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Painful Diabetic Peripheral Neuropathy Study of Chinese OutPatiEnts (PDN-SCOPE): protocol for a multicentre cross-sectional registry study of clinical characteristics and treatment in China

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ABSTRACT

Introduction Painful diabetic peripheral neuropathy (PDN) is a growing public health problem in China. Despite recent progress in treatment, there has been no nationwide study evaluating current medical practices and compliance with treatment guidelines. The primary aims of this study are to investigate the clinical characteristics and treatment practices for PDN and associated anxiety and depression in China.

Methods and analysis Painful Diabetic Peripheral Neuropathy Study of Chinese OutPatiEnts is a cross-sectional, multicentre registry study with a target sample size of approximately 1500 people experiencing PDN. People with PDN will be treated according to current guidelines and local practices. The demographics, medical histories, Visual Analogue Scale pain scores, Patient Health Questionnaire-9 results, Generalised Anxiety Disorder-7 scores and therapies will be recorded to evaluate clinical characteristics of PDN and current treatment practices for pain, anxiety and depression.

Ethics and dissemination Ethical approval has been obtained from the Peking University Third Hospital Medical Science Research Ethics Committee (2018–182).The results of this study will be disseminated through peer-reviewed publications and scientific presentations.

Trial registration number NCT03520608

Strengths and limitations of this study

- The Painful Diabetic Peripheral Neuropathy Study of Chinese OutPatiEnts will be the first nationwide study in China to examine the discordance between real world clinical practices and treatment guidelines.
- The study will enrol over 1500 people with PDN from over 50 centres' outpatient departments covering all regions of China.
- Research participants will be recruited using a multilevel sampling method.
- Douleur Neuropathique 4 Questionnaire, Visual Analogue Scale, the nine-item Patient Health Questionnaire and seven-item Generalized Anxiety Disorder Scale will be used for assessing the severity of PDN and mental health problems (depression and anxiety).
- Demographic and clinical information will be collected by standardised electronic case report forms and maintained by an online electronic data capture system.

INTRODUCTION

Diabetic peripheral neuropathy (DPN) is one of the most common and debilitating complications of chronic diabetes.[1 2] Neuropathic pain is a common disabling symptom. As a subjective experience, there is marked variation in the description of symptoms among patients with similar pathology.

The reported prevalence of painful diabetic peripheral neuropathy (PDN) ranges widely, from 3.3% to 65.3%, because of differences in study design, diagnostic criteria and sampling.[3–10] A South-East Asia PDN epidemiological survey in 2016 found low screening rates, reflecting doctors' poor attention to pain relief.[11] Therefore, PDN may be under-reported in China, resulting in many patients experiencing chronic pain that impairs mental health, work and general quality of life (QoL).[12] Indeed, PDN has a negative impact on physical and mental QoL compared with painless diabetic neuropathy.[2 12 13] For instance, PDN is frequently comorbid with depression and anxiety. DPN pain is a stronger predictor of depression than other diabetic complications and comorbidities. A recent report also found that PDN is an independent risk factor for depression, with 44% of patients with PDN showing symptoms of depression compared with 26% of patients with painless DPN and 10% of patients with other diabetes mellitus (DM).[14] Furthermore, pain reduction through appropriate treatment results in improved QoL,[15]

suggesting that PDN symptom control can reduce depression incidence and severity. Reciprocally, mental health deficits associated with PDN may influence the organic disease, as effective antidepressant treatment is associated with improved glycaemic control.[16] Thus, current guidelines recommend routine depression screening for adult with diabetes.[17]

DPN also carries a considerable economic burden for both the individual and the healthcare system.[18] Despite the potential physical, emotional and socioeconomic impacts of PDN, no recent study has evaluated the pattern of current medical practices at the national level in China. Such periodic surveys are crucial in view of changes in demographics (population ageing) and lifestyle. Although numerous pharmacological agents have been proven effective for treatment of PDN and associated mood disorders,[19] there remain substantial unmet needs in the management of symptoms.[20] We speculate that there is a substantial gap between guideline compliance and actual clinical practices in China. Therefore, we have designed a large, nationwide hospital-based study for PDN in China (Painful Diabetic Peripheral Neuropathy Study of Chinese OutPatiEnts [PDN-SCOPE]) to evaluate the current clinical characteristics and treatments for management of PDN symptoms including pain as well as the incidence, severity and treatment status of associated anxiety and depression.

METHODS

Study design

PDN-SCOPE will be a multicentre cross-sectional survey involving more than 50 hospitals distributed over 23 provinces, 5 autonomous regions and 4 municipalities (all regions except for Taiwan, Hong Kong and Macau). All participating medical institutions will enrol research participants.

Subject recruitment has been conducted since 14 June 2018. The study protocol will be independently approved by the ethics committees of all participating hospitals. Demographic data, clinical information, pain severity, anxiety severity, depression severity and therapeutic drugs taken will be recorded to identify the distinct features of PDN in China. Discordance with current treatment guidelines and differences in patient characteristics among institutions will be analysed.

Sample size estimation

In China, there are great differences in medical resources, clinical diagnosis and treatment levels between different regions, which will lead to differences in the consistency of treatment conditions with consensus or guidelines in different institutions.

The study will describe actual outpatient PDN treatment and inappropriate drug use (defined as contradiction of existing guidelines). We presume that, in 13 of the 51 institutions (about 25% of all institutions), there was inconsistency between clinical treatment and guideline recommendations. We also assume that about 30% outpatients in those 13 institutions were considered to have received treatment that did not comply with the guidelines-recommended first-line medications. In such a condition, to acquire a 5% accurate inconformity rate, which means a 95% CI between 25% and 35% (bilateral width of 10%), 341 patients' data should be collected from these 13 hospitals. Thus, the total sample size required is 341 divided by 0.25, that is 1364. Considering possible centre dropouts and differences in recording compliance among centres, we have increased the required sample size by 10%. Thus, approximately 1500 Chinese patients with PDN will be recruited. The required sample size is calculated by PASS V.14.

Recruit selection

Research subjects will be recruited using a multilevel sampling method.

The first level is the selection of medical institutions (51) covering all provinces and regions by a convenience sampling method. Centres will be selected from regionally representative hospitals which will be willing to participate according to the hospital's size and the participants' degree of adaptability.

The second level is the selection at the department level (neurology and/or endocrine departments) by a convenience sampling method according to participants' degree of adaptability.

The third level is the sampling of outpatient clinicians. One to three doctors will be selected from each department. During these clinicians' service working days, the fourth level sampling was made which sampled half to three clinic day weekly for each clinician.

For the fourth level of sampling, all patients who meet the criteria will be enrolled. As there is no exact PDN outpatients' figure, data collection will be conducted by phase adjustment during recruitment.

The similar number of each centre's sampling working day is premise to ensure sample institution's population representativeness. In order to ensure that a similar number of working days are sampled from each centre, the enrolment tasks are divided into three stages and adjusted according to the progress of the recruitment in the initial step by step stages. The first stage is the run-in period, when patients are enrolled at a slower speed. It will last 1–2 weeks for the first stage, during which, each centre will choose 1.5 clinic days per week, including one neurology clinic day and 0.5 endocrinology clinic day. The subsequent actual sampling working days required will be estimated, based on the information quarried in the first stage, which is mainly the information about the average daily quantity of eligible patients for each institution. In the second stage, the collection speed is adjusted to three clinic days per week, including two neurology clinic days and one endocrinology clinic day. In the third stage, till 1200 cases have been collected, the subsequent clinic day arrangements will be adjusted according to the actual completion quantity of each centre, thus ensuring clinic

day balance. The centres with more enrolment outpatient days will slow down recruitment speed or finish earlier. The number of enrolment outpatient days will increase in hospitals that do not meet the schedule.

Recruitment of practices

Packages containing the information statement, research project protocol consent form will be mailed to all centres. Every centre will receive assignments according to the predetermined institutional recruitment procedure. All local doctors will receive the protocol and training from field workers or through network conferences. Local doctors will be asked to complete an electronic case report form (eCRF) assessing the pain severity and emotional status of each participant as well as relevant risk factors. In order to promote active involvement of participants and local researchers, the survey was designed to be completed in less than 10 min. After explanation of study protocols and goals, signed informed consent will be obtained from all enrolled patients. The required information collection will be conducted by researchers and/or research assistants. All data will be collected using eCRFs and an online electronic data capture (EDC) system. Contributors to the registry will be responsible for data entry and standardisation. We will share the identified data with others when the research is complete and the results are to be published.

Piloting of procedures

A specialist team will be responsible for data collection ensuring confidentiality of information through electronic monitoring. This will be done to ensure standardisation of study methods across sites. Raw data will be codified as described below and entered into the database. The database will be closely monitored for missing and redundant data. Logical checks and numerical range verification will be conducted both automatically and manually. Data management processes include data entry, data submission, query generation, query reply by the corresponding researcher, feedback and query resolution. Medical coding will be in accordance with the Medical Dictionary for Regulatory Activities and WHO Drug Dictionary Enhanced.

Participants

Eligibility

Inclusion criteria

- Eighteen years of age or older.
- Definite diagnosis of type 1 or type 2 diabetes.
- Symptoms, signs and/or electrophysiological evidence of DPN.
- Complaints of spontaneous pain (continuous or intermittent needle pricking, electric shock-like pain, burning pain, etc) or induced pain (hypersensitivity, sensory inversion).
- Pain lasting for at least 3 months.
- Signed informed consent.

Exclusion criteria

Non-diabetic neuropathic pain, non-neuropathic pain or mixed pain, such as from neck/lumbar spine, degenerative disease, arthritis, nerve root compression, paraneoplastic syndrome, cerebrovascular disease, spinal cord diseases or other peripheral neuropathies (immune, toxic and nutritional neuropathies, etc).

Dementia, substance abuse or other conditions seriously impairing cognitive and communication skills.

Recruitment procedure

Patient and public involvement

There were no patients involved in research design and contribution towards development of research questions or outcomes. The scales used in this research are self-reported and will be done by the participants themselves. Where there are difficulties in reading or understanding, researchers or research assistants will read the questions for them and help complete the questionnaires. In all other aspects no patients will be involved in the recruitment and conduct of the study. Additionally, a summary of findings will be provided to all the participating researchers for popularization.

Variables

Demographics

Participants' age, gender, height, weight, body mass index, smoking and drinking history, as well as date of birth, ethnicity, marital status, outpatient clinic card code, telephone and mobile numbers, and address will be recorded.

Diabetes mellitus-related information

Researchers will collect as much information as possible about DM and DPN, including durations, types and diagnoses dates. Laboratory indexes to be recorded are fasting plasma glucose, 2-hour postprandial plasma glucose and glycosylated haemoglobin (HbA1c) levels.

Related medical history of chronic diseases

Participants will be asked whether they have ever been diagnosed with hypertension, hypercholesterolaemia, hypertriglyceridaemia, nephropathy, retinopathy, cardiovascular disease, cerebral vascular disease, peripheral vascular disease, depression or anxiety. If there are definite comorbid diseases, the researchers will record the diagnosis information.

Known risk factors for PDN will be recorded, including diabetes type, cerebral vascular disorder, diabetes duration more than 10 years, hypertension, nephropathy, retinopathy, severity of neuropathy, depression, anxiety, glycosuria, hyperglycaemia, obesity, HbA1C, high-density lipoprotein cholesterol (HDL-C), triglycerides and several gene polymorphisms.[21] The electronic health risk assessment will be programmed to allow tailoring to each participant's potential and existing risk factors, such as other medical histories.

Neuropathic pain assessment

Douleur Neuropathique 4 Questionnaire

The Douleur Neuropathique 4 (DN4) Questionnaire will be used to evaluate the severity of neuropathic symptoms.[22] The DN4 includes seven self-sensory evaluation scale items and three clinical examination manifestation items. DN4 is successfully proven and has been validated and translated in multiple languages. The reported sensitivity and specificity were similar for samples of definite neuropathic and non-neuropathic pain cases.[22–29] DN4 has been verified as a screening tool for neuropathic pain in painful diabetic polyneuropathy.[30] The assessment process is simple, with a total score of ≥4 indicative of neuropathic pain.

Visual Analogue Scale/Score

The Visual Analogue Scale (VAS) is a subjective psychometric response scale used to measure distinct behavioural or physiological phenomena based on linear numerical gradient or yes/no alternatives. For the pain VAS, subjects will mark pain severity on a 10 cm line with '0' at one end indicating pain-free and '10' on the other end indicating worst pain imaginable.[31] Generally, a mark below 3 indicates that the patient is suffering from mild pain affecting sleep but that can be endured, whereas 7–10 indicates intense pain affecting appetite and sleep.

Current depression status

Depression will be assessed using the nine-item Patient Health Questionnaire (PHQ-9).[32] This tool has been used in the primary care setting, and the scores show strong correlation with functional status (SF)−20 scores.[33] Participants will be considered at risk of depression if they have a PHQ-9 score of ≥10, with better diagnostic performance for screening purposes.[34]

Current anxiety status

The 7-item Generalized Anxiety Disorder Scale (GAD-7) has shown good reliability, as well as criterion, construct, factorial and procedural validity. A cut-off point of 5 with that optimised sensitivity (89%) and specificity (82%) was identified. Good agreement between self-report and interviewer-administered versions of the scale has also been reported.[35]

Medications

All medications will be recorded by researchers in eCRFs and uploaded to the EDC system. The pharmacological agents taken at highest dosage and longest duration, including discontinued drugs, will be recorded.

Statistical considerations

The characteristics of consenting and non-consenting people with PDN will be compared to assess consent bias in order to prove this population's representativeness more accurately.

Categorical variables including consent rate (number, percentage and 95% CI) will be calculated and compared by Pearson's χ^2 test. Age, medical history and other continuous data will be expressed as mean and SD. Gender, ethnicity, marital status, type of diabetes (type I or type II), prevalence of comorbidities, pain phenotype and other categorical data will be expressed as frequency and percentage. On the basis of the normality test, VAS scores, PHQ-9 scores and GAD-7 scores will be expressed as mean and SD or median with the 25–75th centile ranges as appropriate. The distributions of pain, anxiety and depression severity will be recorded and compared among demographic and clinical subgroups. The types and distribution of drugs used for pain relief will be described. The proportion of patients taking antidepressant/antianxiety medication drugs (%), and the specific antidepressants/anxiolytics used will be recorded.

DISCUSSION

The PDN-SCOPE Study will gather one of the largest Chinese data sets on the clinical characteristics of PDN and medications used in the outpatient setting. The design will minimise the time burden placed on individual researchers in order to increase recruitment rates. PDN-SCOPE will be one of the first studies to compare practice realities with guidelines and thus provide important information to inform future quality of care initiatives.

This study is novel in that a mobile application or website-based data collection system can be alternatively selected by researchers. With touch screen technology becoming more accessible in the form of computer tablets, iPads and smartphones, there is likely to be increased potential for use of these technologies in health assessment.

Limitations

PDN-SCOPE uses an observational design and so will not provide information on causal relationships. Biases are common in cross-section registry studies. Participants may be less homogeneous in clinical characteristics than the general population. As in all such studies, data may be unavailable or missing. Further, combined treatments can vary widely, so the numbers in specific treatment groups may be small. Finally, since the research principle is not to disturb clinical practice, all recruitment procedures and details will be preserved at each centre.

CONCLUSIONS

Chinese patients with PDN have demonstrated unique clinical characteristics, so a large-scale survey is warranted to identify potential reasons related to local treatment practices. Further, we expect that there is a gap between treatment used in daily clinical practice and guideline standards, at least at certain institutions. A detailed description of the clinical characteristics, demographics, comorbidities, risk factors and treatment profiles of patients with PDN is crucial for the development of more effective pain management strategies. It is expected that the results of PDN-SCOPE will be used to guide clinical

practice for PDN pain and associated anxiety and depression treatment in China.

So far 26 participating hospitals have acquired ethical approval. Privacy of information is guaranteed by specific information collection (address limited to street, without house number) and shielding of names in the database. Participants will be able to withdraw from the study at any time even they are receiving or complete survey.

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Contributors YJZ drafted the manuscript and designed the final protocol; NL and YMZ designed the recruit sampling method and provided expert statistical advice. DSF conceived the study and designed the original study protocol. All authors read and approved the final manuscript.

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Competing interests None declared.

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