A comparison of chronic pain with and without neuropathic characteristics in a Hong Kong Chinese population: An analysis of pain related outcomes and patient help seeking behaviour

Stanley Sau Ching Wong¹, Siu Wai Choi², Chi Wai Cheung@¹*

¹ Laboratory and Clinical Research Institute for Pain, Department of Anaesthesiology, The University of Hong Kong, Hong Kong, HKSAR, ² Department of Oro-maxillofacial surgery, The University of Hong Kong, HKSAR

* cheucw@hku.hk

Abstract

Objective
In Western countries, chronic pain patients with neuropathic characteristics have more intense pain, greater negative impact in quality of life and worse psychological well-being. The aim of this study was to compare the outcomes, impact, and health seeking behaviours in Chinese chronic pain patients with and without neuropathic characteristics in Hong Kong.

Methods
Random telephone survey was conducted on the general Hong Kong population, and based on the Nuprin Pain Report. Specific questions on chronic and neuropathic pain were included. Respondents with pain lasting three months or more were asked to indicate their two most painful sites. Chi-square and Mann-Whitney U-test were used to investigate differences between variables in patients with and without neuropathic characteristics. \( P < 0.05 \) was regarded as significant.

Results
The response rate was 32.3%. Chronic pain patients with neuropathic characteristics reported higher pain scores and longer duration of pain \( (p = 0.0001) \). They reported greater negative impact on work and effect on daily life \( (p = 0.0131) \); were significantly more likely to consult pain specialists \( (p = 0.0006) \), Chinese medicine practitioners \( (p = 0.0203) \), and psychiatrists \( (p = 0.0212) \); and were significantly less likely to be prescribed oral analgesics \( (p = 0.0226) \), to feel ‘very satisfied’ \( (p = 0.0263) \) with prescribed treatment and to find oral analgesics ‘very useful’ \( (p = 0.0215) \). There was no difference in oral analgesic medications taken.
Conclusion

Chinese individuals having chronic pain with neuropathic characteristics had worse pain related outcomes. Differences in help-seeking behaviour were observed. Lack of appropriate analgesic prescription suggests that identification and management of chronic neuropathic pain in Hong Kong needs to be improved.

Introduction

Neuropathic pain is defined as pain caused by a lesion or disease of the somatosensory system [1]. It has an estimated prevalence of between 6.9–10% [2]. Neuropathic pain is an important public health problem. It has a negative impact on quality of life, function, sleep, and depression [3]. Chronic neuropathic pain is also associated with increased health care utilization and increased drug prescription [3, 4]. Neuropathic pain is often chronic and difficult to treat, and has a greater negative impact than non-neuropathic pain [1, 5]. The mechanism of pain underlying neuropathic pain is different from non-neuropathic pain [6]. Therefore, it should be managed as a distinct clinical condition.

Previous studies have compared chronic pain with neuropathic characteristics (NP) with chronic non-neuropathic pain (non-NP). Individuals with chronic neuropathic pain were associated with more severe pain, longer duration of pain, pain in more body locations, lower quality of life, worse sleep quality, increased symptoms of anxiety and depression, and greater use of health care resources [3, 4, 7–9]. In a cross sectional telephone interview, we reported that the prevalence of pain with neuropathic characteristics (acute and chronic) was 9.03% in a Chinese population in Hong Kong [10]. In addition, 14.7% of Chinese patients suffering from chronic pain in Hong Kong had neuropathic characteristics [10]. These figures indicate that this is a significant health care problem in Chinese people. Currently, there is no information comparing the severity, outcomes, impact, and help seeking behaviours between individuals with chronic NP and chronic non-NP in a Chinese population. Population studies on chronic pain with neuropathic characteristics in a Chinese population were previously difficult to conduct due to the absence of validated neuropathic pain questionnaires in the Chinese language. Currently, the Identification Pain Questionnaire for neuropathic pain has been validated in Chinese, and can be used to identify individuals suffering from pain with a significant neuropathic component [11]. The aim of this cross sectional study was to compare the outcomes, impact, and help seeking behaviours between individuals with chronic NP and chronic non-NP in a Chinese population in Hong Kong.

Materials and methods

This cross-sectional survey conducted on the general population of Hong Kong was approved by the Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster and registered at ClinicalTrials.gov (registration number NCT01878877). The study was conducted via a telephone survey adapted from the Nuprin Pain Report, especially developed for this current investigation, and tailored to the Cantonese speaking population, based on a similar study conducted by our department in 1999 [12, 13]. The full surveys (in English and Chinese, S1 Appendix and S2 Appendix) included specific questions to assess the prevalence of chronic pain with neuropathic characteristics (NP) as well as pain-relieving modalities. Changes made to the pain categories included in the Nuprin Pain Report were the
Inclusion of oro-facial pain, other pain sites not listed, and difficult to describe pain sites. Qualitative aspects on perceived causes of pain, treatment sought and satisfaction with treatment were included in this current survey. According to the 2012 Hong Kong Census, Cantonese was the most common language used in Hong Kong, therefore, only those who could understand and speak Cantonese were included in this survey [14]. Randomization was achieved by using telephone numbers generated using a computer program. Telephone calls were made in the evening on weekdays, between the hours of 18:00 to 22:30, and if more than one adult member of the household was available for interview, the adult with the nearest upcoming birthday was selected for interview.

All the interviews, which required approximately 15 minutes to complete, were performed by trained interviewers from the Public Opinion Program (POP) at the Faculty of Social Sciences (The University of Hong Kong), from May 30th 2013 until June 28th 2013. Verbal consent was obtained before the interview.

Respondents who indicated that they had suffered chronic or recurrent pain for a period of at least three months met the study definition of chronic pain. Respondents who met the chronic pain criteria were asked to name the two most painful sites, and to quantify their pain using the numerical rating scale, (NRS), with a score of 0 meaning no pain, and 10 being the worst pain imaginable. The two most painful sites were considered for further analysis regardless of how many pain sites the respondents actually reported.

The Identification Pain Questionnaire for neuropathic pain has been translated and validated in Chinese and this Chinese version was used to identify respondents who suffered from pain with neuropathic characteristics [11]. The questions were: 1) Did the pain feel like pins and needles 2) Did the pain feel hot/burning 3) Did the pain feel numb 4) Did the pain feel as though you had electric shocks 5) Is the pain made worse with the touch of clothing or bed sheets 6) Is the pain limited to your joints? Respondents would score one mark if they answered ‘yes’ to questions 1 to 5, and would have one mark deducted from their score if they answered ‘yes’ to question 6. A score of three or more indicated the presence of pain with neuropathic characteristics (NP) [11]. This questionnaire was chosen for its ease of use over the telephone.

Sociodemographic data collected included gender, self-reported age, marital status, type of employment, employment status (whether in current employment) and educational level. The type of medical treatment sought, satisfaction with treatment, self-treatment and type of medications used were also recorded.

All analyses were conducted using SPSS (version 21.0.0). Demographic data from respondents who indicated that they had suffered from recurrent or chronic pain for at least three months, and those who were identified as suffering from neuropathic pain, were described using means, standard deviations and percentages, as appropriate. Differences in demographic data between those who were suffering from chronic, non-neuropathic pain and those who were suffering from chronic neuropathic pain were investigated using chi-squared test, or Mann-Whitney U test, as appropriate. Binary logistic regression was then used to investigate which demographic characteristics could predict chronic neuropathic pain. Chi-square test was used to investigate differences between high pain scores, defined as \( \geq 7 \) on the NRS, reported pain sites, the most painful sites, treatment sought both from professionals and self-treatment, medications taken, satisfaction with treatment, self-perceived cause of pain, effect of pain on work, and effect of pain on daily life and sick leave taken between those with and without neuropathic pain. Mann-Whitney U test was used to investigate differences in continuous outcomes, including highest and average pain score and duration of pain suffering between those with and without neuropathic pain characteristics. A p value of 0.05 was regarded as significant.
As was reported in our previous publication, the target sample size was calculated on the presumption of a 20% prevalence rate in chronic pain [10]. The 20% chronic pain prevalence was estimated as having doubled from the 10% prevalence of chronic pain estimated from a population based study collected in 1999 [13]. Based on a 95% confidence level with ±2.5% margin of error, it was calculated that a minimum of 1000 successful interviews was required.

**Results**

**Response rate and characteristics of respondents**

A total of 4858 successful calls were made and 1570 respondents interviewed, corresponding to a response rate of 32.32%. This was lower than the response rate of 47.7% in the 1999 survey, but the current study still reaches the required power. Out of the 1570 respondents interviewed in 2013, 715 (45.54%) were male and 855 (54.46%) were female.

A total of 468 respondents were identified to have chronic pain. Out of these respondents with chronic pain, 80 were identified as having pain with neuropathic characteristics (NP).

The demographic data of those with and without neuropathic pain characteristics are shown in Table 1. There were a significantly larger proportion of females with chronic NP, compared to those with chronic non-NP (80.0% vs 70.0%, p = 0.003). There were no other demographic differences between the two groups, with the exception that a higher proportion of respondents with chronic NP reported being unemployed due to health problems (11.3% vs 1.3%, p = 0.0001). A significantly higher proportion of respondents suffering from chronic NP reported feeling under ‘much more pressure than others’ (20.3% vs 7.4%, p = 0.0012) (Table 1).

**Risk factors for chronic neuropathic pain**

Binary logistic regression identified female sex (odds ratio (OR), (95% C.I), 3.714 (1.585 to 8.707) p = 0.003), working part time (OR (95% C.I), 2.503 (1.034 to 6.061) p = 0.042), being a full-time student (OR (95% C.I), 8.211 (1.300 to 51.852) p = 0.025), and feeling very much under pressure (OR (95% C.I), 4.000 (1.764 to 9.069) p = 0.001) as risk factors for having chronic NP (Table 2).

**Location and number of severe pain sites**

Average pain scores were similar between chronic non-NP and chronic NP respondents. Highest pain score was significantly higher in respondents with chronic NP (7.75 (1.698) [3–10] versus 6.43 (2.141) [1–10] (p = 0.0001) (Table 3). Respondents with chronic NP were more likely to report having pain sites with a pain score of ≥7 (overall p = 0.0001) (Table 3). Average pain scores across different body locations were similar between respondents in the two groups (ranging between 1 to 10 on the NRS). The exception was backache (mean 7.17 vs 5.66, p = 0.015) and joint pain (mean 7.2 vs 5.98, p = 0.018), which were higher in the chronic NP group (Table 4).

Muscle (36.3% vs 21.9%, p = 0.0096) and joint pain (48.8% vs 36.3%, p = 0.0435) were more frequently reported to be the two most painful sites in respondents with chronic NP (Table 4). Respondents with chronic NP suffered from pain for a longer duration of time compared to those with chronic non-NP ((58.0 [3–60] versus 50.3 [0.25–768] months (p = 0.035)) (Table 3).

**Help sought and satisfaction with treatment**

Respondents sought help and received treatment from a number of different professionals. A significantly higher proportion of those with chronic NP consulted a pain specialist (16.3% vs
4.6%, p = 0.0006), a traditional Chinese medical practitioner (40.0% vs 2.63%, p = 0.0203), and a psychiatrist (8.8% vs 2.8%, p = 0.0212) (Table 5). Compared with respondents with chronic NP, significantly more chronic non-NP respondents were prescribed oral medication by healthcare professionals (47.2% vs 60.1%, p = 0.0226), whilst more chronic NP respondents were prescribed cupping (2.4% vs 0.3%, p = 0.0170) (Table 5). Regarding satisfaction with treatment prescribed by health care professionals, significantly fewer respondents with chronic NP felt their treatment was ‘very successful’ (2.9% vs 11.8%, p = 0.0263) (Table 5).

Table 1. Socio-demographic information of respondents with chronic pain with neuropathic characteristics (NP) and chronic non-neuropathic pain (non-NP).

|                          | Chronic NP (n = 80) | Chronic non-NP (n = 388) | p value |
|--------------------------|---------------------|--------------------------|---------|
| Sex                      |                     |                          |         |
| Male                     | 20                  | 30                       | 0.1257  |
| Female                   | 80                  | 70                       | 0.3361  |
| Age [mean (SD)]          | 53.56 (15.4)        | 55.07 (14.39)            | 0.434   |
| Marital status (%)       |                     |                          |         |
| Single                   | 15                  | 16                       | 1       |
| Married                  | 72.5                | 71.4                     | 0.8924  |
| Divorced                 | 5                   | 5.2                      | 1       |
| Widowed                  | 7.5                 | 6.2                      | 0.6201  |
| Not known                | 0                   | 1.3                      |         |
| Educational level (%)    |                     |                          |         |
| Primary school or below  | 30                  | 28.08                    | 0.7856  |
| Secondary school         | 53.75               | 48.2                     | 0.3915  |
| University or above      | 15                  | 23.2                     | 0.1362  |
| Unknown                  | 1.25                | 0.52                     | 0.4309  |
| Occupational status (%)  |                     |                          |         |
| Full time                | 21.3                | 39.7                     | 0.0021  |
| Part time                | 13.8                | 10.1                     | 0.3236  |
| Unemployed               | -                   | 1.8                      |         |
| Homemaker                | 18.8                | 17.5                     | 0.7506  |
| Student                  | 3.8                 | 1.3                      | 0.1413  |
| Part time student        | -                   | 1.2                      |         |
| Retired                  | 31.0                | 27.1                     | 0.4932  |
| Unemployed due to health problems | 11.3 | 1.3 | 0.0001 |
| Occupational type (%)    |                     |                          |         |
| Professional             | 7.5                 | 16.1                     | 0.0549  |
| Administrative and service industry | 20 | 23.64 | 0.5603 |
| Manual labour work       | 7.5                 | 8.57                     | 1       |
| Student                  | 3.75                | 1.82                     | 0.3868  |
| Homemaker                | 18.75               | 17.66                    | 0.8725  |
| Others                   | 42.5                | 32.21                    | 0.0915  |
| Perceived Pressure (%)   |                     |                          |         |
| I'm under much more pressure than others | 20.3 | 7.4 | 0.0012 |
| I'm under more pressure than others | 27.8 | 21.9 | 0.3026 |
| I'm under the same pressure as others | 32.9 | 43 | 0.1038 |
| I'm under less pressure than others | 19 | 27.7 | 0.1227 |

Values in %.

https://doi.org/10.1371/journal.pone.0204054.t001
Oral analgesics and rest were the most commonly self-prescribed treatment modalities for both groups (Table 6). Respondents with chronic NP were significantly more likely to obtain oral analgesic medications (67.5% vs 51.0%, p = 0.0094) and nutritional therapy (43.8% vs 29.6%, p = 0.0176). Significantly fewer chronic NP respondents chose 'no self-help modalities' (3.8% vs 11.6%, p = 0.0410) (Table 6). There was no difference in the level of satisfaction with self-prescribed treatment modalities between the two groups (Table 6). Neither were there any differences between the two groups in the type of pain medications used (Table 7). Significantly fewer chronic NP respondents found oral analgesic medications 'very useful' (3.75% vs 11.8%, p-value 0.0215) (Table 7).

| Characteristic                      | Odds ratio (95% CI) | P value |
|-------------------------------------|---------------------|---------|
| **Age**                             |                     |         |
| 18–29 reference                     |                     |         |
| 30–49                               | 1.719 (0.290 to 10.203) | 0.551   |
| Aged 50 or above                    | 2.432 (0.399 to 14.813) | 0.335   |
| **Gender**                          |                     |         |
| Male reference                      |                     |         |
| Female                              | 3.714 (1.585 to 8.707) | 0.003   |
| **Marital status**                  |                     |         |
| Single reference                    |                     |         |
| Married/cohabit                     | 1.042 (0.404 to 2.689) | 0.932   |
| Divorced/separated                  | 0.350 (0.069 to 1.783) | 0.206   |
| Widowed                             | 1.028 (0.279 to 3.790) | 0.967   |
| **Education level**                 |                     |         |
| None reference                      |                     |         |
| Completed primary education         | 1.119 (0.334 to 3.744) | 0.856   |
| Completed middle school             | 1.358 (0.397 to 4.647) | 0.626   |
| Completed high school               | 1.414 (0.411 to 4.865) | 0.583   |
| Matriculation                       | 0.455 (0.065 to 3.212) | 0.43    |
| Undergraduate                       | 2.205 (0.460 to 10.569) | 0.323   |
| Postgraduate                        | 0.559 (0.122 to 2.560) | 0.454   |
| **Occupation status**               |                     |         |
| Working full time                   |                     |         |
| Working part time                   | 2.503 (1.034 to 6.061) | 0.042   |
| Unemployed                          | 1.498 (-)            | 1       |
| Home-maker                          | 2.396 (0.692 to 8.298) | 0.168   |
| Student (full time)                 | 8.211 (1.300 to 51.852) | 0.025   |
| **Occupation**                      |                     |         |
| Professional                        |                     |         |
| Clerical and service industry       | 1.339 (0.406 to 4.416) | 0.632   |
| Manual                              | 1.618 (0.387 to 6.769) | 0.51    |
| Others                              | 0                   | 1       |
| **Perceived pressure**              |                     |         |
| Feel under less pressure than peers |                     |         |
| Feel somewhat under pressure        | 1.117 (0.565 to 2.207) | 0.751   |
| Feel the same pressure as peers     | 1.855 (0.906 to 3.799) | 0.091   |
| Feel very much under pressure       | 4.000 (1.764 to 9.069) | 0.001   |

https://doi.org/10.1371/journal.pone.0204054.t002

Oral analgesics and rest were the most commonly self-prescribed treatment modalities for both groups (Table 6). Respondents with chronic NP were significantly more likely to obtain oral analgesic medications (67.5% vs 51.0%, p = 0.0094) and nutritional therapy (43.8% vs 29.6%, p = 0.0176). Significantly fewer chronic NP respondents chose 'no self-help modalities’ (3.8% vs 11.6%, p = 0.0410) (Table 6). There was no difference in the level of satisfaction with self-prescribed treatment modalities between the two groups (Table 6). Neither were there any differences between the two groups in the type of pain medications used (Table 7). Significantly fewer chronic NP respondents found oral analgesic medications ‘very useful’ (3.75% vs 11.8%, p-value 0.0215) (Table 7).
Respondent perceived cause of pain and effect on daily life

The most commonly perceived cause of pain for both chronic non-NP and chronic NP was 'too much physical activity' (Table 8). Significantly more respondents with chronic non-NP perceived 'old age' as being the cause of pain (1.3% vs 8.2%, p = 0.0278) (Table 8). Respondents with chronic NP were significantly more likely to perceive 'too much pressure outside of work' to be the cause of their pain (3.8% vs 0.5%, p = 0.0372) (Table 8). With respect to the effect of pain on work, significantly more chronic NP respondents reported 'not being able to work again' (7.4% vs 1.8%, p = 0.0131), and 'not working' (50.0% vs 36.3%, p = 0.0239) compared to chronic non-NP respondents (Table 9). Chronic NP respondents were also significantly less likely to report 'not affect work' (15.0% vs 36.1%, p = 0.0002) (Table 9). In respondents who were working, there was no significant difference between the numbers of days of sick leave taken between the two groups (Table 9). A significantly higher proportion of respondents with

Table 3. Pain characteristics of pain respondents.

| No. of pain sites with NRS score ≥ 7 | Neurpathic Responses in % | Non-neurpathic Responses in % | P value |
|--------------------------------------|---------------------------|-------------------------------|---------|
| 0                                    | 23.8                      | 49.5                          | 0.0001  |
| 1                                    | 41.3                      | 33                            | 0.1579  |
| 2                                    | 33.8                      | 16.2                          | 0.0009  |
| Average pain category                |                           |                               |         |
| (mild, NRS 1 to 3)                   | 2                         | 9                             | 0.0412  |
| (moderate, NRS 4 to 6)               | 22                        | 41                            | 0.0117  |
| (severe, NRS 7 to 10)                | 76                        | 50                            | 0.0041  |
| Highest/Average pain score (NRS)     | Mean (SD) [range]         |                               |         |
| Highest pain score                   | 7.75 (1.698) [3–10]       | 6.43 (2.141) [1–10]           | 0.0001  |
| Average pain score                   | 2.68 (0.612)              | 2.44 (0.78)                   | p > 0.05|
| Pain duration                        |                           |                               |         |
| Duration of pain (in months)         | 58.0 [3–600]              | 50.3 [0.25–768]               | P = 0.035|

Values in % and mean (SD) [range].

NRS = Numerical rating scale

https://doi.org/10.1371/journal.pone.0204054.t003

Table 4. Pain locations and severity of pain.

| Reported pain site | Responses in % | Average Pain score (Mean (SD)) | Reported as being one of two most painful sites (%) |
|--------------------|----------------|--------------------------------|---------------------------------------------------|
|                    | Neurpathic     | Non-neurpathic P value         | Neurpathic Non-neurpathic P value                  | Neurpathic Non-neurpathic P value                  |                                                           |
| Headache           | 65             | 50.8                           | 0.0264                                           | 7.44 (1.90)                                      | 5.63 (2.37)                                               | 0.391                                                   | 16.3                                      | 13.7                                      | 0.5963                                   |
| Backache           | 66.3           | 51.5                           | 0.019                                            | 7.17 (1.93)                                      | 5.66 (1.91)                                               | 0.015                                                   | 27.5                                      | 21.9                                      | 0.3062                                   |
| Muscle pain        | 85             | 60.8                           | 0.0001                                           | 6.74 (2.06)                                      | 5.60 (2.28)                                               | 0.195                                                   | 36.3                                      | 21.9                                      | 0.0096                                   |
| Joint pain         | 85             | 71.9                           | 0.0166                                           | 7.20 (2.20)                                      | 5.98 (2.25)                                               | 0.018                                                   | 48.8                                      | 36.3                                      | 0.0435                                   |
| Toothache          | 41.3           | 25.5                           | 0.0061                                           | 6.83 (1.33)                                      | 5.37 (2.39)                                               | 0.321                                                   | 3.8                                       | 5.4                                       | 0.7809                                   |
| Oral/facial pain   | 27.5           | 15.5                           | 0.0147                                           | 6.25 (3.00)                                      | 5.22 (2.64)                                               | 0.843                                                   | 3.8                                       | 2.1                                       | 0.41                                    |
| Menstrual pain     | 11.3           | 13.1                           | 0.0712                                           | 6.00 (1.00)                                      | 6.73 (1.87)                                               | 0.856                                                   | 3.8                                       | 3.9                                       | 1                                       |
| Stomach ache       | 30             | 29.6                           | 0.0006                                           | 6.40 (1.52)                                      | 4.98 (1.73)                                               | 0.268                                                   | 6.3                                       | 9                                         | 0.515                                    |
| Abdominal          | 42.5           | 32.5                           | 0.0932                                           | 6                                           | 4.70 (2.85)                                               | 0.504                                                   | 1.3                                       | 5.2                                       | 0.229                                    |
| Others             | 6.3            | 7.5                            | 0.8168                                           | 7.00 (3.16)                                      | 7.25 (2.00)                                               | 0.644                                                   | 2.5                                       | 4.1                                       | 0.7504                                   |

Values in % and mean (SD).

https://doi.org/10.1371/journal.pone.0204054.t004
Table 5. Professionals consulted, medication received from professionals and satisfaction with prescribed treatment.

| Professional consulted | Responses in % (Chronic pain with neuropathic characteristics) | Responses in % (Chronic non-neuropathic pain) | P value |
|------------------------|-------------------------------------------------------------|----------------------------------------------|---------|
| General practitioner   | 57.5                                                        | 48.5                                         | 0.1765  |
| Specialist             | 47.5                                                        | 39.4                                         | 0.2116  |
| Chinese medical doctor | 40                                                          | 2.63                                         | 0.0203  |
| Physiotherapist        | 30                                                          | 22.4                                         | 0.151   |
| Bone setter            | 23.8                                                        | 15.2                                         | 0.0703  |
| Pain specialist        | 16.3                                                        | 4.6                                          | 0.0006  |
| Psychiatrist           | 8.8                                                         | 2.8                                          | 0.0212  |
| Not consulted professional | 8.8                                 | 17                                           | 0.0646  |
| Pharmacist             | 3.8                                                         | 2.6                                          | 0.473   |
| Massage therapist      | 0                                                           | 1                                            | -       |
| Others                 | 0                                                           | 0.5                                          | -       |

**Treatment/therapy prescribed**

|                      | Responses in % (Chronic pain with neuropathic characteristics) | Responses in % (Chronic non-neuropathic pain) | P value |
|----------------------|-------------------------------------------------------------|----------------------------------------------|---------|
| Oral medication      | 47.2                                                        | 60.1                                         | 0.0226  |
| Physiotherapy        | 22.4                                                        | 25.8                                         | 0.5814  |
| Acupuncture          | 18.4                                                        | 19.6                                         | 0.8244  |
| Surgery              | 3.2                                                         | 5.7                                          | 1       |
| Topical medication   | 2.4                                                         | 7                                            | 0.4501  |
| Cupping              | 2.4                                                         | 0.3                                          | 0.017   |
| Injected medication  | 1.6                                                         | 1.3                                          | 0.3423  |
| Body check           | 1.6                                                         | 3.4                                          | 1       |
| Psychotherapy        | 0.8                                                         | 1.3                                          | 1       |
| Massage              | 0.8                                                         | 4.4                                          | 0.3338  |
| Dental treatment     | 0                                                           | 1.5                                          | -       |
| Bone setter          | 0                                                           | 0.5                                          | -       |

**Level of satisfaction with treatment**

|                          | Responses in % (Chronic pain with neuropathic characteristics) | Responses in % (Chronic non-neuropathic pain) | P value |
|--------------------------|-------------------------------------------------------------|----------------------------------------------|---------|
| Very successful          | 2.9                                                         | 11.8                                         | 0.0263  |
| Helped somewhat          | 64.3                                                        | 52.1                                         | 0.0833  |
| Didn’t help much         | 21.4                                                        | 22.3                                         | 1       |
| Didn’t help at all       | 10                                                          | 12.8                                         | 0.6863  |
| Medical professional did not suggest any treatment | 1.4 | 1 | 0.564 |

Values in %

https://doi.org/10.1371/journal.pone.0204054.t005

chronic NP reported that their pain ‘affected their daily lives a lot’ (50.0% vs 26.7%, p < 0.0001) (Table 9).

**Discussion**

This is the first population-based study comparing outcomes, impact and health seeking behaviour between individuals experiencing chronic pain with neuropathic characteristics (NP) and chronic non-neuropathic pain (non-NP) in a Chinese population. While several population surveys have been done in Western countries, there is a paucity of data evaluating chronic neuropathic pain in Asian populations. In addition to our report, there is one other recent Asian based population survey evaluating the prevalence and impact of chronic neuropathic pain in a Japanese population [15].

In this study, the highest pain score was significantly greater in chronic NP. Other population studies have also reported higher pain severity amongst chronic pain patients with
neuropathic characteristics [3, 4, 8, 9, 15]. Since the intensity of chronic pain usually fluctuates, we evaluated both the highest and average pain scores. There was no significant difference in average pain scores between the two groups. However, the mean average NRS pain scores for both groups was below 3/10, which corresponds to a low intensity of pain [16], and is unlikely

Table 6. Respondent self-prescribed treatment and satisfaction with self-prescribed treatment.

| Medication type                  | Responses in % (Chronic pain with neuropathic characteristics) | Responses in % (Chronic non-neuropathic pain) | P value |
|----------------------------------|-----------------------------------------------------------------|-----------------------------------------------|---------|
| Oral analgesic                   | 67.5                                                            | 51                                            | 0.0094  |
| Rest                             | 65                                                              | 58.5                                          | 0.3176  |
| Nutritional therapy              | 43.8                                                            | 29.6                                          | 0.0176  |
| Relaxation techniques            | 40                                                              | 34.3                                          | 0.3686  |
| Vitamins                         | 20                                                              | 19.3                                          | 0.8774  |
| Topical medication               | 6.3                                                             | 5.7                                           | 0.7943  |
| No self-help modalities          | 3.8                                                             | 11.6                                          | 0.041   |
| Massage                          | 2.5                                                             | 1.8                                           | 0.655   |
| Exercise                         | 2.5                                                             | 2.8                                           | 1       |
| Nutritional intake               | 2.5                                                             | 1.8                                           | 0.655   |
| Others                           | 2.5                                                             | 3.4                                           | 1       |
| Smoking cessation                | 1.3                                                             | 2.8                                           | 0.7004  |
| Antacids                         | 0                                                               | 1.5                                           | -       |

**Level of satisfaction**

| Very successful                  | 8.1                                                             | 13.9                                          | 0.2488  |
| Helped somewhat                  | 74.3                                                            | 64.2                                          | 0.1051  |
| Didn’t help much                 | 13.5                                                            | 14.2                                          | 1       |
| Didn’t help at all               | 4.1                                                             | 7.7                                           | 0.3263  |

Values in %

https://doi.org/10.1371/journal.pone.0204054.t006

Table 7. Oral analgesic medications taken and satisfaction with oral analgesic medication.

| Medication type                  | Responses in % (Chronic pain with neuropathic characteristics) | Responses in % (Chronic non-neuropathic pain) | P value |
|----------------------------------|-----------------------------------------------------------------|-----------------------------------------------|---------|
| Paracetamol                      | 42.5                                                            | 39.7                                          | 0.7073  |
| Aspirin                          | 10                                                              | 6.7                                           | 0.3416  |
| Anti-rheumatic analgesic         | 8.8                                                             | 6.4                                           | 0.4658  |
| Anti-depressant                  | 6.3                                                             | 2.6                                           | 0.1518  |
| Addictive analgesics (opioids)   | 3.8                                                             | 1                                             | 0.1004  |
| NSAID                            | 1.3                                                             | 2.4                                           | 1       |
| Chinese medicine                 | 0                                                               | 1.3                                           | -       |
| None                             | 41.3                                                            | 40.2                                          | 0.9007  |
| Others                           | 12.6                                                            | 16                                            | 0.72    |

**Level of satisfaction**

| Very useful                      | 3.75                                                            | 13.14                                         | 0.0215  |
| Somewhat useful                  | 42.5                                                            | 36.86                                         | 0.4552  |
| Not very useful                  | 7.5                                                             | 4.38                                          | 0.2314  |
| Not useful at all                | 1.25                                                            | 4.12                                          | 0.2199  |
| Did not answer                   | 45                                                              | 41.49                                         | 0.6595  |

Values in %

https://doi.org/10.1371/journal.pone.0204054.t007
to significantly affect quality of life. Instead, the highest pain scores, which corresponded to moderate to severe pain, is more likely to significantly impact individuals. Duration of pain was significantly longer and number of pain sites with an NRS score over 7/10 was higher in respondents with chronic NP. These finding are also similar to most other population studies [3, 4, 7, 8]. The results here show that chronic NP was associated with worse outcomes in terms of pain intensity and duration amongst Chinese patients in Hong Kong. The reason for this is unclear. It may be due to a difference in underlying pathological process of neuropathic pain compared to non-neuropathic pain. Another explanation is that treatment for chronic neuropathic pain may be less effective, thus resulting in worse outcomes. Apart from pain severity and duration, chronic neuropathic pain has been shown by others to have a greater

Table 8. Self-perceived cause of pain.

| Response | Responses in % (Chronic pain with neuropathic characteristics) | Responses in % (Chronic non-neuropathic pain) | P value |
|----------|---------------------------------------------------------------|------------------------------------------------|--------|
| Too much physical activity | 18.8 | 18.6 | 1 |
| Sickness | 11.3 | 7.2 | 0.2531 |
| Work related injury | 10 | 6.7 | 0.3416 |
| Posture problems | 10 | 8.2 | 0.6598 |
| Weak disposition | 7.5 | 7.7 | 1 |
| Too much pressure at work | 5 | 4.1 | 0.7605 |
| Too much pressure outside of work | 3.8 | 0.5 | 0.0372 |
| Dietary problems | 2.5 | 4.1 | 0.7504 |
| Lack of good quality sleep | 2.5 | 1.3 | 0.3423 |
| Non-work related injury | 1.3 | 2.1 | 1 |
| Environmental problems | 1.3 | 1.8 | 1 |
| Mental pressure | 1.3 | 0.5 | 0.4309 |
| Old age | 1.3 | 8.2 | 0.0278 |
| Overweight | 0 | 1.3 | - |
| Pregnancy | 0 | 0.5 | - |
| Smoking | 0 | 0.5 | - |
| Allergies | 0 | 1 | - |
| Menstrual problems | 0 | 1 | - |
| Fatigue | 0 | 0.3 | - |
| Weather | 0 | 0.8 | - |
| Old injury | 0 | 1.3 | - |
| Lack of exercise | 0 | 1 | - |
| Working long hours | 0 | 0.3 | - |
| Exercise | 0 | 0.8 | - |
| Dental cavities | 0 | 1 | - |
| Wisdom tooth | 0 | 0.3 | - |
| Tooth Structure | 0 | 0.3 | - |
| Medication induced | 0 | 0.3 | - |
| Hunger | 0 | 0.3 | - |
| Miscellaneous reasons | 3.8 | 1.8 | 0.3857 |
| Others (not stated) | 12.1 | 6.4 | 0.2 |
| Don’t know | 7.5 | 9.5 | 0.6745 |
| Did not reply | 0 | 0.3 | - |

Values in %

https://doi.org/10.1371/journal.pone.0204054.t008
negative impact on function, quality of life, sleep, and mental health compared with chronic non-neuropathic pain [3, 9, 15]. Similar to these studies, we found that chronic NP was associated with greater negative impact on work and daily life. This may be due to the greater pain severity associated with chronic NP. In addition, the quality of neuropathic pain itself may also lead to increased impairment. The characteristic of neuropathic pain has been shown to negatively impair physical and mental quality of life independent of pain intensity and duration [3].

A significantly higher proportion of respondents with chronic NP consulted a pain specialist, traditional Chinese medical practitioner, and psychiatrist. Chronic neuropathic pain is difficult to treat, and is associated with more severe and prolonged pain. Therefore individuals with chronic neuropathic pain are probably more likely to be referred to a pain specialist. The percentage of respondents with chronic NP and non-NP who consulted a pain specialist was 16.3% and 4.6%, respectively. This shows that the majority of patients with chronic pain regardless of the type of pain did not receive input from a pain specialist. This may be partly because many of the respondents only had pain of mild intensity, which did not warrant pain specialist consultation. However, 50% of the respondents with chronic NP in this survey reported that their daily life was affected a lot by their pain. Therefore, this low figure more likely reflects a lack of awareness of the availability of pain specialist amongst the general public and other health care professionals. Pain specialists are able to implement a more holistic, bio-

| Effect of pain on work | Responses in % (Chronic pain with neuropathic characteristics) | Responses in % (Chronic non-neuropathic pain) | P value |
|------------------------|---------------------------------------------------------------|-----------------------------------------------|---------|
| Not working            | 50                                                           | 36.3                                          | 0.0239  |
| Not affecting work     | 15                                                           | 36.1                                          | 0.0002  |
| Sick leave             | 13.7                                                         | 8.8                                           | 0.2087  |
| Could not work again   | 7.4                                                          | 1.8                                           | 0.0131  |
| Change in job nature   | 3.7                                                          | 6.7                                           | 0.4468  |
| Others                 | 3.7                                                          | 1                                             | 0.1004  |
| Could not concentrate on work | 1.3                                                  | 1.5                                           | 1       |
| Lower work efficiency  | 1.3                                                          | 2.1                                           | 1       |
| Affect mood at work    | 1.3                                                          | 0.5                                           | 0.4309  |
| Feeling tired at work  | 1.3                                                          | 0.5                                           | 0.4309  |
| Withstand pain         | 1.3                                                          | 0.8                                           | 0.5288  |
| Change of job          | 0                                                            | 0.5                                           | -       |
| Affect ability to function | 0                                                  | 2.1                                           | -       |
| Resting at work        | 0                                                            | 1                                             | -       |
| Did not answer         | 0                                                            | 0.3                                           | -       |

| Number of days taken off work in past year | Responses in % | P value |
|--------------------------------------------|----------------|---------|
| 0                                          | 81             | 81.2    | 1       |
| 1 to 10                                    | 12.7           | 15.6    | 0.838   |
| More than 10                               | 6.3            | 3.2     | 0.747   |

| Effect of pain on daily life | Responses in % | P value |
|------------------------------|----------------|---------|
| Affected a lot               | 50             | 26.7    | 0.0001  |
| Affected somewhat            | 27.5           | 29.5    | 0.788   |
| Affected a little             | 21.3           | 28.8    | 0.2152  |
| Not affected at all           | 1.3            | 15      | 0.0002  |

Values in %
https://doi.org/10.1371/journal.pone.0204054.t009
psychosocial approach, which is particularly important for the management of patients with complex pain problems. Patients with chronic pain, especially those with chronic neuropathic pain, may benefit more with additional pain specialist input. It is important to increase the awareness of other healthcare professionals about the availability and work of pain specialists in order to improve the quality of management for these patients. We also found that a significantly greater proportion of respondents with chronic NP sought help from a traditional Chinese medical practitioner. Traditional Chinese medicine is a popular option amongst Chinese people, and is also becoming more popular in Western countries. Chinese medical formulations such as aconitum may improve neuropathic pain, but overall there is little evidence to support the use of traditional Chinese medicine for neuropathic pain [17]. A recent Cochrane review concluded that there is currently insufficient evidence to support or refute the use of acupuncture for neuropathic pain [18]. Despite the lack of supporting evidence, the popularity of traditional Chinese medicine for chronic NP observed here may be due to cultural influences and the difficulty in effectively reducing neuropathic pain with conventional treatment [1, 19]. Respondents with chronic NP were also more likely to have seen a psychiatrist, suggesting a greater association with psychiatric issues. This appears to agree with results from a French general population survey, where respondents experiencing chronic pain with neuropathic characteristics had worse depression and anxiety scores compared to those without neuropathic characteristics [3]. Pain and depression have a bidirectional relationship, and a higher pain severity is linked with more severe depression [20]. It is possible that higher pain intensity contributed to more severe depression in individuals with chronic NP, resulting in more psychiatric consultations. However, this explanation may be over simplistic, and shared biological mechanisms between neuropathic pain and depression may be present.

Respondents with chronic NP were significantly less likely to be prescribed oral analgesics drugs by health care professionals. This is in contrast to results from other surveys, which showed a higher analgesic prescription rate for chronic NP [3, 15]. In addition, there was no difference in the type of oral analgesic drugs taken between the two groups. Pharmacological treatment of neuropathic pain is different from non-neuropathic pain [1, 19]. However, the most common oral analgesic taken by both group of respondents in this survey was paracetamol. These results suggest that chronic NP in Hong Kong was undertreated, and many patients did not receive the most appropriate analgesics. Pharmacological treatment with oral medication with anti-neuropathic pain medication remains an integral part of neuropathic pain management [1]. Adequate training of health care professionals is needed to increase the prescription of appropriate anti-neuropathic medication for chronic neuropathic pain.

We found that female sex, working part time, being a full-time student, and feeling ‘very much under pressure’ were associated with a significantly higher risk of chronic NP. Female gender and feeling under pressure were also found to be risk factors for chronic pain in our previous report in a Chinese population, and are therefore not specific to chronic NP [10]. Interestingly, being a full-time student and working part time was not a risk factor for having chronic pain in our previous report, suggesting that these may be specific to chronic NP [10].

'Too much physical activity’ was the most commonly perceived cause of pain for both types of pain, and there were no differences between the two groups. Respondents with chronic NP were significantly more likely to perceive ‘too much pressure outside of work’ as a cause for pain. On the other hand, there were no differences between the two groups with regards to ‘too much pressure at work’. Although more respondents with chronic NP thought ‘too much pressure outside of work’ were a cause for pain, the actual figure was only 3.8%. This may be an incidental finding. In an animal study, chronic stress was shown to worsen neuropathic pain [21]. However, if mental pressure was associated specifically with neuropathic pain, then a significant difference should also be observed with ‘too much pressure at work’.
One of the limitations of this study is the low response rate (32.32%). This is lower than the response rate of some other previous population surveys for neuropathic pain, which had response rates of over 50% [9, 15]. This lower response rate should not have affected the power of the study, but may have introduced selection bias. Another limitation is that telephone calls were made in evening hours, and therefore individuals who work at night are likely to be under-represented. People who no longer use their home phones are also likely to be under-represented since only landline phone numbers were used. Similar to other population surveys on neuropathic pain, we have used a validated neuropathic pain questionnaire to identify individuals suffering from pain with neuropathic characteristics. However, a definite diagnosis of neuropathic pain requires a combination of positive history, physical signs, and confirmatory tests, which is not possible in a population survey [1]. Furthermore, while telephone surveys on neuropathic pain have been conducted in the past [22, 23], assessment of neuropathic pain can be difficult via telephone call. Therefore, it is possible that some individuals with true chronic neuropathic pain were missed. Finally, a telephone survey in a large metropolis in Hong Kong may not be fully representative of the whole of China. However, Hong Kong should be similar to other major cities in this rapidly developing country.

In conclusion, we report that individuals with chronic NP have greater pain severity, longer pain duration, and greater negative impact on work and daily activities compared with individuals with chronic non-NP in a Chinese population. This is in agreement with results from surveys in other populations. Individuals with chronic NP were less likely to be satisfied with prescribed treatment and less likely to find oral analgesics effective. They were also less likely to be prescribed oral analgesics by healthcare professionals, and there was no distinction between the two groups in terms of type of oral analgesic taken. Chronic NP is a significant health care burden amongst Chinese individuals in Hong Kong and appears to be inadequately managed. Education for health care professionals and the general public is necessary to correctly identify and treat chronic neuropathic pain as a distinct entity.

Supporting information

S1 Appendix. Full questionnaire survey in English. (DOCX)

S2 Appendix. Full questionnaire survey in Chinese. (DOCX)

Acknowledgments

The authors would like to thank the Public Opinion Programme in the Faculty of Social Science at the University of Hong Kong for conducting the interviews. We would also like to thank Miss Winnie Lee and Dr Robert Chung for statistical expertise.

Author Contributions

Conceptualization: Chi Wai Cheung.

Formal analysis: Stanley Sau Ching Wong, Siu Wai Choi.

Methodology: Siu Wai Choi.

Supervision: Chi Wai Cheung.

Writing – original draft: Stanley Sau Ching Wong.

Writing – review & editing: Stanley Sau Ching Wong, Chi Wai Cheung.
References

1. Colloca L, Ludman T, Bouhasira D, Baron R, Dickenson AH, Yarnitsky D, et al. Neuropathic pain. Nature reviews Disease primers. 2017; 3:17002. Epub 2017/02/17. https://doi.org/10.1038/nrdp.2017.2 PMID: 28205574; PubMed Central PMCID: PMCPMC5371025.

2. van Hecke O, Austin SK, Khan RA, Smith BH, Torrance N. Neuropathic pain in the general population: a systematic review of epidemiological studies. Pain. 2014; 155(4):654–62. Epub 2013/12/03. https://doi.org/10.1016/j.pain.2013.11.014 PMID: 24291734.

3. Attal N, Lanteri-Minet M, Laurent B, Ferconmann J, Bouhassira D. The specific disease burden of neuropathic pain: results of a French nationwide survey. Pain. 2011; 152(12):2836–43. Epub 2011/10/25. https://doi.org/10.1016/j.pain.2011.09.014 PMID: 22019149.

4. Torrance N, Smith BH, Bennett MI, Lee AJ. The epidemiology of chronic pain of predominantly neuropathic origin. Results from a general population survey. The journal of pain: official journal of the American Pain Society. 2006; 7(4):281–9. Epub 2006/04/19. https://doi.org/10.1016/j.jpain.2005.11.008 PMID: 16618472.

5. Dworkin RH, Backonja M, Rowbotham MC, Allen RR, Argoff CR, Bennett GJ, et al. Advances in neuropathic pain: diagnosis, mechanisms, and treatment recommendations. Archives of neurology. 2003; 60(11):1524–34. Epub 2003/11/19. https://doi.org/10.1001/archneur.60.11.1524 PMID: 14623723.

6. Costigan M, Scholz J, Woolf CJ. Neuropathic pain: a maladaptive response of the nervous system to damage. Annual review of neuroscience. 2009; 32:1–32. Epub 2009/04/30. https://doi.org/10.1146/annurev.neuro.051508.135531 PMID: 19400724; PubMed Central PMCID: PMCPMC2768555.

7. Hariff G, Amine M, Ait Ouazar M, Boujemaoui A, Ouilki I, Rekkab I, et al. Prevalence of chronic pain with neuropathic characteristics in the Moroccan general population: a national survey. Pain medicine (Malden, Mass). 2013; 14(2):287–92. Epub 2012/12/18. https://doi.org/10.1111/pme.12009 PMID: 23241023.

8. Bouhassira D, Lanteri-Minet M, Attal N, Laurent B, Touboul C. Prevalence of chronic pain with neuropathic characteristics in the general population. Pain. 2008; 136(3):380–7. Epub 2007/09/25. https://doi.org/10.1016/j.pain.2007.08.013 PMID: 17885574.

9. Smith BH, Torrance N, Bennett MI, Lee AJ. Health and quality of life associated with chronic pain of predominantly neuropathic origin in the community. The Clinical journal of pain. 2007; 23(2):143–9. Epub 2007/01/24. https://doi.org/10.1097/AJP.0b013e3180319978 PMID: 17237663.

10. Cheung CW, Choi SW, Wong SSC, Lee Y, Irwin MG. Changes in Prevalence, Outcomes, and Help-seeking Behavior of Chronic Pain in an Aging Population Over the Last Decade. Pain practice: the official journal of World Institute of Pain. 2017; 17(5):643–54. Epub 2016/10/14. https://doi.org/10.1111/papr.12496 PMID: 27735140.

11. Chan BK, Tam LK, Wat CY, Chung YF, Tsui SL, Cheung CW. Opioids in chronic non-cancer pain. Expert opinion on pharmacotherapy. 2011; 12(5):705–20. Epub 2011/01/25. https://doi.org/10.1517/14656662.2011.536335 PMID: 21254859.

12. Sternbach RA. Survey of Pain in the United States: The Nuprin Pain Report. The Clinical journal of pain. 1986; 2(1):49–53. 000025 08-1986020 10-00008.

13. Ng KF, Tsui SL, Chan WS. Prevalence of common chronic pain in Hong Kong adults. The Clinical journal of pain. 2002; 18(5):275–81. Epub 2002/09/10. PMID: 12218497.

14. CS B. Official Languages Division 2015. Available from: http://www.csb.gov.hk/english/aboutus/org/socard/1470.html.

15. Inoue S, Taguchi T, Yamashita T, Nakamura M, Ushida T. The prevalence and impact of chronic neuropathic pain on daily and social life: A nationwide study in a Japanese population. European journal of pain (London, England). 2017; 21(4):727–37. Epub 2017/01/21. https://doi.org/10.1002/ejp.977 PMID: 28107599; PubMed Central PMCID: PMCPMC5363338.

16. Breivik H, Borgegovink PC, Allen SM, Rosseland LA, Romundstad L, Hals EK, et al. Assessment of pain. British journal of anaesthesia. 2006; 96(1):99–108. Epub 2006/01/05. https://doi.org/10.1093/bja/aen103 PMID: 16487245.

17. Feng L, Liu WK, Deng L, Tian JX, Tong XL. Clinical efficacy of aconitum-containing traditional Chinese medicine for diabetic peripheral neuropathic pain. The American journal of Chinese medicine. 2014; 42(1):109–17. Epub 2014/01/29. https://doi.org/10.1142/S0192415X14500074 PMID: 24467538.

18. Ju ZY, Wang K, Cui HS, Yao Y, Liu SM, Zhou J, et al. Acupuncture for neuropathic pain in adults. The Cochrane database of systematic reviews. 2017; 12:Cd012057. Epub 2017/12/03. https://doi.org/10.1002/14651858.CD012057.pub2 PMID: 29197180.

19. Finnerup NB, Attal N, Haroutontian S, McNicol E, Baron R, Dworkin RH, et al. Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis. The Lancet Neurology. 2015; 14
20. Kroenke K, Wu J, Bair MJ, Krebs EE, Damush TM, Tu W. Reciprocal relationship between pain and depression: a 12-month longitudinal analysis in primary care. The journal of pain: official journal of the American Pain Society. 2011; 12(9):964–73. Epub 2011/06/18. https://doi.org/10.1016/j.jpain.2011.03.008 PMID: 21680251; PubMed Central PMCID: PMCPMC3222454.

21. Li MJ, Liu LY, Chen L, Cai J, Wan Y, Xing GG. Chronic stress exacerbates neuropathic pain via the integration of stress-affect-related information with nociceptive information in the central nucleus of the amygdala. Pain. 2017; 158(4):717–39. Epub 2017/02/23. https://doi.org/10.1097/j.pain.0000000000000827 PMID: 28225710.

22. Zghoul N, Ross EL, Edwards RR, Ahmed A, Jamison RN. Prevalence of chronic pain with neuropathic characteristics: a randomized telephone survey among medical center patients in Kuwait. Journal of pain research. 2017; 10:679–87. Epub 2017/04/25. https://doi.org/10.2147/JPR.S123966 PMID: 28435312; PubMed Central PMCID: PMCPMC5388267.

23. VanDenKerkhof EG, Mann EG, Torrance N, Smith BH, Johnson A, Gilron I. An Epidemiological Study of Neuropathic Pain Symptoms in Canadian Adults. Pain research & management. 2016; 2016:9815750. Epub 2016/07/23. https://doi.org/10.1155/2016/9815750 PMID: 27445636; PubMed Central PMCID: PMCPMC4904601.