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1 **Title: Divergent sensory phenotypes in non-specific arm pain:**  
2 **comparison with cervical radiculopathy**

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23 **Title: Divergent sensory phenotypes in non-specific arm pain:**  
24 **comparison with cervical radiculopathy**

25 **ABSTRACT**

26 Objective: The primary research question under review was whether distinct sensory  
27 phenotypes were identifiable in individuals with non-specific arm pain (NSAP) and if they  
28 differed from people with cervical radiculopathy. A secondary question considered whether  
29 the frequency of features of neuropathic pain, kinesiophobia, high pain ratings, hyperalgesia  
30 and allodynia differed according to sub-groups of sensory phenotypes.

31

32 Design: A cross sectional study

33

34 Setting: Higher education institution

35 Participants: Forty office people with NSAP, 17 with cervical radiculopathy, and 40 age-  
36 gender-matched healthy controls.

37

38 Interventions: Nil

39

40 Main Outcome Measures: Participants were assessed using quantitative sensory testing (QST)  
41 comprising thermal and vibration detection thresholds, and thermal and pressure pain  
42 thresholds; clinical examination and relevant questionnaires. Sensory phenotypes were  
43 identified for each individual in the patient groups using z-score transformation of the QST  
44 data.

45

46 Results: Individuals with NSAP and cervical radiculopathy present with a spectrum of  
47 sensory abnormalities; a dominant sensory phenotype was not identifiable in individuals with  
48 NSAP. No distinct pattern between clinical features and questionnaire results across sensory  
49 phenotypes was identified in either group.

50

51 Conclusion: When considering sensory phenotypes, neither individuals with NSAP nor  
52 cervical radiculopathy should be considered homogenous. Therefore, people with either  
53 condition may warrant different intervention approaches according to their individual sensory

54 phenotype. Issues relating to the clinical identification of sensory hypersensitivity and the  
55 validity of QST are highlighted.

56

57 **Abbreviations: QST: quantitative sensory testing; NSAP: Non-specific arm pain;**

58 **LANSS: Leeds assessment for neuropathic symptoms and signs**

59

60 **Keywords:** Sensory threshold; pain threshold; non-specific arm pain (repetitive strain  
61 injury); cervical radiculopathy; musculoskeletal arm pain.

62

## 63 INTRODUCTION

64

65 Work related upper limb disorders are a significant public health problem with a prevalence  
66 of 29% (Eurostat),<sup>1</sup> 50% of which are described as non specific.<sup>2</sup> Non-specific arm pain  
67 (NSAP) commonly affects computer users and is frequently associated with poor prognoses.<sup>3</sup>  
68 The absence of consistent information regarding the pathology and pathophysiology  
69 underlying NSAP has obvious implications for clinical decision making. Given growing  
70 computerisation of the global workforce as well as the intensification of work, improving our  
71 understanding of work related non-specific conditions is imperative for improving  
72 intervention selection and outcomes.

73

74 Quantitative sensory testing (QST) is a non-invasive means of assessing sensory and pain  
75 perception, which potentially provides insights into underlying pathophysiological  
76 mechanisms of a condition,<sup>4</sup> and has seen growing use in the investigation of patient  
77 populations such as complex regional pain syndrome, whiplash and neuropathic pain.<sup>5-10</sup> In  
78 studies of NSAP, the presence of hypoesthesia to vibration has previously been recorded,<sup>11-</sup>  
79 <sup>13</sup> which may suggest the presence of a minor neuropathy<sup>11 12</sup> and/or altered central  
80 processing,<sup>13</sup> possibly secondary to pain.<sup>14</sup> Furthermore, we recently reported the presence of  
81 sensory hypersensitivity to pressure, cold and heat as characteristic of NSAP, while  
82 hypoesthesia to vibration explained a small percentage of the variance (11%).<sup>15</sup> In addition,  
83 in comparison to people with cervical radiculopathy and healthy controls, people with NSAP  
84 had normal thermal detection thresholds, whereas sensory hypoesthesia, to both thermal and  
85 vibration stimuli, was evident in people with cervical radiculopathy.<sup>15</sup>

86

87 The German Research Network on Neuropathic Pain has suggested that detailed analyses of  
88 sensory profiles may yield information regarding the underlying sensory phenotype in  
89 individuals and within patient populations and that this may help to direct clinical decision  
90 making.<sup>16</sup> They presented data from a large group of people with various neuropathy and  
91 neuropathic pain conditions with key sensory phenotypes identified i.e. sensory loss, sensory  
92 hypersensitivity, both sensory hypersensitivity + sensory loss and no abnormality.<sup>6</sup> Each of  
93 the phenotypes was represented both within each patient population and across the different  
94 conditions studied.<sup>6</sup> A further study by Gierthmühlen et al.<sup>5</sup> identified the presence of  
95 different sensory phenotypes in people with complex regional pain syndrome, with some  
96 people exhibiting increased sensitivity while others demonstrated decreased sensitivity to

97 thermal and mechanical stimuli; thus, comparison of mean values may not thoroughly  
98 represent sensory findings in patient groups. Therefore, while results from between group  
99 comparisons identified the presence of sensory hypersensitivity as well as hypoaesthesia to  
100 vibration in NSAP, the presence of various sensory phenotypes or indeed a dominant sensory  
101 phenotype is not yet known in this group.

102

103 The use of QST in clinical practice has limitations in that equipment is not widely available  
104 and as such, understanding the relationship between QST findings and clinical features of  
105 pain and clinical signs of sensory loss or sensory hypersensitivity is important. Previous  
106 reports suggest that pain and disability ratings are poorly correlated with QST findings;<sup>17</sup>  
107 however, data on the relationship between clinical features of pain in study populations sub-  
108 grouped according to sensory phenotype is lacking and warrants further investigation.

109

110 The primary research question under review in this study was whether distinct phenotypes are  
111 identifiable in NSAP and if they differ to cervical radiculopathy, a known neuropathic  
112 disorder. A secondary question considered whether the frequency of features of neuropathic  
113 pain, kinesiophobia, high pain ratings, hyperalgesia and allodynia differed according to sub-  
114 groups of sensory phenotypes. We hypothesised that individuals with NSAP would present  
115 with a spectrum of sensory phenotypes within the group and that group sensory phenotypes  
116 would differ between NSAP and cervical radiculopathy. We also hypothesized that people  
117 with sensory hypersensitivity on QST would present with higher pain ratings, clinical  
118 features of hyperalgesia and higher scores on kinesiophobia and neuropathic pain screening  
119 scales.

120

## 121 **METHODS**

### 122 **Design**

123 A cross-sectional observational study investigating sensory profiles in participants with  
124 NSAP, cervical radiculopathy and healthy controls was undertaken. Volunteers were  
125 screened for inclusion criteria for each particular group, the criteria for which have been  
126 previously reported.<sup>15</sup> Subsequently, participants underwent a physical examination and QST  
127 and were asked to complete a series of questionnaires for self-reported pain features and  
128 kinesiophobia. All aspects of group allocation and data collection were performed by one  
129 investigator (NM). The order of QST testing was randomized. The study was approved by the  
130 Human Research Ethics Committee for Life Sciences in University College Dublin and the

131 involved hospitals. All participants were unpaid volunteers and all provided written informed  
132 consent before inclusion.

133

### 134 **Participants**

135 In relation to NSAP, volunteers with arm pain, aged between 18-65 years old that were  
136 recruited from metropolitan hospitals, medical and physiotherapy practices and via a multi-  
137 media campaign were screened for inclusion in this study (through a medical history and  
138 physical examination). Participants were assigned to the NSAP group if they had pain in the  
139 arm in the absence of a specific diagnosis,<sup>18</sup> were office workers who had significant upper  
140 limb pain as defined by a numerical pain rating of  $\geq 3/10$ ,<sup>19,20</sup> for longer than 3 months, who  
141 spent more than 40% of their working week using desktop equipment,<sup>12</sup> and who had been  
142 employed using desk-top equipment for at least two years.<sup>21</sup>

143 Participants with possible cervical radiculopathy were recruited from metropolitan hospitals  
144 as well as medical and physiotherapy practices. They were assigned to the cervical  
145 radiculopathy group if they had *all* of the following: radicular pain in the upper limb  
146 ( $\geq 3/10$ ),<sup>19,20</sup> a positive upper limb neurodynamic test, a positive Spurling's test, MRI  
147 confirmation of nerve compression,<sup>22-24</sup> as well as at least one concordant clinical sign of  
148 conduction loss<sup>25</sup> (i.e. one of diminished/absent reflexes, myotomal weakness or sensory loss  
149 in a dermatomal pattern).

150 Control participants were included if they did not have a history of significant neck, scapular  
151 or shoulder pain over the previous 12 months and did not use desktop equipment for more  
152 than 40% of their working week.<sup>12</sup> As participants from the cervical radiculopathy group  
153 were older than the non-specific arm pain group, control participants were age- and gender-  
154 matched to each group.

155 Volunteers were excluded from the study if they had any of the following: generalized  
156 neurological disorders, generalized musculoskeletal/inflammatory disorders, a history of low  
157 back pain and/or low back related leg pain over the previous six months, a history of  
158 migraine over the previous six months, previous trauma to the upper quadrant, diabetes,  
159 endocrine disorders, epilepsy or if they had been diagnosed with any mental health /  
160 psychiatric disorders.

161

162

163

### 164 **Measurements**

165 ***Sensory assessment***

166 A previously published QST protocol was undertaken<sup>26</sup> measuring the following parameters:  
167 cold, warm and vibration detection thresholds; cold, heat and pressure pain thresholds. All  
168 measures were recorded on three sites on each upper limb. Thermal and vibration tests were  
169 performed using a NeuroSensory Analyser (TSA 2001 II Medoc, Israel). For thermal testing,  
170 a Peltier thermode (16 x 16mm) was attached directly over sites in the hand innervated by  
171 C6, C7 and C8. A Vibrometer (VSA 3000 II 2001 Medoc, Israel) was used to measure  
172 vibration thresholds with readings taken over sites of the hand innervated by C6, C7 and C8.  
173 Pressure pain thresholds were determined using a hand held pressure algometer with a probe  
174 size of 1cm<sup>2</sup> (Somedic AB, Farsta, Sweden) and an application rate of 40 kPa/s over the  
175 median nerve (cubital fossa), ulnar nerve (between olecranon and medial epicondyle of the  
176 humerus) and radial nerve (mid-lower third of the humerus). Triplicate recordings were taken  
177 at each site for all QST parameters and the mean values used for analyses. In order to assess  
178 the presence of widespread sensitivity, thermal testing and pressure pain thresholds were  
179 recorded at a site remote from the upper quadrant, in this case, unilaterally over Tibialis  
180 anterior muscle. All aspects of QST have been found to have acceptable reliability.<sup>27-29</sup>

181

182 Hyperalgesia to pin prick was assessed by recording pain responses to a pin-prick stimulus  
183 applied in the affected area compared to an unaffected area i.e. the contralateral limb where  
184 possible, otherwise the nearest pain-free area was used. The presence of hyperalgesia was  
185 determined if the response in the affected area was more painful than in the unaffected area.<sup>30</sup>  
186 Allodynia was assessed by moving a brush over the affected area and comparing the response  
187 to that in an unaffected area. The stimulus was applied with a single light stroke of at least  
188 2cm in length. Brush stroke allodynia was considered present if the participant reported the  
189 stimulus as painful.<sup>30</sup>

190

191 ***Self-reported measures of pain and fear avoidance***

192 All participants in the patient groups completed the following questionnaires: the Leeds  
193 Assessment for Neuropathic Symptoms and Signs (LANSS) questionnaire with a score of  
194  $\geq 12$  (out of 24) indicating the possible presence of neuropathic pain;<sup>31</sup> the Tampa Scale of  
195 Kinesiophobia<sup>32</sup> with a score of  $\geq 37$  (out of 68) considered to indicate the presence of  
196 significant fear-avoidant pain beliefs,<sup>33</sup> and all provided an average numerical pain rating  
197 (NPRS) for the previous 24 hours.

198



199 **Data Analysis**

200 Data were analysed using SPSS software, version 19.0 (SPSS, USA).

201 ***Preliminary data management***

202 QST data were log-transformed before statistical analyses in order to achieve normal  
203 distribution of the data,<sup>4</sup> which subsequent analysis revealed was successful. Friedman's tests  
204 were used to assess the effect of test site between upper limb sites (C6, C7 & C8 dermatomes  
205 or median, ulnar & radial nerves) for QST parameters. As no significant differences were  
206 identified for QST parameters between these sites, data were averaged and the resultant value  
207 used for subsequent analyses.

208 ***Z-transformation***

209 To compare sensory phenotypes of individuals with NSAP or cervical radiculopathy with  
210 age-matched healthy controls, QST data were z-transformed to generate z-scores, which  
211 allows scores from individuals with a condition to be directly compared to 'normals' in order  
212 to identify any abnormality in that individual, as has been previously advocated for  
213 assessment of individual sensory profiles.<sup>6 16</sup> QST data were z-transformed using the mean  
214 (SD) of their respective control group as reference data i.e. control participants were divided  
215 into two groups; one group of 40 participants matched, according to age and gender, to the 40  
216 participants with NSAP and a further group of 14 participants matched to the cervical  
217 radiculopathy group. The formula used for z-transformation was:  $Z\text{-score} = (X \text{ single}$   
218  $\text{participant} - \text{Mean controls}) / \text{SD controls}$ .<sup>4</sup> For clarity of data presentation, the algebraic sign  
219 of the resulting z-score was adjusted appropriately so that it reflected patients' sensitivity for  
220 each parameter i.e. values above zero indicated increased sensitivity to the tested stimuli;  
221 values below zero indicated reduced sensitivity to the tested stimuli.

222

223 Sensory phenotypes for each participant were assessed by generating sensory phenotype  
224 graphs using resultant z-scores. Z-scores of  $> 1.96$  was considered indicative of increased  
225 sensitivity to the tested stimuli compared with controls (hyperalgesia/allodynia), while z-  
226 scores of  $< -1.96$  was considered indicative of sensory loss.<sup>6</sup> Each individual was classified  
227 according to their sensory phenotype into one of six possible phenotypes: (1) sensory loss<sub>small</sub>  
228 i.e. small fibre sensory loss as determined in this study by the presence of cold and/or warm  
229 hypoaesthesia; (2) sensory loss<sub>large</sub> i.e. large fibre sensory loss as determined by the presence  
230 of vibration hypoaesthesia; (3) sensory loss<sub>mixed</sub> i.e. a combination of small and large fibre  
231 sensory loss; (4) sensory hypersensitivity as determined by the presence of hyperalgesia in  
232 response to cold pain, and/or heat pain and/or pressure pain thresholds; (5) a combination of

233 sensory hypersensitivity + sensory loss, and (6) no abnormality.<sup>6</sup> When sensory  
234 hypersensitivity was recorded, data were inspected to see if hypersensitivity was localised to  
235 upper limb sites or if it was widespread i.e. included sensory hypersensitivity at the Tibialis  
236 Anterior site.

237 The frequencies of different sensory phenotypes in each patient group were recorded and  
238 between-group comparisons of sensory phenotypes were conducted using percentage risk  
239 difference with 95% confidence intervals.

240

241 *Sample size:*

242 The sample size was calculated based on mean and standard error vibration threshold data  
243 from a study by Greening et al., (2003). A sample of size of 40 participants with NSAP, 40  
244 participants with cervical radiculopathy and 40 matched control subjects was required to  
245 detect a medium effect size (0.5) with 0.8 power and 0.05 two tailed significance level.

246

## 247 **RESULTS**

### 248 **Characteristics of NSAP and cervical radiculopathy groups**

249 The baseline characteristics of participants are presented in Table 1. The groups were similar  
250 with regards to pain duration; however, the cervical radiculopathy group were older  
251 ( $p<0.001$ ) and more disabled ( $p=0.002$ ) than the NSAP group. The cervical radiculopathy  
252 sample was smaller than anticipated ( $n=17$ ), primarily due to the strict inclusion criteria. The  
253 control group for the NSAP group comprised of 40 age- and gender- matched healthy people,  
254 while the control group for the cervical radiculopathy group comprised of 14 age- and  
255 gender- matched healthy people.

256 Individual sensory phenotypes are presented in Table 2. Overall, both groups presented with  
257 divergent sensory phenotypes; 45% of the NSAP group and 35% of the cervical  
258 radiculopathy group presented with the phenotypes 'sensory hypersensitivity' and 'sensory  
259 hypersensitivity + sensory loss'. A further 30% of both groups had evidence of 'sensory  
260 loss'. No sensory abnormality was evident in 25% ( $n=10$ ) of the NSAP group and 35% ( $n=6$ )  
261 of the cervical radiculopathy group.

262 Results from risk difference analyses revealed no significant differences between the groups  
263 with respect to the frequency of sensory phenotype. Equal numbers of participants presented  
264 with localised and widespread sensory hypersensitivity in both groups.

265

### 266 **Clinical features and questionnaire results across sensory phenotypes**

267 The frequency of LANSS scores  $\geq 12$ , Tampa scale of kinesiophobia scores  $\geq 37$ , pain  
268  $> / < 5 / 10$ , hyperalgesia and allodynia across each sensory phenotype in both patient groups is  
269 depicted in Table 3. No distinct pattern was evident with respect to the representation of  
270 questionnaire results, high pain levels or clinical measures of hypersensitivity across sensory  
271 phenotypes in either patient group. Those with widespread sensory hypersensitivity did not  
272 present with higher scores on any clinical measure than those with localised or no sensory  
273 hypersensitivity.

274

## 275 **DISCUSSION**

### 276 *Sensory phenotypes in NSAP and cervical radiculopathy*

277 The results of this study provide evidence of bi-directional sensory abnormalities in  
278 individuals with NSAP with evidence that a distinct sensory phenotype is not evident in these  
279 individuals. While bi-directional sensory abnormalities were also evident in individuals with  
280 cervical radiculopathy, it was notable that 35% of the cervical radiculopathy group presented  
281 with no sensory abnormality using QST. The presence of bi-directional sensory abnormalities  
282 in both groups in this study is consistent with data from a similar cohort of people with neck  
283 and arm pain,<sup>34</sup> as well as other cohorts with neuropathies and complex regional pain  
284 syndrome.<sup>5 6</sup> This further supports the argument for assessment of sensory phenotypes in  
285 patient populations on the basis that heterogeneity with respect to sensory phenotypes exists  
286 within patient cohorts; hence, people with the same condition could warrant different  
287 approaches to assessment and treatment.<sup>6 35</sup>

288

289 The identification of different sensory phenotypes within NSAP is an important finding.  
290 Whilst we previously reported group data indicating that sensory hypersensitivity was a key  
291 characteristic in this group,<sup>15</sup> the current findings indicate that just over 50% of the NSAP  
292 group did not have signs of sensory hypersensitivity and presented with either sensory  
293 hypoaesthesia or no sensory abnormality. The identification of the absence or presence of  
294 sensory hypersensitivity is important as the presence of sensory hypersensitivity has been  
295 shown to be a predictor of poor prognosis and poor treatment response in other  
296 musculoskeletal populations,<sup>7 38 39</sup> and thus, may be an important consideration in NSAP and  
297 cervical radiculopathy. Further, the presence of sensory hypersensitivity is important  
298 clinically in considering appropriate interventions in order to prevent acute exacerbations of  
299 symptoms. For example, people with sensory hypersensitivity have previously been shown to  
300 have less effective descending pain modulation in response to exercise,<sup>40</sup> therefore, selected

301 exercise dosages would need careful consideration in a patient with a dominance of sensory  
302 hypersensitivity. However, for those identified with sensory hypoaesthesia or no sensory  
303 abnormality, it is possible that their prognosis is more favourable, although prospective  
304 studies are required to elucidate this further.

305

306 Almost half of the NSAP group and 35% of the cervical radiculopathy group in this study  
307 presented with sensory hypersensitivity, which likely reflects mechanisms of peripheral and  
308 central sensitisation. In addition, 27% of the NSAP group presented ‘sensory loss + sensory  
309 hypersensitivity’. This may reflect the interplay between the mechanisms of hypoaesthesia  
310 and hypersensitivity. The presence of pain has been shown to cause an increase in detection  
311 thresholds;<sup>14</sup> in contrast, the presence of neuronal insult, as has been suggested in NSAP<sup>36</sup>  
312 may lead to sensitisation of peripheral and central pathways.<sup>37</sup> Both scenarios could explain  
313 the presentation of sensory hypersensitivity in addition to sensory loss.

314 .

315

### 316 *Clinical features and sensory phenotypes*

317 How to identify sensory hypersensitivity in clinical practice is an important consideration.  
318 Currently, there are neither established guidelines nor validated measures to do this and  
319 whether QST could fill this void is hampered by the limited availability of equipment in  
320 clinical practice, as well as the large variability in normative data and lack of established cut-  
321 off values. Recent guidelines for the assessment of neuropathic pain recommend that if QST  
322 is used in clinical practice, it should only form part of an overall clinical assessment.<sup>42</sup> This  
323 raises the question whether self-reports of pain intensity and features of bedside examination  
324 are valid means of assessing sensory hypersensitivity. Previous meta-analysis indicated that  
325 QST measures of sensory hypersensitivity and self-reported pain and disability were poorly  
326 correlated;<sup>41</sup> however, it was highlighted in that study that many of the study participants  
327 included in the analysis may not have been sensitised, in which case a strong relationship  
328 between QST and self-reports of pain and disability would not be expected.<sup>41</sup> In the current  
329 study, we aimed to investigate whether particular clinical features would be more frequent  
330 among sub-groups of sensory phenotypes. Specifically, we hypothesized that higher levels of  
331 pain, higher scores on neuropathic pain and kinesiophobia questionnaires and clinical features  
332 of hypersensitivity (pin-prick hyperalgesia and allodynia) would be more evident in those  
333 with the phenotype ‘sensory hypersensitivity’; however, we did not find a distinct pattern in

334 either the NSAP or cervical radiculopathy groups, even when comparing those with a sensory  
335 abnormality to those without a sensory abnormality.

336 Relatively few people with NSAP in this study (28%) presented with kinesiophobia with no  
337 demonstrable pattern noted across different phenotypes. The cervical radiculopathy group  
338 presented with kinesiophobia more frequently (59% of participants), with 24% of those with  
339 kinesiophobia demonstrating sensory hypersensitivity as their dominant sensory phenotype.  
340 Both groups had over 60% of participants presenting pain rating  $\geq 5$ , but no discernible  
341 pattern was evident regarding which sensory phenotypes presented with higher pain ratings.  
342 Indeed, nine of the 13 people with no sensory abnormality in the NSAP group had a pain  
343 rating of  $\geq 5$ . In considering these findings, it is important to note that the small sample size  
344 and particularly the small numbers in each subgroup, mean these data should be considered  
345 preliminary and as such, further studies on larger sample sizes are warranted.

346

347 Nonetheless, the challenge of how to assess the presence of sensory hypersensitivity in  
348 clinical practice without using QST remains. One reason for the poor relationship between  
349 QST and clinical measures may be that the clinical measures tested to date against QST are  
350 not measuring the same construct. Two clinical measures that may be useful are pin-prick  
351 hyperalgesia and brush stroke allodynia<sup>43</sup> but these measures were rarely positive in this  
352 study, despite the frequent presence of sensory hypersensitivity to other measures e.g. heat  
353 and cold. Recently, stronger correlations were identified between pain ratings on application  
354 of ice versus cold pain thresholds;<sup>44</sup> therefore, this may be a better clinical measure of cold  
355 sensitivity. A final consideration is that, QST, which quantifies responses to experimentally  
356 induced pain may evoke different central nervous system responses than spontaneous pain,  
357 normally experienced by patients, as has been demonstrated by brain imaging studies.<sup>45</sup>  
358 Therefore, the development of better clinical tools for the assessment of sensory  
359 hypersensitivity is needed. The recommendation that assessment of descending pain  
360 modulation and pain magnitude rating for a suprathreshold stimulus might facilitate a better  
361 understanding of a sensitized nociceptive system rather than threshold measures may also  
362 hold validity.<sup>46</sup>

363

### 364 **Study Limitations**

365 Due to the relatively small sample size of this study, particularly for cervical radiculopathy,  
366 and the small numbers in each sensory phenotype group, these results should be considered  
367 as preliminary findings.

368

369

370 **Conclusion**

371 The results of this study demonstrate divergent sensory phenotypes in NSAP as well as in  
372 cervical radiculopathy with implications for clinical decision making. NSAP and cervical  
373 radiculopathy should not be considered homogenous groups and individuals may warrant  
374 different intervention approaches according to their sensory phenotype. Researchers should  
375 also consider this when stratifying people for intervention studies. Identifying the presence of  
376 sensory hypersensitivity is difficult in clinical practice and while some studies have reported  
377 criteria for classifying pain;<sup>47-49</sup> validated tools are still lacking with further research needed  
378 in this regard.

379

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