgesic treatment choices.

Introduction

A third of patients receiving anticancer treatment report moderate to severe pain and over 50% of patients with advanced cancer report moderate to severe pain. Forty percent of patients with cancer are affected by neuropathic pain which is associated with higher levels of pain and reduced quality of life (van den Beuken-van Everdingen et al. 2007, Breivik et al. 2009, Bennett et al. 2012, Rayment et al. 2012, ONS 2015). As survival rates for cancer rise (Kumar 2011), the burden of living with chronic pain from cancer and its treatment is rapidly becoming a global health problem. Furthermore, the reduction in cancer pain prevalence seen in the second half of the 20th century (following publication of the WHO analgesic ladder in cancer pain) has stalled in the past decade (van den Beuken-van Everdingen et al. 2018). Accurately diagnosing cancer pain based on aetiology and neurological mechanisms is essential to provide targeted and effective treatments for cancer patients (Mulvey et al. 2014, Mulvey et al. 2017).

Approximately 76% of cancer pains are caused by the tumour itself (tumour-related cancer pain) and is regarded as a mixed-mechanism pain (Grond et al. 1996). Tumour-related cancer pain is difficult to treat as nociceptive, inflammatory and neuropathic mechanisms commonly co-exist, particularly in bone (Grond et al. 1999, Caraceni et al. 2005, Piano et al. 2012, Pina et al. 2014, Paice et al. 2016)metastases (Paley et al. 2011, Falk et al. 2014). As cancer treatments become more sophisticated, exposure to anti-cancer therapies (such as chemotherapy, surgery or radiotherapy) is recognised as an important cause of pain in patients with cancer (Paice et al. 2016). Between 10-20% of cancer pains are caused by anti-cancer therapies (treatment-related cancer pain) (Grond et al. 1996, Grond et al. 1999, Bennett et al. 2012) which are considered more similar to classic peripheral neuropathic pain in mechanism and character (Paice et al. 2016). The remainder of pains in cancer patients are due to co-morbid diseases unrelated to cancer. Identifying the most predominate pain mechanism(s) is essential to diagnosing cancer pain and tailoring treatment plans.

A 2012 systematic review estimated that 40% of cancer patients with pain have a dominance of neuropathic mechanisms, which can be either tumour-related or treatment-related (Bennett et al. 2012). Neuropathic cancer pain (NCP) is associated with greater analgesic requirements and oncological treatments, as well as poorer quality of life and lower performance status (Rayment et al. 2012). Patients with NCP experience chronic and acute

exacerbations of pain (pain flares) that peak multiple times per day (Fallon 2013). These spontaneous pain flares are usually located in areas where there is observed sensory dysfunction (hypersensitivity and/or hyposensitivity) (Fallon 2013, Haanpaa 2013, Baron et al. 2017). Patients with NCP also experience other sensations such as dysesthesia, allodynia and hyperalgesia (Fallon 2013, Haanpaa 2013, Paice et al. 2016).

Pain assessment and diagnostic guidelines propose the use of objective measurable tests such as quantitative sensory testing (QST,

Table 1) to support the diagnosis of neuropathic pain (Cruccu et al. 2009, Cruccu et al. 2010, Haanpaa et al. 2011, Piano et al. 2012, Piano et al. 2013, Finnerup et al. 2016). QST has been used most frequently in the assessment of peripheral neuropathic pain syndromes to defined thermal and mechanical stimuli (Rolke et al. 2006, Roldan et al. 2015). In cancer, QST has primarily focused on the assessment of peripheral neuropathy associated with exposure to chemotherapy (Lipton et al. 1987, Lipton et al. 1991, Augusto et al. 2008, Boyette-Davis et al. 2011, Boyette-Davis et al. 2012, Boyette-Davis et al. 2013, Vichaya et al. 2013). These data show a consistent a pattern of loss in function of small and large sensory fibres associated with painful CIPN symptoms, characterised by increased thresholds to vibration, light touch (von Frey hair) and pinprick stimuli. These data demonstrate the potential for QST to link patient reported symptoms with underlying pathophysiological mechanisms.

Nevertheless, the standardised QST protocol is labour intensive, requires expensive equipment and highly trained operators to complete the tests and interpret the data (Cruz-Almeida et al. 2014). Shorter QST protocols that are both clinically predictive and simple to operate and interpret are likely to be more clinically useful (Cruz-Almeida et al. 2014). The first step towards developing a clinically relevant bedside QST protocol is to systematically review the literature to identify which QST parameters most frequently identify sensory abnormalities in tumour-related and treatment-related cancer. This will indicate which QST parameters to take forward into clinical trial testing.

Aim Objectives

The aim of this systematic review is to describe QST parameters commonly used in the assessment of cancer pain (tumour-related or treatment-related pain) and identify which ones consistently demonstrate abnormal sensory processing in this patient population.

Methods

A systematic literature review was undertaken of studies which reported the use of QST in the assessment of cancer pain. This review was conducted in accordance with Centre for Reviews and Dissemination Guidelines (Centre for Reviews and Dissemination 2009) which include the PRISMA guidance on reporting study selection, (Moher et al. 2009) and included on the PROSPERO international register of systematic reviews (CRD42018090092).

Eligibility Criteria / Types of studies to be included

Studies were eligible for inclusion if they:

1. were original observational or experimental studies
2. included adults (≥ 16 years old) with a cancer diagnosis and reporting pain (tumour- or treatment-related pain)
3. had reported using standardised quantitative sensory testing (QST) procedures
4. included patients from primary, secondary or community care settings
5. were written in English language
6. were available in full-text version
7. were published in a peer-reviewed journal

The following were excluded:

1. studies that had recruited patients with cancer and non-cancer pain aetiologies where the QST data were not reported separately for cancer and non-cancer patients
2. case reports and systematic reviews
3. studies that had only include data on acute post-surgical pain outcomes
4. intervention studies where:
    - baseline data were only reported on pain free participants
    - only post-intervention data were available

Information sources and search strategy

Electronic databases Ovid Medline EMBASE, AMED, CINAHL, SCOPUS and CENTRAL were searched from inception to March 2018. Searches were updated in January 2019. A search strategy was developed for Ovid Medline based on primary search terms for 'quantitative sensory testing', 'cancer', 'pain', 'cancer pain' and 'assessment' (Table 2). Additional search terms which encompassed the main attributes of psychophysiology and pain classification were also included in the searchers. Search terms were tailored to each subsequent database, as required. Full search strategy is described in Table 2.

Study selection process

Three reviewers (ASR, MRM, MEM) independently applied the eligibility criteria to the search results by examining the titles and abstracts. Full texts were retrieved for articles that met the inclusion criteria or could not be excluded based on abstract or title. Full text of relevant articles were assessed for inclusion independently by two authors with reasons for exclusion documented. Disagreement on included studies was discussed with an independent reviewer (MB) and consensus was reached.

Data collection and synthesis

Data was extracted on: study characteristics (publication year, aim, design and country); participants (number, age, gender, cancer diagnosis, pain aetiology, control subjects); setting (e.g. primary care, secondary care, research institution); outcome measures (QST, patient reported outcome measures (PROMS)); results (QST, PROMS); authors conclusion. Where data were not available, attempts were made to contact the authors for the missing information.

It was intended that the data would be synthesised narratively. This synthesis was structured around the different QST modalities and (if sufficient data were available) cancer pain aetiology (i.e. tumour or treatment related pain). Where the data were available, the proportion of studies that included participants with advanced cancer, as well as the numbers and proportions of participants in each study who had advanced cancer was calculated. Demographic and clinical variables (including cancer types) were also summarised across all included studies.

Quality of included studies

Methodological and reporting quality of each included study was assessed using a modified version the National Heart, Lung and Blood institute Study Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies (U.S. Department of Health & Human Services 2019,). The criteria assessed the quality of reporting of evidence upon which the conclusions of this systematic review are drawn.

A. Research question or objective clearly stated?
B. Study population clearly defined?
C. Subjects selected or recruited from the same or similar populations?
D. QST parameters clearly defined and implemented consistently across all study participants?
E. Mechanism based justification for the use of individual QST parameter(s) based on underlying pathophysiological pain mechanisms?
F. Outcome measures clearly defined and implemented consistently across all study participants?

Results

Included studies

Our searches identified 189 potentially relevant studies, of which 41 full text reports were examined (Figure 1). A total of 18 studies met the eligibility criteria (Figure 1) (Lipton et al. 1991, Forsyth et al. 1997, Dougherty et al. 2004, Binder et al. 2007, Cata et al. 2007, Dougherty et al. 2007, Caraceni et al. 2008, Attal et al. 2009, Boyette-Davis et al. 2011, Hershman et al. 2011, Scott et al. 2012, Boyette-Davis et al. 2013, Krøigård et al. 2014, Fallon et al. 2015, Velasco et al. 2015, Andersen et al. 2016, Andriamamonjy et al. 2017, Ventzel et al. 2017). Three studies included patients with tumour-related cancer pain (Lipton et al. 1991, Scott et al. 2012, Andersen et al. 2016). Fifteen studies included patients with chemotherapy induced peripheral neuropathy (CIPN) (Forsyth et al. 1997, Dougherty et al. 2004, Binder et al. 2007, Cata et al. 2007, Dougherty et al. 2007, Caraceni et al. 2008, Attal et al. 2009, Boyette-Davis et al. 2011, Hershman et al. 2011, Boyette-Davis et al. 2013, Krøigård et al. 2014, Fallon et al. 2015, Velasco et al. 2015, Andriamamonjy et al. 2017, Ventzel et al. 2017). Across all included studies 789 participants were included: 510 had cancer pain, 73 had non-painful cancer (QST data not extracted) and 206 were pain-free control participants.

Study characteristics

Eight studies were conducted in the USA and ten in Europe. Sixteen studies were observational: eight cross-sectional (Lipton et al. 1991, Dougherty et al. 2004, Binder et al. 2007, Cata et al. 2007, Dougherty et al. 2007, Krøigård et al. 2014, Andriamamonjy et al. 2017, Ventzel et al. 2017), seven prospective (Forsyth et al. 1997, Caraceni et al. 2008, Attal et al. 2009, Boyette-Davis et al. 2011, Boyette-Davis et al. 2013, Velasco et al. 2015, Andersen et al. 2016), and one used cross-sectional and prospective groups (Hershman et al. 2011). Two studies were experimental trials of analgesic interventions; only baseline (pre intervention) QST data were extracted (Scott et al. 2012, Fallon et al. 2015). Three studies also included cancer patients without pain (Binder et al. 2007, Krøigård et al. 2014, Andersen et al. 2016). For each study, only QST data on patients who reported pain were extracted. The most common cancers were colorectal and breast (Table 3).

Of the 15 CIPN studies, five included patients with acute pain symptoms (Forsyth et al. 1997, Binder et al. 2007, Caraceni et al. 2008, Velasco et al. 2015, Andriamamonjy et al. 2017) and 10 included patients with chronic pain symptoms (Dougherty et al. 2004, Cata et al. 2007, Dougherty et al. 2007, Attal et al. 2009, Boyette-Davis et al. 2011, Hershman et al. 2011, Boyette-Davis et al. 2013, Krøigård et al. 2014, Fallon et al. 2015, Ventzel et al. 2017) following chemotherapy administration. Data from the three tumour-related pain studies could not be categorised as acute/chronic due to the ongoing nature of advancing disease over an extended period of time. The three studies reporting data on tumour-related pain all included patients with chronic pain (i.e. pain longer than 3 months). Across all studies, the mean (SD, range) age was 58 (6.6, 48-73) and 63% of cancer pain participants were female. Age and gender of non-pain participants were not extracted.

Quality assessment of included studies

A summary of the quality of included studies is reported in Table 4. All studies reported a clearly stated research question and/or the objectives [A], except Lipton et al (Lipton et al. 1991) for whom the research objectives were not explicitly stated. The study populations were clearly described in all studies [B] and recruited from the same or similar populations [C]. All studies described the QST parameters that were employed, or indicated that the DNFS QST protocol (Rolke et al. 2006) was adhered to [D]. In addition, all studies clearly defined the outcome measures for each QST parameter that was implemented in the study [F].

Studies varied in terms of the extent to which the choice of QST parameters was justified by a priori theory of underlying pain mechanisms [E]. Few studies made direct links between pain symptoms, the underlying neurobiological mechanism, and the selection of the appropriate QST parameter. Four studies presented no justification for the selection of QST parameters they used (Forsyth et al. 1997, Cata et al. 2007, Caraceni et al. 2008, Krøigård et al. 2014). Six studies cited previous literature on sensory symptoms associated with tumour-related or treatment-related cancer pain (Dougherty et al. 2007, Boyette-Davis et al. 2011, Hershman et al. 2011, Boyette-Davis et al. 2013, Fallon et al. 2015, Andersen et al. 2016). Three studies justified QST selection by linking individual symptoms to QST parameters and associated underlying pathophysiological mechanisms. Andriamamonjy et al (Andriamamonjy et al. 2017) linked previously reported transient cold-induced distal allodynia with the assessment of thermal detection and thermal pain thresholds in oxaliplatin induced neuropathy Attal et al (Attal et al. 2009) justified the selection of QST parameters based on their ability to detect sensory loss, hyperalgesia or allodynia which were previously reported to be associated with oxaliplatin therapy. Dougherty et al (Dougherty et al. 2004) linked individual CIPN symptoms to QST parameters and underlying pathophysiological mechanisms: sensory data on mechanical, heat and cold perception pain to assess function in specific fibre types within areas of sensory disturbance in patients with painful CIPN. In two studies sensory abnormalities of CIPN were profiled using all 13 QST parameters described in the DFNS protocol. The authors of these studies stated their intention was to characterise large and small fibre function in CIPN patients and relate sensory profiles to underlying pathophysiological mechanisms (Binder et al. 2007, Ventzel et al. 2017).

Thermal detection thresholds (CDT/WDT)

Cold (CDT) and warm (WDT) detection thresholds were the most commonly assessed QST parameters in fifteen studies of which nine (60%) identified abnormal thermal detection thresholds. Lipton et al (Lipton et al. 1991) found elevated thermal detection thresholds in the feet of 50% of a heterogeneous cohort of 29 patients with tumour-related pain (Table 5). Scott et al. observed a variety of hypo- and hyper-sensitivity to warm and cool stimuli (Scott et al. 2012). Anderson et al. did not observe altered cool or warm perception (Andersen et al. 2016). Of the 12 CIPN studies that evaluated thermal detection thresholds, four reported elevated WDT (Dougherty et al. 2007, Boyette-Davis et al. 2011, Boyette-Davis et al. 2013,

Ventzel et al. 2017), two reported elevated CDT (Forsyth et al. 1997, Dougherty et al. 2004), and one reported that both CDT and WDT were elevated (Cata et al. 2007).

Thermal pain thresholds (CPT/HPT)

Cold (CPT) and heat (HPT) pain thresholds were reported in twelve studies of which six (50%) reported abnormal thermal pain thresholds. Only Andersen et al. (Andersen et al. 2016) evaluated thermal pain thresholds in tumour-related pain, but found no difference. Six of 11 CIPN studies that evaluated HPT and/or CPT identified abnormal thermal pain processing (Table 5). Four studies observed a reduction in CPT (cold-hyperalgesia) in response to Oxaliplatin (Binder et al. 2007, Attal et al. 2009, Velasco et al. 2015) and Bortezomib (Cata et al. 2007). Three studies found elevated HPT (heat hypoalgesia) associated with exposure to Bortezomib, Paclitaxel and Vincristine (Cata et al. 2007, Boyette-Davis et al. 2011, Boyette-Davis et al. 2013). Attal et al. observed reduced HPT (heat hyperalgesia) in response to Oxaliplatin (Attal et al. 2009). Velasco et al. and Attal et al. also observed increased pain response induced by supra-threshold cold stimuli (cold hyperalgesia) (Attal et al. 2009, Velasco et al. 2015).

Paradoxical heat sensations (PHS)

PHS were evaluated in two studies (Binder et al. 2007, Ventzel et al. 2017) one of which, Ventzel et al., found 65% of colorectal cancer patients exposed to Oxaliplatin and 44% of breast cancer patients exposed to Docetaxel experienced PHS mediated by elevated WDT.

Mechanical detection threshold (MDT)

MDT were reported in thirteen studies of which eight (62%) detected sensory abnormalities. Two of three tumour-pain studies evaluated MDT (Table 5) (Scott et al. 2012, Andersen et al. 2016). Neither observed differences in MDT when comparing a painful region with a control region in patients with tumour-related pain. Eleven CIPN studies assessed MDT at the site of pain (finger tips or toes), of which eight (72%) found elevated MDT (Table 5). One study found that reduced Aβ-fibre function preceded and predicted dysfunction in Aδ-fibres and C-fibres (Dougherty et al. 2007). Three CIPN studies did not observed altered MDT (Binder et al. 2007, Attal et al. 2009, Hershman et al. 2011).

Mechanical pain threshold (MPT)

MPT were reported in twelve studies of which seven (58%) identified altered pinprick sensitivity. Two studies evaluated MPT in patients with tumour-related pain (Table 5) (Scott et al. 2012, Andersen et al. 2016). Neither observed differences in MPT. Of the ten CIPN studies that assessed MPT, seven (70%) reported altered pinprick sensations. Four studies found elevated MPT (pinprick hypoalgesia) (Cata et al. 2007, Dougherty et al. 2007, Boyette-Davis et al. 2011, Boyette-Davis et al. 2013). In contrast, three studies reported reduced MPT (pinprick hyperalgesia) (Dougherty et al. 2004, Binder et al. 2007, Fallon et al. 2015).

Mechanical pain sensitivity (MPS)

Four studies evaluated MPS of which one (25%) found alerted pain response to supra-threshold pinprick pain (Binder et al. 2007, Scott et al. 2012, Fallon et al. 2015, Ventzel et al. 2017). Scott et al. observed pinprick hyper- and hypoalgesia (45% and 9% respectively), indicating mixed pathophysiology in cancer induced bone pain (CIBP) patients (Table 5) (Scott et al. 2012). Fallon et al., Binder et al., and Ventzel et al. all observed no difference in MPS (Table 5) (Binder et al. 2007, Fallon et al. 2015, Ventzel et al. 2017).

Dynamic mechanical allodynia (DMA)

DMA was assessed in four studies using light tactile stimuli e.g. soft burst of which one (25%) identified altered light touch perception. Scott et al. observed DMA in 13% of CIBP patients centrally augmented pain sensitisation present in a sub-set of CIBP patient (Table 5) (Scott et al. 2012). The authors also observed tactile hypoaesthesia in response to dynamic soft brush stimulus in 22% of CIPB patients. The other three studies that evaluated DMA found no altered sensations (Table 5) (Binder et al. 2007, Attal et al. 2009, Ventzel et al. 2017).

Temporal pain summation (Wind-up ratio (WUR))

Augmented temporal pain summation was assessed using the pinprick wind-up ratio (WUR) in three studies (Binder et al. 2007, Fallon et al. 2015, Ventzel et al. 2017). None (0%) of these CIPN studies observed increased WUR in painful regions in comparison to normative data sets (Binder et al. 2007), contralateral pain free region (Fallon et al. 2015) or between hands and feet (Table 5) (Ventzel et al. 2017).

Vibration detection threshold (VDT)

VDT were evaluated in seven studies of which six (86%) identified altered vibration perception. Lipton et al. identified elevated VDT in the feet of tumour-related pain patients (Table 5) (Lipton et al. 1991). Of the six CIPN studies that evaluated vibration perception, five observed elevated VDT (Table 5) (Forsyth et al. 1997, Caraceni et al. 2008, Attal et al. 2009, Hershman et al. 2011, Ventzel et al. 2017). In two prospective cohorts, cumulative Paclitaxel (Caraceni et al. 2008) and Oxaliplatin (Attal et al. 2009) doses correlated with increasingly elevated VDT. However, in another prospective cohort, Hershaman et al. observed elevated VDT within a month of first Paclitaxel cycle which returned to baselined (pre-treatment) levels by 12 months (Hershman et al. 2011). In a cross-sectional cohort, Ventzel et al. found significantly elevated VDT in the hands (but not feet) of colorectal and breast cancer patients exposed to Oxaliplatin or Docetaxel respectively (Ventzel et al. 2017). In another cross-sectional cohort, Hershman et al. identified significant negative correlation between increased sensations of numbness and pain in hands and feet and reduced vibration perception (Hershman et al. 2011).

Pressure pain threshold (PPT)

Pressure pain thresholds (PPT) were assessed in two studies (Binder et al. 2007, Ventzel et al. 2017). Binder et al. found no difference in PPT between those with painful CIPN and pain free patients (Binder et al. 2007). Ventzel et al. found PPT within normative data range for both Oxaliplatin and Docetaxel treated patients (Ventzel et al. 2017).

Variation in QST procedures

Studies varied in terms of the different procedures used to evaluate the same or similar QST parameters. Lipton et al. (Lipton et al. 1991) and Forsyth et al. (Forsyth et al. 1997) reported measuring 'thermal detection threshold' (TDT) via a forced choice paradigm which most closely mimics evaluating CDT in terms of thermal range used (i.e. 20-30^{o}C). Scott et al. (Scott et al. 2012) qualitatively determined presence or absence of thermal hyperaesthesia, hypaesthesia or allodynia using cool and warm thermos rollers set at fixed temperatures (25^{o}C and 40^{o}C). In contrast, 12 studies quantitatively evaluated thermal detection and pain thresholds using computer controlled devices via a Peltier thermode (Dougherty et al. 2004, Binder et al. 2007, Cata et al. 2007, Dougherty et al. 2007, Attal et al. 2009, Boyette-Davis et

al. 2011, Boyette-Davis et al. 2013, Krøigård et al. 2014, Velasco et al. 2015, Andersen et al. 2016, Andriamamonjy et al. 2017, Ventzel et al. 2017).

Techniques to assess vibration perception also varied. Two studies evaluated VDT using a forced choice paradigm to distinguish between two metal rods vibrating at increasingly similar frequencies (Lipton et al. 1991, Forsyth et al. 1997). Two studies used a standardised 64Hz tuning fork which decreases in frequency until the vibration is no longer felt (disappearance threshold) (Binder et al. 2007, Ventzel et al. 2017). Three studies used electronic vibrameters which increase in frequency until the vibration is felt (perception threshold) (Caraceni et al. 2008, Attal et al. 2009, Hershman et al. 2011). Studies that evaluated MDT all used von Frey monofilaments in a method of limits paradigm. However, punctate sensitivity was evaluated quantitatively using calibrated weighted needle pinprick stimulators (Binder et al. 2007, Ventzel et al. 2017) or qualitatively single pinprick stimulus (Neurotips™ Owen Mumford) (Scott et al. 2012, Fallon et al. 2015).

All of the four studies that included MPS in their methodology used noxious pin prick stimuli, two of which (Scott et al. 2012, Fallon et al. 2015) specified the Neurotips™ Owen Mumford, whilst the remaining two studies (Binder et al. 2007, Ventzel et al. 2017) documented that they followed the QST-protocol of the German Research Network on Neuropathic Pain (DNFS). Similarly, the three studies who included WUR in their methodology all used pin prick stimuli (256mN) and compared a single stimulus to ten repeated stimuli with the participant giving a pain rating from 0-10.

Techniques to measure dynamic allodynia varied slightly. Of the four studies that included an assessment of dynamic allodynia, two studies (Binder et al. 2007, Ventzel et al. 2017) followed the DNFS protocol which describes using three light tactile stimulators: a cotton wisp (~3mN), a cotton wool tip fixed to an elastic strip (~100mN) and a standardised brush (~200-400mN). The remaining two studies just used a standardised brush (Attal et al. 2009, Scott et al. 2012).

Finally, for the two studies that measured PPT (Binder et al. 2007, Ventzel et al. 2017), both studies followed the DNFS QST-protocol which uses a pressure gauge device (FDN200, Wagner Instruments, USA).

Discussion

Across all studies, 50% (9/18) reported sensory abnormities using thermal detection thresholds (cold and warm), 44% (8/18) reported abnormal mechanical detection thresholds using von-Frey filaments and 39% (7/18) found abnormal pin-prick thresholds. Abnormal vibration and thermal pain (heat/cold) thresholds were reported in a third of included studies respectively.

This systematic review demonstrates a paucity of published data characterising the phenotype of cancer pain using quantitative pain assessment techniques. Three studies were identified that characterised tumour-related pain using QST, of which only two reported data on sensory abnormalities (Lipton et al. 1991, Scott et al. 2012). Fifteen studies were identified that characterised sensory abnormalities in CIPN using QST. These treatment-related pain studies included a heterogeneous sample of patients with chronic and acute painful CPIN. The in the number of QST studies profiling sensory abnormalities associated with CIPN has increased in the past two decades. However, overall the number of QST studies profiling cancer pain are small and the data should be interpreted with caution for this reason. There are more recent emerging studies using QST to quantify pain in cancer patients; although they didn't meet the eligibility criteria for this systematic review, they are interesting for reference (Kaunisto et al. 2013, Sipila et al. 2017, Griffiths et al. 2018).

Of the three tumour-related pain studies (Lipton et al. 1991, Scott et al. 2012, Andersen et al. 2016), Liption et al. and Scott et al. reported abnormalities in thermal detection and mechanical or vibration detection, indicative of Aβ and Aδ fibre dysfunction. These limited data suggest that systemic and localised loss in Aβ-fibre function, characterised by reduced light touch sensation (hypoaesthesia) may be common in tumour-related cancer pain. Andersen et al. found no sensory abnormalities; however, this study excluded patients with any kind of peripheral nerve dysfunction and therefore were very unlikely to come across any sensory abnormalities using QST.

The data presented in Table 5 indicate that CIPN is predominately characterised by increased vibration and mechanical detection thresholds (reduced Aβ function), as well as increased thermal detection and thermal pain thresholds (reduced Aδ and C-fibre function). Altered pin-prick (mechanical pain) thresholds were also observed; however, whether this manifested as a hypo- or hyper-sensitivity (loss or gain in Aδ fibre function) was treatment-

dependent. Across all treatment-related studies, none identified altered perception of supra-thresholds stimuli, such as mechanical pain sensitivity, dynamic mechanical allodynia, pressure pain threshold or temporal summation (wind-up pain). However, the inclusion of chronic and acute pain patients across the CIPN studies should also be considered. Patients with chronic pain typically experience higher levels of pain intensity, reduced wellbeing and poorer quality of life (Smith et al. 2007, Rayment et al. 2012). Chronic pain is also thought to be associated with more central pathophysiological pain processes (Loeser 2019) which, in the context of this systematic review, may influence QST findings based on peripheral cutaneous examination techniques. None of the included CIPN studies explicitly stated using QST to examine central pain mechanisms.

We acknowledge that a limitation of this systematic review is the lack of available data on which to base conclusions, particularly for tumour-related pain. Despite a comprehensive search strategy developed in line with international guidelines (Centre for Reviews and Dissemination 2009, Moher et al. 2009) and broad eligibility criteria, very few studies were identified. Due to the paucity of available quantitative data, it was not possible to undertake a pooled analysis of QST data across all studies. Instead a narrative synthesis was undertaken to summarise the main findings and identify commonalities in the patterns of sensory abnormalities reported in tumour-related and treatment-related cancer pain.

The most commonly used QST parameters were thermal detection thresholds (CDT, WDT) and mechanical detection. PPT and WUP were only included in 3 and 2 studies respectively and revealed no sensory abnormalities. No studies reported finding DMA in tumour or treatment related cancer pain, although this is contrary to anecdotal clinical experience of bedside assessment in many patients. As DMA is a centrally mediated phenomenon, this might suggest that tumour related pain is caused by peripheral sensitisation rather than central sensitisation. However, these conclusions are speculative due to the lack of available data.

The majority of CIPN studies did not make explicit statements linking the selection of individual QST parameters to underlying pain mechanisms or patient reported symptoms. Therefore, it remains unclear whether the data presented on treatment-related cancer pain represents sensory abnormalities common to CIPN, or if it reflects the QST parameters that were most frequently selected by the researchers. Although, the latter is unlikely as reduced

tactile sensitivity has been widely reported as a common side effect of chemotherapy. Nevertheless, future cancer pain research should consider profiling all 13 DNFS parameters to gain a clearer understanding of which sensory abnormalities are most relevant to the diagnosis and management of pain in patients with cancer.

The increasing abundance of QST evidence from CIPN studies (of a variety of chemotherapeutic agents) indicates dysfunction in myelinated and unmyelinated cutaneous sensory fibres. Similar quantitative sensory data in patients with tumour-related pain are lacking; although evidence presented here suggests dysfunction in both myelinated and unmyelinated cutaneous sensory fibres. Further research is required to map the sensory phenotypes of tumour-related pain to improve our understanding of the underlying pathophysiological mechanisms. Studies should include a heterogeneous population of cancer types to better understand whether patterns of sensory dysfunction are disease specific or unique to individual pain profiles which span cancer diagnostic groups.

Interestingly, none of the included studies evaluated descending pain control mechanisms. Increasing evidence is emerging to support the theory that descending inhibitory (anti-nociceptive) and facilitatory (pro-nociceptive) pathways are fundamental to our understanding of chronic and neuropathic pain as seen in cancer patients. Data from animal models of neuropathic pain reveals a multitude of descending pain control mechanisms associated with hypersensitivity to noxious and non-noxious stimuli, as well as spontaneous pain and central sensitization (Wang et al. 2013). These data demonstrate the complexities associated with understanding the interactions between descending inhibitory pathways and the clinical presentation of pain in patients with cancer (De Felice et al. 2011). QST may be a potential biomarker for describing the function of these descending pain modulatory pathways. For example, the conditioned pain modulation (CPM) paradigm has demonstrated that reduced efficiency of descending control of pain is associated with the development of chronic pain states in cancer and non-cancer populations (Yarnitsky et al. 2014, Yarnitsky 2015). Quantifying the function of descending pain modulatory pathways using QST would further our understanding of the role that such neurobiological mechanisms have on the clinical presentation of pain in cancer patients.

In conclusion, this systematic review highlights the lack of published studies characterising the sensory phenotype of pain in cancer, with particularly few studies looking at tumour-

related chronic or neuropathic pain. This limits our understanding of the underlying pathophysiological mechanisms of cancer pain. Understanding the multiple mechanisms driving cancer pain will enable rational individualised analgesic treatment choices (Vardeh et al. 2016). Future studies should justify the selection of individual test parameters from standardised QST protocols (Rolke et al. 2006) and consider incorporating CPM into their protocols to evaluate the important role of descending pain mechanisms in cancer pain.

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Legends for figures and tables

Figure 1 - PRISMA flow diagram of searches, screening, eligibility and inclusion

Figure 1 legend

* hand searching reference lists of included studies

Table 1 – QST modalities and associated peripheral nerve fibres tested

Table 1 legend:

Summary of Quantitative Sensory Testing (QST) modalities, associated bedside equivalent examinations and peripheral nerve fibres tested

Table 2 – Search Strategy

Table 3 – Description of included studies

Table 3 legend:

† Gender of cancer pain participants only (gender of control participants not reported)

Δ decision made that this is tumour-related PN because patients with neurotoxic chemo-therapeutic agents and other neurotoxic medications were excluded

ð data are mean (SD)

§ data are median (range)

‡ 8 (15%) reported moderate-severe pre-treatment tumour pain. Therefore, only baseline data (pre-intervention) extracted

- unable to extract age data for only pain patients

≠ data are mean (range)

∑ 9/16 participants had pain

¶ control subjects consisted of 20 health pain-free volunteers and 5 pain-free chemotherapy naïve multiple myeloma ϕ data are mean (SD, min-max)

* Cross-sectional group / Prospectively cohort

± data presented for Docetaxel group of whom 80% reported pain. Oxaliplatin group 70% reported no pain; therefore, data not extracted

∫ calculated by hand

ɤ data are presented for Oxaliplatin and Docetaxel groups respectively

ϕ data are mean (SD, min-max)

PN = Peripheral Neuropathy

CIPN = Chemotherapy Induced Peripheral Neuropathy

Table 4 – Assessment of Quality

Table 4 legend:

+ high reporting quality, – low reporting quality, ? Unable to judge

Assessment criteria

A. Research question or objective clearly stated?
B. Study population clearly defined?
C. Subjects selected or recruited from the same or similar populations?
D. QST parameters clearly defined and implemented consistently across all study participants?
E. Mechanism based justification for the use of individual QST parameter(s) based on underlying pathophysiological pain mechanisms?
F. Outcome measures clearly defined and implemented consistently across all study participants?

Table 5 – Quantitative Sensory Testing (QST) parameters used in cancer pain assessment

Table 5 legend

* Control participants referred to in methods but not data are reported on them in results.
† Mean data are summarised unless stated otherwise
VT = Vibration Threshold
TDT = Thermal Detection Threshold
CDT = Cold Detection Threshold
WDT = Warm Detection Threshold
TSL = Thermal Sensory Limen
PHS = Paradoxical Heat Sensation
CPT = Cold Pain Threshold
HPT = Heat Pain Threshold
MDT = Mechanical Detection Threshold
MPT = Mechanical Pain Threshold
MPS = Mechanical Pain Sensitivity
DMA = Dynamic Mechanical Allodynia
WUR = Wind Up Ratio
VDT = Vibration Detection Threshold
PPT = Pressure Pain Threshold
SCS = Suprathreshold Cold Stimulus
ICS = Intense Cold Stimulus

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Table 1 – QST modalities and associated peripheral nerve fibres tested

Type of Stimulus	Nerve Fibre Tested	QST Method	Bedside Examination
Mechanical Detection Threshold	Aβ	Von Frey Filaments	Brush, cotton swab
Dynamic Mechanical Allodynia	Aβ	Brush, cotton wisp, wool tip	Brush, cotton swab
Vibration	Aβ	Calibrated Tuning Fork	Tuning fork
Cold Detection Threshold	Aδ	Computer controlled thermal testing device	Cold/ warm/ hot thermo rollers/ test tubes
Warm Detection Threshold	C		
Cold Pain Threshold	Aδ, C		
Heat Pain Threshold	Aδ, C		
Mechanical Pain Threshold	Aδ	Needle Stimulators (pin prick)	Toothpick, pin
Mechanical Pain Sensitivity	Aδ		Toothpick, pin
Wind-up (Temporal Summation)	Aδ		Toothpick, pin
Pressure Pain Threshold	Aδ, C	Algometer	Examiner's thumb

Table 1 legend: Summary of Quantitative Sensory Testing (QST) modalities, associated bedside equivalent examinations and peripheral nerve fibres tested

Table 2 – Search Strategy

Quantitative sensory testing		**Pain**		**Cancer**		**Assessment**
quantitative sensory test*	AND	neuropath*	AND	cancer	AND	Assess*
QST		pain		malignancy		identif*
psychophysical		somatosensory		radiotherapy		categor*
psycho-physical		somato-sensory		chemotherapy		phenotype
cold threshold		sens*		metastatic		profile
warm threshold				bone pain		outcome
pain threshold				tumour		management
detection threshold				neoplasm		
				thoracotomy		
				mastectomy		
Combined with OR		*Combined with OR*		*Combined with OR*		*Combined with OR*
Limits: Human, Adult						

Table 3 – Description of included studies

Author (Year) Country	Cancer Type	Type of pain	Total study sample	Cancer Pain Subjects	Control Subjects	Gender		Age Mean (range)
						M†	F†	
Tumour-related pain								
Lipton (1991) USA	Breast, Colon, Myeloma, Lymphoma, Leukaemia, Gastric, Prostate, Ovarian.	Tumour: Systemic PN in hands and feet[Δ]	129	29	100	14	15	56.8[∂]
Scott (2012) UK	Prostate, Breast, Lung, Renal, Colorectal, Unknown Primary.	Tumour: CIBP	23	23	0	13	10	73 (33–83)[§]
Anderson (2016) Denmark	Breast	Tumour: Breast	54	8[‡]	0	0	8	-
Treatment-related pain - CIPN								
Forsyth (1997) USA	Breast (metastatic)	Treatment: Paclitaxel	37	37	0	0	37	50.7 (25–69)[≠]

Dougherty (2004) USA	Breast, Laryngeal, Lymphoma, Melanoma, Lunch, Prostate.	Treatment: Paclitaxel	29	12	17	4	8	53.8 (18)[∂]
Binder (2007) Germany	Colon, Oesophagus, Gastric.	Treatment: Oxaliplatin	16	9[Σ]	0	4	5	64.6 (12.4)[∂]
Cata (2007) USA	Myeloma, Lymphoma.	Treatment: Bortezomib	41	16	25[¶]	12	4	61.7 (8)[∂]
Doughty (2007) USA	Haematological, Ewing's sarcoma, Breast.	Treatment: Vincristine	18	18	0	10	8	49.3 (12.1)[∂]
Caraceni (2008) Italy	Breast (metastatic)	Treatment: Paclitaxel	44	44	0	0	44	48.5 (33–64)[≠]
Attal (2009) France	Colorectal, Pancreas, Oesophagus, Lung, Gastroduodenal, Gallbladder, Unknown primary.	Treatment: Oxaliplatin	48	48	0	33	15	58.9 (11.5)[∂]
Boyette-Davis (2011) USA	Myeloma	Treatment: Bortezomib	37	11	26	7	4	58.2 (3.4)[∂]
Hershman (2011) USA	Breast (early stage)	Treatment: Paclitaxel	100	50/50*	0	0	100	51 (34-80) / 48

								(28-78)[*§]
Boyette-Davis (2013) USA	Lung, Breast, Haematological, Ewing's Sarcoma.	Treatment: Paclitaxel & Vincristine	32	14	18	5	9	60.1 (2.3)[∂]
Kroigard (2014) Denmark	Colorectal, Breast.	Treatment: Docetaxel	40	20[±]	0	14	6	53.1 (8)[ʃ]
Fallon (2015) UK	Colorectal, Myeloma, Lung, Ovary, Breast.	Treatment: Oxaliplatin, Paclitaxel, Taxotere, Bortezomib, Cisplatin, Carboplatin	51	51	0	19	32	61 (20 -89)[§]
Velasco (2015) Spain	Colorectal (stag not reported).	Treatment: Oxaliplatin	40	20	20	13	7	59 (8.4)[∂]
Andriamamonjy (2017) France	Gastrointestinal (any stage).	Treatment: Oxaliplatin	12	12	0	7	5	64.5 (11.7)[∂]
Ventzel (2017) Denmark	Colorectal, Breast.	Treatment: Oxaliplatin & Docetaxel	38	38	0	11/9[ɣ]	0/18[ɣ]	66.5 (5.9), 56.0 (8.4)[ɣ]
		Totals	789	510	181	161	320	58 (6.6, 48-73)[ϕ]

Table 3 legend:

† Gender of cancer pain participants only (gender of control participants not reported)

Δ decision made that this is tumour-related PN because patients with neurotoxic chemo-therapeutic agents and other neurotoxic medications were excluded

∂ data are mean (SD)

§ data are median (range)

‡ 8 (15%) reported moderate-severe pre-treatment tumour pain. Therefore, only baseline data (pre-intervention) extracted

- unable to extract age data for only pain patients

≠ data are mean (range)

∑ 9/16 participants had pain

¶ control subjects consisted of 20 health pain-free volunteers and 5 pain-free chemotherapy naïve multiple myeloma ϕ data are mean (SD, min-max)

* Cross-sectional group / Prospectively cohort

± data presented for Docetaxel group of whom 80% reported pain. Oxaliplatin group 70% reported no pain; therefore, data not extracted

∫ calculated by hand

ɤ data are presented for Oxaliplatin and Docetaxel groups respectively

ϕ data are mean (SD, min-max)

PN = Peripheral Neuropathy

CIPN = Chemotherapy Induced Peripheral Neuropathy

Table 4 – Assessment of Quality

Author, year	A	B	C	D	E	F
Andersen et al, 2016	+	+	+	+	+	+
Andriamamonjy et al, 2016	+	+	+	+	+	+
Attal et al, 2009	+	+	+	+	+	+
Binder et al, 2007	+	+	+	+	+	+
Boyette-Davis et al, 2013	+	+	+	+	+	+
Boyette-Davis et al, 2011	+	+	+	+	+	+
Caraceni et al, 2008	+	+	+	+	–	+
Cata et al, 2007	+	+	+	+	–	+
Dougherty et al, 2007	+	+	+	+	+	+
Dougherty et al, 2004	+	+	+	+	+	+
Fallon et al, 2015	+	+	+	+	+	+
Forsyth et al, 1997	+	+	+	+	–	+
Hershman et al, 2011	+	+	+	+	+	+
Kroigard et al, 2014	+	+	+	+	–	+
Lipton et al, 1991	?	+	+	+	+	+
Scott et al, 2012	+	+	+	+	+	+
Velasco et al, 2015	+	+	+	+	+	+
Ventzel et al, 2017	+	+	+	+	+	+

Table 4 legend:

+ high reporting quality, – low reporting quality, ? Unable to judge

Assessment criteria

A. Research question or objective clearly stated?

B. Study population clearly defined?

C. Subjects selected or recruited from the same or similar populations?

D. QST parameters clearly defined and implemented consistently across all study participants?

E. Mechanism based justification for the use of individual QST parameter(s) based on underlying pathophysiological pain mechanisms?

F. Outcome measures clearly defined and implemented consistently across all study participants?

Table 5 – Quantitative Sensory Testing (QST) parameters used in cancer pain assessment

Author (Year)	QST reported in Methods	Test site	Control site / Comparison group	Abnormal QST† (clinical sign)
Tumour-related pain				
Lipton (1991)	VT, TDT	Hands and feet	Comparison between hand and feet	37% of cases had elevated VT (mechanical hypoaesthesia) in feet. 50% of cases had elevated TDT (thermal hypoaesthesia) in feet. No sensory dysfunction in hands.
Scott (2012)	DMA, MDT, MPT, MPS, WDT (40°C), CDT (25°C)	Skin overlying area of CIBP	Contralateral or proximal non-painful site	Brush allodynia 13%, brush hypoaesthesia in 22%, pinprick hyperalgesia in 45%, pinprick hypoalgesia in 9%, warm allodynia in 43%, cold allodynia in 35%, thermal (warm or cool) hypoaesthesia in 26%.
Andersen (2016)	MDT, MPT, WDT, CDT, HPT,	Pathological side	Contralateral or proximal non-painful site	None
Treatment-related pain - Chemotherapy Induced Peripheral Neuropathy (CIPN)				
Forsyth (1997)	VT, TDT	Hands and feet	Control participants*	VT 'abnormal' (hypo/hyper-aesthesia) in foot in 74% of cases in feet. TDT elevated (thermal hypoaesthesia) in 43% of cases in feet and 12% of cases in hands.
Dougherty (2004) USA	MDT, MPT, CDT, CPT, WDT, HPT	Pain area (tip of index finger), broader area (thenar eminence), distal non-painful area (forearm)	Control participants	MDT elevated (mechanical hypoaesthesia) in all areas. MPT reduced in pain and boarder areas. CDT reduced (cold allodynia). No difference in WDT, HPT or CPT.
Binder (2007)	CDT, WDT, TSL, PHS, CPT, HPT, MDT, MPT, MPS,	Dorsum right hand	Normative data set (data not reported)	CPT reduced (cold allodynia), MPT reduced (mechanical hyperalgesia)

Author (Year)	QST reported in Methods	Test site	Control site / Comparison group	Abnormal QST† (clinical sign)
	DMA, WUR, VDT, PPT			
Cata (2007) USA	MDT, MPT, CDT, CPT, WDT, HPT	Pain area (tip of index finger), boarder area (thenar eminence), distal non-painful area (forearm)	Control participants	MDT elevated in all areas. MPT elevated in pain area only. WDT and HPT elevated in all areas. CPT reduced in all areas. No differences in CDT.
Doughty (2007)	MDT, MPT, CDT, CPT, WDT, HPT	Pain area (tip of index finger), boarder area (thenar eminence)	Distal non-painful area (forearm)	MDT elevated (mechanical hypoaesthesia) at painful site and proximally. Elevated MPT (mechanical hypoalgesia) and WDT (thermal hypoaesthesia) at painful site.
Caraceni (2008)	VDT	Hands and feet	Comparison between hand and feet	Elevated VDT (mechanical hypoaesthesia) correlated with cumulative paclitaxel dose. Deficits in foot greater than hand.
Attal (2009)	DMA, VDT, MDT, MPT, CDT, WDT, CPT, HPT	Hands and feet	Comparison between hand and feet	VDT elevated (mechanical hypoaesthesia), CPT & HPT decreased (cold/heat allodynia), increased suprathreshold cold pain (cold hyperalgesia)
Boyette-Davis (2011)	MDT, MPT, WDT, HPT, CDT, CPT	Pain area (tip of index finger), boarder area (thenar eminence), distal non-painful area (forearm)	Control participants	MDT twice that of controls (mechanical hypoaesthesia) in painful and boarder area at BL and 12 months. MPT elevated (mechanical hypoalgesia) at fingertips only at BL and FU. WDT and HPT elevated (thermal hypo-aesthesia/algesia) in all areas at BL. At FU WDT and HPT deficits remained in painful area
Hershman (2011)	MDT, VDT	Hands and feet	Correlation with NP symptom items; pre/post intervention QST data comparison	Cross-sectional data: VDT negatively correlated with numbness and discomfort in hands (mechanical hypoesthesia). Prospective data: significantly elevated VDT (mechanical hypoalgesia) one-month after Paclitaxel normalised by 12. No change in MDT at any time point.

Author (Year)	QST reported in Methods	Test site	Control site / Comparison group	Abnormal QST† (clinical sign)
Boyette-Davis (2013)	MDT, MPT, WDT, HPT, CDT, CPT	Pain area (tip of index finger), boarder area (thenar eminence), Distal non-painful area (forearm)	Control participants	MDT deficits at BL and FU in painful and boarder area (mechanical hypoaesthesia). Persistent MPT deficits in painful area (mechanical hypoalgesia). BL WDT elevated at all three areas (thermal hypoaesthesia). HPT elevated at FU at all three areas (thermal hypoalgesia).
Kroigard (2014)	CDT, WDT, HPT, MDT, MPT	Not reported	Not reported	MDT elevated (hypoaesthesia)
Fallon (2015)	MDT, MPT, MPS, WUR	Site of pain	Contralateral or proximal non-painful site	MDT elevated (mechanical hypoaesthesia), MPT reduced (mechanical hyperalgesia)
Velasco (2015)	CDT, WDT, CPT, HPT, SCS , ICS	Thenar eminence of hand	Control participants	CPT reduced (cold allodynia), increased SCS pain (cold hyperalgesia)
Andriamamonjy (2017)	CDT, WDT, CPT, HPT	Thenar and fingertips	Within patients comparison between thenar and fingertip	CDT and WDT reduced (thermal hyperesthesia). No differences in CPT or HPT.
Ventzel (2017)	CDT, WDT, TSL, PHS, CPT, HPT, MDT, MPT, MPS, DMA, WUR, VDT, PPT	Hands and feet	Unclear	MDT and VDT elevated (mechanical hypoaesthesia). PHS mediated by elevated WDT

Table 5 legend

* Control participants referred to in methods but not data are reported on them in results.
† Mean data are summarised unless stated otherwise
VT = Vibration Threshold
TDT = Thermal Detection Threshold
CDT = Cold Detection Threshold
WDT = Warm Detection Threshold
TSL = Thermal Sensory Limen
PHS = Paradoxical Heat Sensation
CPT = Cold Pain Threshold
HPT = Heat Pain Threshold
MDT = Mechanical Detection Threshold
MPT = Mechanical Pain Threshold
MPS = Mechanical Pain Sensitivity
DMA = Dynamic Mechanical Allodynia
WUR = Wind Up Ratio
VDT = Vibration Detection Threshold
PPT = Pressure Pain Threshold
SCS = Suprathreshold Cold Stimulus
ICS = Intense Cold Stimulus

Figure 1 - PRISMA flow diagram of searches, screening, eligibility and inclusion

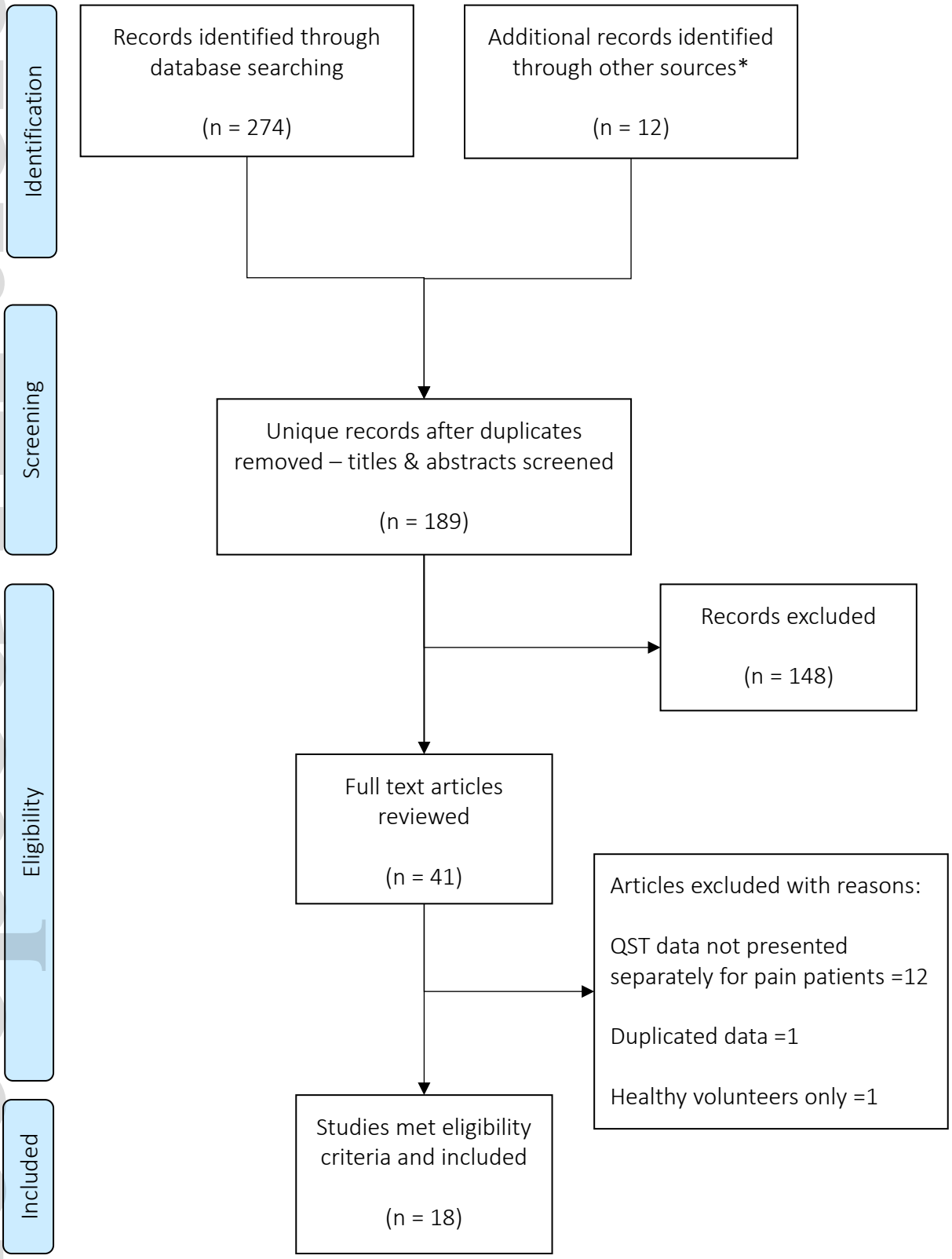

Figure 1 legend

* hand searching reference lists of included studies