Neuropathic pain screening for diabetes mellitus: a conceptual analysis

Rastreamento de dor neuropática para diabetes mellitus: uma análise conceitual

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ABSTRACT

BACKGROUND AND OBJECTIVES: The assessment and early diagnosis of neuropathic pain associated to Peripheral Diabetic Neuropathy has been a challenge in clinical practice, requiring the systematization of risk tracking through the identification of specific instruments to guide treatment. The objective of this study was to identify specific instruments for tracking neuropathic pain and Peripheral Diabetic Neuropathy in order to build a protocol.

CONTENTS: Integrative review using the indexed databases Scielo, Cochrane and Pubmed between 2007 and 2020, identifying the most used validated instruments in high predictive value for tracking Peripheral Diabetic Neuropathy and neuropathic pain, building a specific protocol directing clinical treatment. 44 selected articles pointed out 14 different instruments for screening of Peripheral Diabetic Neuropathy and neuropathic pain, most prevalent being: the Screening Instrument for Assessment of Peripheral Diabetic Neuropathy (MNSI), Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) and Douleur Neuropathique (DN4) for clinical assessment of neuropathic pain and Brief Pain Inventory (BPI) for numerical pain assessment, highlighted by their predictive values above 80%.

CONCLUSION: Such instruments enable the development of a neuropathic pain screening protocol that will assist in the early diagnosis of this complication in Diabetes, directing clinical and physiotherapeutic treatment.

Keywords: Diabetes mellitus, Diabetic neuropathies, Pain measurement, Physical therapy specialty.

RESUMO

JUSTIFICATIVA E OBJETIVOS: A avaliação e o diagnóstico precoce da dor neuropática associada à neuropatia diabética periférica tem sido um desafio na prática clínica, sendo necessária a sistematização de um rastreamento de risco por meio da identificação de instrumentos específicos que direcionem o tratamento. O objetivo deste estudo foi identificar instrumentos específicos para rastreamento da dor neuropática e Neuropatia Diabética Periférica para construção de um protocolo.

CONTEÚDO: Revisão integrativa utilizando as bases de dados indexadas Scielo, Cochrane e Pubmed entre 2007 e 2020, identificando os instrumentos validados mais utilizados com alto valor preditivo para rastreamento da Neuropatia Diabética Periférica e dor neuropática, construindo um protocolo específico direcionando o tratamento clínico. Quarenta e quatro artigos selecionados apontaram 14 diferentes instrumentos para o rastreamento da Neuropatia Diabética Periférica e dor neuropática, entre os mais prevalentes: o Instrumento de Rastreio para classificação da Neuropatia Diabética Periférica (MNSI), *Leeds Assessment of Neuropathic Symptoms and Signs* (LANSS) e *Douleur Neuropathique* (DN4) para avaliação clínica da dor neuropática e *Brief Pain Inventory* (BPI) para avaliação numérica da dor, destacados por seus valores preditivos acima de 80%.

CONCLUSÃO: Tais instrumentos possibilitaram o desenvolvimento de um protocolo de rastreamento da dor neuropática que auxiliará no diagnóstico precoce desta complicação na diabetes, direcionando o tratamento clínico e fisioterapêutico.

Descritores: Diabetes *mellitus*, Fisioterapia, Medição da dor, Neuropatia diabética.

INTRODUCTION

Diabetes Mellitus (DM) is a relevant public health problem in Brazil and worldwide due to the magnitude of the number of individuals affected with type 2 DM (DM2), which corresponds to 90 to 95% of those affected by the disease. In Brazil, the estimated prevalence of DM2 in the population is 8 to 9% in the 20 to 79 age group[1-3], with the highest rates in the country's Capitals. According to the IDF-Atlas of Diabetes International, in 2017[4], the projection of Brazilians with DM for 2045 will be 42 million, that is, 15% of the Brazilian population will develop DM[1-6].

DM is a chronic disease characterized by a metabolic disorder presenting several clinical manifestations caused by defects in the action of insulin and consequent uncontrolled glycemia, thus, the increase in serum glycemic concentration can cause numerous changes in the

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different systems of the human organism, including the peripheral nervous system[1,5,6]. The long-term degeneration of sensory fibers in the axons determines the clinical alteration named Diabetic Neuropathy (DN), whose most common and prevalent form is Distal Symmetric Polyneuropathy (DSP) affecting 17% of people with over five years of diagnosis of DM and 42 to 65% after 10 years of illness. Neuropathic pain associated with DM has a prevalence of approximately 20% among people who have already developed Peripheral Diabetic Neuropathy (PDN), resulting from the degeneration of fine sensitive fibers of type A-Delta and C caused by chronic hyperglycemia, oxidative stress and inflammation[7-10].

In addition to neuropathic pain, alterations in sensitivity, balance, decreased mobility, muscle strength, irritability, depression, anxiety and changes in sleep quality are clinically associated with DSP; a set of symptoms that causes loss of productivity over the course of daily and professional activities over time, resulting in damage to sociability and quality of life[11-14].

The screening for the diagnosis of DN and neuropathic pain in clinical practice is complex, there is no golden standard protocol, that is, a specific protocol, for pain assessment in DM. Currently, physiotherapeutic evaluation is performed through clinical history, neurological exams and physical examination that make it possible to differentiate the type and etiology of pain, as well as characteristics of neuropathy. The evaluation is aimed at quantifying, through validated instruments, the presence of some of the alterations: tactile, thermal, painful, vibratory, pressure, tendon reflexes, hyperalgesia, allodynia and periods of worsening of nocturnal symptoms[13,15,16].

In order to systematize the screening of PDN and neuropathic pain, there is a need to identify validated instruments for screening DN and neuropathic pain with precision, and then to make an assessment protocol of neuropathic pain in people with DM.

METHODS

Integrative literature review whose objective is to gather and synthesize the results of research on a particular topic or subject, systematically and orderly, contributing to a complete understanding of the subject to be studied[17], as a methodology that provides the synthesis of knowledge and the incorporation of applicability results of significant studies into practice.

This study's execution was guided by the following steps: 1) identification of the theme and selection of the hypothesis or research question; 2) establishment of criteria for inclusion and exclusion of studies, as well as researching literature; 3) definition of the information to be extracted from the selected researches; 4) categorization and evaluation of the included studies; 5) interpretation of results and 6) synthesis of the evidenced knowledge[18,19]. In order to operationalize this integrative review, the guiding question is: "what assessment instruments can be used to screen DN and neuropathic pain in order to create a protocol to guide the physiotherapeutic treatment of people with DM"?

Inclusion criteria were defined by selecting articles published in Portuguese and English; full articles that portrayed the theme about integrative review on instruments for the assessment and screening of DN and neuropathic pain, published and indexed in the following databases: National Library of Medicine of the USA (Pubmed), Scielo and Cochrane Library, between 2007 and 2020.

The exclusion criteria were based on publications in the form of theses, dissertations, monographs, books, any sort of reviews, experience reports, articles that depicted neuropathic pain not related to DM or that were related to DM in experimental animals.

The articles were collected and based on sources that are specialized in biological and health sciences, using the following descriptors and their combinations: type 2 DM, diabetic neuropathies and pain assessment, in Portuguese and English, with the exact term and associated descriptors. The terms were selected in the Health Sciences Descriptors (DeCS) and in the Subject Headings Section Department (MESH), combined by the Boolean operators AND and OR. The figure 1 shows the articles selected and included in this research.

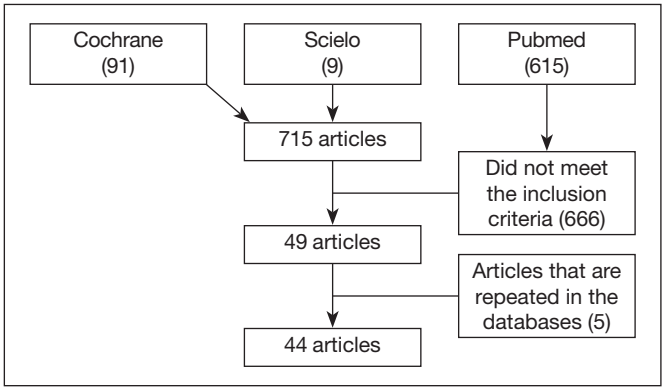

Figure 1. Flowchart of selection and identification of studies

Articles from the 3 selected databases and the number of articles that fall within the inclusion and exclusion criteria of the study are present. To extract the considerable information for this study, the content was collected and processed in four phases: recognition, selection, critical or reflective and interpretive reading. A title and summary analysis was performed to confirm the inclusion within the described criteria and later, in the collection phase, the data was organized, analyzed, and interpreted according to each identified theme. For this purpose, a data collection instrument was developed by the authors, based on Joanna Data extraction from Briggs Institute (JBI)[20], and adapted to the research objectives with the following items: identification of the original article, methodological characteristics, level of evidence, types of diagnosis and main results and conclusions.

The data were extracted from the studies included in the corpus by one of the authors and the critical evaluation was carried out by two reviewers before inclusion in the review, none of which was aware of the results obtained by each author until the end of this process. In the absence of consensus among the reviewers, the differences that arose were resolved through discussion with the inclusion of an experienced third reviewer.

The results were presented in a descriptive way, allowing the reader to evaluate the applicability of the elaborated review, providing bases for clinical decision on the tracking of neuropathic pain and neuropathy in people with DM, as well as the identification of knowledge gaps, such as development and improvement of future research.

After a thorough analysis of the articles described above, and level of evidence classification according to the Oxford Centre for Evi-

dence-based Medicine[21], the reviewers selected the data obtained from validated instruments with higher prevalence and high predictive value in review, validation and intervention studies for the construction of a neuropathic pain screening protocol in DM 2.

RESULTS

Of the 44 articles included in the integrative review, 43 (97.72%) articles were published in the English language and only one (2.27%) in Portuguese. Of the 13 years of research evaluated, most articles were published in 2014 (7 or 15.9%), with a similar distribution of publications in the other years. The largest concentration of published studies on the subject was on the American continent: 22 (50%), followed by 12 (27.3%) on the European continent, 7 (15.9%) on the Asian continent and the remainder on the Australian and African continent.

Regarding each selected research study plan, 22 (50%) were clinical trials, followed by 14 (31.82%) cross-sectional studies and the others, in a smaller proportion, were systematic and multicentric studies. According to the classification in level of evidence, 22 (50%) presented the classification 1B (Figure 1), referring to randomized controlled clinical trials conducted in a clinical study center, with a small confidence interval and with reference to diagnostic criteria; pointing out the importance of the instrument to obtain new treatments results in the area. As for the listed categories, in the studies related to neuropathic pain, the peculiarities about DN and screening instruments in DM were analyzed. After that, it was possible to separate the articles and make a synthesis of the studies that were identified and included in this integrative review, as well as the main results of all screening instruments for DN and pain that can be seen in table 1.

Table 1. Summary of selected studies on the evaluation of DN and Neuropathic Pain from 2007 to 2020, according to bibliographic bases and level of evidence, 2020

Authors	Objectives	Study design and level of evidence (Oxford Centre for Evidence-based Medicine)	Results and conclusion
Sertbas et al.[22] USA	Investigate fluorescence as a treatment method based on the diagnosis of DN and neuropathic pain in DM.	Randomized clinical trial. 160 patients. Pain was assessed by DN4 to investigate the effectiveness of treatment. 1B	DN4 has very effectively detected fluorescence treatment for DN and neuropathic pain.
Alexander et al.[23] Germany	To evaluate the treatment of neuropathic pain with pregabalin using pain scales.	Review of clinical studies. 1766patients. Pain evaluated by BPI and DN4 with pregabalin treatment. 1B	30 to 50% of people evaluated with BPI and DN4 achieved improvement with pregabalin.
Selvarajah et al.[24] Europe	Determine the best treatment route for neuropathic pain. Amitriptyline and/or pregabalin.	Clinical study with 392 patients. Pain assessment by NRS after 7 days and 6 weeks of treatment with amitriptyline and/or pregabalin. 1B	After evaluation, the treatment can be complementary to both drugs: amitriptyline and pregabalin
Marcus et al.[25] USA	To observe the clinical difference of evolution of neuropathic pain in DM.	Clinical study with 452 patients evaluated with BPI in 5 weeks of conventional treatment for neuropathic pain. 1B	BPI identified clinical improvement in most patients evaluated with conventional treatment for neuropathic pain.
Ahn et al.[26] Boston	To evaluate the clinical and mechanistic effects of Chinese and Japanese acupuncture on painful DN.	Randomized study. Acupuncture performed once a week for 10 weeks. Pain was assessed using the McGill Short Form Pain questionnaire (SF-MPQ). 1B	Clinically, patients allocated to Japanese acupuncture reported decreased pain associated with neuropathy, while the group allocated to traditional acupuncture reported minimal effects.
Van Nooten et al.[27] USA	To evaluate sleep and neuropathic pain in DN by treatment with 8% capsaicin.	Randomized study. Patients were assessed through pain scales and a scale to assess sleep quality with capsaicin 8%. 1B	The improvement of pain from the proposed treatment was evidenced by means of low scores attributed to the BPI pain scale.
Garoushi, Johson and Tashani[28] Líbya	Develop an Arabic version of the LANSS scale and evaluate its validity and reliability in diabetic patients in Benghazi, Libya.	Cross-sectional study on translation and validation of LANSS for Arabic. Simultaneous validity was tested and compared with the self-completed LANSS assessment of neuropathic symptoms and signs (S-LANSS). 2B	It was concluded that the Arabic version of the LANSS pain scale was valid and reliable for use in diabetic patients in Libya.
Barbosa et al.[29] Portugal	Validate the translation into Portuguese of the MNSI questionnaire in diabetic patients.	Cross-sectional study. 76 diabetic patients underwent evaluation of the presence of DN by MNSI translated into Portuguese. 2B	The MNSI in the Portuguese version is reliable and a valid tool for detecting DN.

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Table 1. Summary of selected studies on the evaluation of DN and Neuropathic Pain from 2007 to 2020, according to bibliographic bases and level of evidence, 2020 – continuation

Authors	Objectives	Study design and level of evidence (Oxford Centre for Evidence-based Medicine)	Results and conclusion
Chevtchouk, Silva and Nascimento[30] Brazil	Assess neuropathic pain and peripheral vascular disease in diabetics and compare it with time to diagnosis of type 1 diabetes (DM 1) and type 2 diabetes (DM 2).	Cross-sectional study with 225 individuals with diabetes evaluated by the DN4 questionnaire and the ankle-brachial index (ABI). 2B	There was a predominance of neuropathic pain in patients over 60 years of age with an ABI> 1.3. The neuropathic pain diagnosed by DN4 was related to abnormal ABI in 64.2% of the patients.
Salcini et al.[31] Oxford	To measure the plasma levels of PTX3 and TBP2 in patients with DM2 with complaints of pain.	Clinical trial. Plasma levels of PTX3 and TBP2 were measured in patients with DM2 and pain and their levels compared to healthy individuals using LANNS for pain assessment. 1B	Plasma levels of PTX3 may be useful for discriminating nociceptive pain from neuropathic pain in diabetic patients, assessed using the LANNS scale.
Kelle et al.[32] USA	To evaluate the cross-sectional area (CSA) correlations of the peripheral nerves in patients with PDN.	Clinical trial. The CSA was evaluated in a group of patients with painful DN (n = 53) and a control group (n = 53). The CSAs of the nerves were recorded, and their associations with pain intensity according to the VAS numeric pain score and the LANSS pain scale score were evaluated. 1B	No correlations were detected between the CSAs of the nerves examined and the parameters of interest.
Hotta et al.[33] Japan	To examine the long-term efficacy and safety of duloxetine in the treatment of Japanese patients with diabetic neuropathic pain.	Randomized, controlled, double-blind trial. 258 Japanese adults with DN and pain were used to test the dose of 40 mg / day or 60 mg / day of duloxetine for 52 weeks of treatment. The pain was evaluated through the BPI 1B	There was significant improvement in pain with treatment. The use of duloxetine resulted in significant improvement of pain assessed by BPI.
Papp et al.[34] Nova York	To test instruments for the evaluation of pain in DN and chronic low back pain in patients with HIV.	Cross-sectional study. Participants were divided into three focus groups based on their pain condition. The following instruments were tested: VAS, Bref Pain Inventory and SF-MPQ. 2B	These instrument themes are relevant for understanding the properties of validity and scale of commonly used pain intensity measures.
Mathieson et al.[35] Austrália	To evaluate the psychometric properties of the questionnaires DN4, ID Pain, LANSS, PainDETECT and Neuropathic Pain Questionnaire.	Systematic review of the literature. 1A	DN4 and Neuropathic Pain Questionnaire were more suitable for clinical use. Screening questionnaires should not replace a complete clinical evaluation.
Gao et al.[36] China	To assess the efficacy and safety of duloxetine (60 mg once daily) in Chinese individuals with DN.	Randomized clinical trial. 405 patients were divided into two groups and evaluated by MNSI, and those with a score of ≥ 4 were evaluated with BPI to quantify the mean weekly pain intensity. 1B	Patients treated with duloxetine had significantly greater pain relief compared to placebo-treated patients, according to the instruments.
Bramson et al.[37] USA	To assess the efficacy and safety of tanezumab, against nerve growth factor, in neuropathic pain in patients with diabetes.	Clinical trial. One group of patients received intravenous tanezumab 50µg/kg or 200µg/kg and another group received placebo. Assessments included baseline change in mean daily pain (primary endpoint) and BPI. 1B	Tanezumab provided effective reduction of pain.
Kessler et al.[38] USA	To evaluate the safety and efficacy of a plasmid (VM202) given by intramuscular injections in patients with DN pain.	Clinical trial, double blind. Patients were randomized to receive 8 or 16 mg injections of VM202 or placebo. Divided doses were administered on Day 0 and Day 14. Pain was assessed by BPI and MNSI. 1B	Through treatment with VM202, There was a significant improvement in pain with the evaluation of the BPI and MNSI instruments.
Celik et al.[39] Istambul	To evaluate the usefulness of the DN4 questionnaire to define the frequency and severity of neuropathic pain and its correlation with clinical practice in diabetic polyneuropathy.	Cross-sectional study. The presence of neuropathic pain was assessed by the DN4 questionnaire and by physical sensitivity examination. Those with a DN4 score ≥4 were considered to have neuropathic pain. 2B	The use of the DN4 questionnaire in daily clinical practice is an effective tool to detect the presence of neuropathic pain in patients with polyneuropathy.

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Table 1. Summary of selected studies on the evaluation of DN and Neuropathic Pain from 2007 to 2020, according to bibliographic bases and level of evidence, 2020 – continuation

Authors	Objectives	Study design and level of evidence (Oxford Centre for Evidence-based Medicine)	Results and conclusion
De Vos et al.[40] Netherlands	To investigate whether there is efficacy in spinal cord stimulation (SCS) in patients with DN and pain.	Randomized clinical trial. Two groups: one of clinical practice with SCS and another control group. Both were evaluated with EuroQoL 5D, McGill Pain Questionnaire (MPQ) and VAS to measure pain intensity. 1B	SCS improved patients' pain and quality of life according to the scales used.
Agrawal et al.[41] USA	To evaluate the efficiency of Nitro Sense Derma Protect as a source of nitric oxide (NO) for patients with painful DN.	Randomized clinical trial. Divided in 2 groups: placebo and treatment (24 mg for 3 hours, every day for a period of 3 weeks). Pain was assessed by VAS and SF-MPQ. 1B	NitroSense Derma Protect treatment controls painful DN.
Dobrota et al.[42] Croatia	To identify how neuropathic pain in diabetic patients interferes with their quality of life	Cross-sectional study. 80 patients were evaluated by the VAS, LANNS, SF-36 and BDI scales. 2B	Pain in diabetics is an important factor that influences quality of life.
Freeman et al.[43] USA	To characterize the clinical profile of various neuropathic pain disorders and to identify whether the patterns of sensory symptoms / signs exist.	Clinical trial. The Neuropathic Pain Symptom Inventory (NPSI) and quantitative sensory tests (QST) were used for evaluation. Based on 4 previous clinical trials 1B	Based on the NPSI identified 3 dimensions of pain: triggered, deep, and punctual. Based on the signs of QST, 2 dimensions of pain were identified: evoked by cold and evoked by touch.
Hamdan et al.[44] Spain	To compare the diagnostic accuracy of LANSS and DN4 for the detection of peripheral neuropathic pain in the Spanish population.	Cross-sectional study. 192 patients were evaluated, comparing the validity of the DN4 and LANSS questionnaires, studying sensitivity and specificity, and using the receiver operator characteristic curve ROC analysis. 2B	The sensitivity of the DN4 questionnaire was 95.04% and that of the LANSS questionnaire was 80.17%. The specificity of the DN4 instrument was 97.18% and that of the LANSS instrument was 100%. The area under the ROC curve was significantly higher for the DN4 than the LANSS questionnaire ($p < 0.05$).
Pedras, Carvalho and Pereira[45] Portugal	To characterize in a sociodemographic and clinical manner the patients with diabetic ulcer indicated for amputation surgery.	Cross-sectional study. 206 patients were evaluated. Sociodemographic and clinical characteristics, pain intensity and pain interference were evaluated by Bref Pain Inventory and DN4. 2B	About 59% of patients experienced pain in the lower limb that significantly interfered in all areas of their functioning.
Ziegler et al.[46] Germany	To evaluate the effect of duloxetine and anticonvulsants in patients with painful DN.	Randomized clinical trial. A total of 2,575 patients with painful DN were treated for 6 months and the results from BPI assessment for pain scores were observed. 1B	41.5% of the patients reported chronic pain and improvement through duloxetine and anti-convulsive treatment when comparing BPI pain scores.
Ajroud-Driss et al.[47] USA	To assess the safety and efficacy of intramuscular injections of plasmid DNA (VM202) in patients with PDN.	Cohort study. 12 Patients received two sets of injections for 2 weeks. Safety was assessed through pain scales: VAS, SF-MPQ, BPI. These instruments measured the pain again for 12 months. 2B	The results with BPI-PDN and SF-MPQ showed similar patterns to VAS scores, thus demonstrating efficiency in treatment with injections in painful DN.
Lee et al.[48] USA	To evaluate the effectiveness of electroacupuncture in the treatment of DN.	Randomized, controlled, double-blind study. 45 patients with more than 6 months of painful DN, with pain intensity greater than 4 per BPI were evaluated. They were divided into three intervention groups for 30 minutes for 8 weeks. 1B	From the pain scale, it was possible to observe improvement of pain and effectiveness of electroacupuncture.
Spallone et al.[49] USA	To evaluate the validity and diagnostic accuracy of the DN4 interview in the identification of neuropathic pain of diabetic polyneuropathy.	Cross-sectional study. 158 patient's diabetic polyneuropathy and neuropathic pain was assessed using DN4, nerve conduction studies, history of pain, VAS and SF-MPQ. 2B	The DN4 interview scores showed high diagnostic precision for painful diabetic polyneuropathy, with sensitivity of 80% and specificity of 92%, being a reliable screening tool for diabetic polyneuropathy pain.

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Table 1. Summary of selected studies on the evaluation of DN and Neuropathic Pain from 2007 to 2020, according to bibliographic bases and level of evidence, 2020 – continuation

Authors	Objectives	Study design and level of evidence (Oxford Centre for Evidence-based Medicine)	Results and conclusion
Walsh, Rabey and Hall et al.[50] Ireland	To assess the similarity between LANNS and DN4 in the identification of neuropathic pain.	Cross-sectional study. 45 patients were evaluated to observe the occurrence of neuropathic pain through the mentioned scales, being used to compare the Pearson coefficient. 2B	Neuropathic pain was identified in 33% by LANNS and 42% by DN4. The conclusion is that the two questionnaires are congruent in the evaluation.
Kluding et al.[51] Canada	To examine the feasibility and efficacy of a moderately intense aerobic and resistance exercise program in people with painful DN.	Cross-sectional study. 17 people with painful DN performed aerobic exercises and strengthening for 10 weeks. Outcome measures included VAS scales, MNSI, nerve function measures and intraepidermal nerve fiber density, and branching in distal and proximal lower extremity cutaneous biopsies. 2B	After supervised exercise, improvement in nerve function and branching was detected, as well as improvement in MNSI and VAS.
Adelmanesh et al.[52] Persia	To assess the validity, reliability, and sensitivity of the Persian version of the MPQ in patients with neuropathic and non-neuropathic pain.	Transversal study. 184 patients with subacute and chronic non-neuropathic pain and 74 patients with PDN with pain participated in the study and responded to the questionnaire. 2B	The Persian translation of the expanded and revised version of the MPQ is a highly reliable, sensitive and valid instrument for assessing pain in patients with or without neuropathic etiology.
Searle, Bennett and Tennant[53] Ukraine	Examine whether the LANSS selection tool can meet the expectations of the Rasch model.	Retrospective study. Original LANSS data from a previous study of 2,480 patients with chronic pain were used. The following assessments have been made and adapted to the model for reliability of scale and functionality. 2C	The analysis shows that LANSS can be used in specific populations of patients with neuropathic pain.
Erbas et al.[54] Turkey	To determine the prevalence of PDN and neuropathic pain in patients attending university outpatient clinics in Turkey.	Cross-sectional multicenter. A total of 1113 patients were evaluated through clinical neurological examinations through LANSS and nerve conduction. 2B	DN coadjusted 40.4% of the patients and the prevalence of neuropathic pain in the population of diabetic patients was 14.0%, according to the scale evaluated.
Abbott et al.[55] England	To evaluate, in the diabetic population in general, the prevalence of symptoms of painful neuropathy, the relationship between symptoms and clinical severity of neuropathy, as well as relating gender and ethnicity.	Observational cohort. 15692 people with DM in England were evaluated using a neuropathy symptom score (NSS) and neuropathy disability score (NDS). 2B	Painful symptoms occurred in 26% of patients without neuropathies and 60% of patients with severe neuropathy, with a higher risk in females, smokers and alcoholics.
Hoffman et al.[56] USA	To compare changes in pain, function and health status in individuals with PDN with pregabalin treatment.	Randomized controlled. 401 patients were included in the 12-week pregabalin treatment and the groups were compared through the BPI and EuroQoL 5D pain scales. 1B	A reduction of 30% served as determinant of a clinically important difference, through the results of pain scales.
Petrikonis et al.[57] Lituania	To evaluate the neuropathic pain profile and its association with quantitative sensorial tests in diabetic painful polyneuropathy.	Cross-sectional study. 61 patients were evaluated by clinical neurological exams and quantitative sensory tests. Patients were interviewed using the Neuropathic Pain Scale (NPS) and MPQ. 2B	The intensity of the deep and superficial pain did not differ, but the patients rated the deep pain as more unpleasant.
Moreira et al.[58] Brazil	To evaluate the impact of depressive symptoms and neuropathic pain on the quality of life of patients with diabetic distal polyneuropathy.	Cross-sectional study. 204 patients with type 2 diabetes with polyneuropathy were evaluated by the Neuropathic Symptom Score and Neuropathic Compromise Score. Severity of neuropathic pain was assessed by VAS; depressive symptoms, through the Beck Depression Inventory (BDI); and quality of life through the World Health Organization Quality of Life abbreviated scale (Whoqol-bref). 2B	Depression and quality of life are fully linked to the severity of pain in diabetic polyneuropathy.

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Table 1. Summary of selected studies on the evaluation of DN and Neuropathic Pain from 2007 to 2020, according to bibliographic bases and level of evidence, 2020 – continuation

Authors	Objectives	Study design and level of evidence (Oxford Centre for Evidence-based Medicine)	Results and conclusion
Scherens et al.[59] Germany	Investigate the prevalence and type of neuropathy and compare the performance of the diagnosis.	Prospective study. 42 patients underwent a clinical examination, nerve conduction studies, Quantitative Sensory Tests (QST) and skin biopsy on the dorsum of the foot. Most patients (> 90%) had signs of small fiber loss or dysfunction. 2C	All patients with DN should complement their diagnosis with Skin biopsy.
Dworkin et al[60] USA	To develop a single measure of the main symptoms of neuropathic and non-neuropathic pain that can be used in studies of epidemiology, natural history, pathophysiological mechanisms and response to treatment.	Clinical trial. The SF-MPQ pain descriptors have been expanded and revised, adding to the relevant symptoms for neuropathic pain performed by an Assay based on longitudinal studies and clinical trials in 882 patients. 1B	The data suggest that SF-MPQ has excellent reliability and validity.
Tavakoli et al[61] United Kingdom	Define sensitive diagnostic tests for DN to better evaluate the implementation of interventions for painful DN.	Systematic review. Identify placebo treatments for PDN after BPI, QST, MPQ, DN4 and NPS assessment. 1A	Specific diagnostic tests for painful DN are important to detect better treatment results.
Crawford et al.[62] USA	Determine whether the Inventory of Pain Symptoms (PNS) adequately assess patient with neuropathic pain and DN.	Qualitative Study. Tests were carried out in 6 countries to observe the cultural adaptation associated with neuropathic symptoms. 2B	Based on the study, this instrument can be used alternatively in the evaluation of neuropathic pain in all countries observed.
Veves et al[63] USA	Describe the epidemiology, pathophysiology, diagnosis and treatment for painful DN from 1997 to 2007.	Systematic review. Quantifying neuropathic pain is difficult, especially for clinical trials, although this has improved recently with the development of neuropathic pain-specific tools, such as the Neuropathic Pain Questionnaire and the Neuropathic Pain Symptom Inventory. 1A.	Best treatment results can be achieved through the specific diagnosis by Neuropathic Pain Scale (NPS), MPQ and BPI.
Armstrong et al.[64] USA	To evaluate the efficacy of duloxetine in the treatment of PDN pain.	Multicentric study. Treatment was reactivated with duloxetine 20 mg once daily, 60 mg twice daily or placebo. The groups were divided randomly. Functional results reported by the patient were measured by Short Form 36 (SF-36), the interference portion of BPI and EuroQol 5D Health Questionnaire (EQ-5D).	Through the instruments used, it was observed that the treatment with duloxetine was significantly superior to placebo in all domains.

PNS = Pain Symptom Inventory, QST = Standardized Quantitative Sensory Tests, NPS = Neuropathic Pain Scale, LANSS = Leeds Assessment of Neuropathic Symptoms and Signs, VAS = Visual Analog Scale, BPI = Brief Pain Inventory, DN4 = Douleur Neuropathique 4, MNSI = Screening Instrument for Assessment of Diabetic Neuropathy, NSS = Neuropathy Symptom Score, NDS = Neuropathy Disability Score, NRS = Numeric Rating Scale.

From the studies that were included in this review, 14 different instruments were identified to track PDN, neuropathic pain symptoms and numerical pain scales; eight instruments for neuropathic pain screening: McGill Short Form Pain questionnaire (SF-MPQ), Leeds Assessment of Neuropathic Symptoms and Signs (LANSS), Douleur Neuropathique 4 (DN4), ID -Pain, PainDETECT, Neuropathic Pain Symptoms Inventory, Neuropathic Pain Questionnaire; three instruments for numerical pain assessment: Visual Analog Scale (VAS), Brief Pain Inventory (BPI) and Numeric Rating Scale (NRS); and four assessment instruments for PDN: Screening Instrument for Assessment of Diabetic Neuropathy (MNSI), Neuropathic Symptoms Score (NSS), Neuropathic Commitment Score (NDS) and Quantitative Sensitive Tests (QST).

Through the number of instruments found for each type of assessment in publications, the most prevalent used for tracking neuropathic pain were 10 (28.57%) DN4 and 9 (25.71%) LANNS; for numerical pain assessment 26 (61, 53%) BPI; and for the evaluation of DN was 4 (40%) MNSI. The studies reveal very relevant values about the specificity and sensitivity computation above 80 to 95%, predictive value in an average of 92%, positive likelihood of 3.09, mean alpha index of 0.6 and confidence index of 95 % of the instruments with the highest prevalence in research.

About the instruments prevalence and predictive values, it is possible to make a protocol that better performs the screening of DN and neuropathic pain in people with DM in greater accuracy to be used as a standard in the pre-physical therapy evaluation: MNSI, BPI, LANNS and DN4.

DISCUSSION

Physical therapy, through anamnesis and physical examination, as well as specific clinical scenarios of burning and shock neuropathic pain, as well as allodynia, compose important characteristics to tracking neuropathic pain directed to define a more specific treatment program, mainly in diagnosis to discern that from other types of pain, such as nociceptive pain. This diagnosis is required for the adequate and specific treatment of incapacitating lesion and specific symptoms of fine fiber lesions[65,66].

In order to direct pain screening, easy-to-apply instruments, already validated in Portuguese, have facilitated clinical practice to guide physiotherapeutic treatment by: tracking DN by MNSI, discriminating the etiology of pain through symptoms by LANNS, quantifying the damage of neuropathic pain and pain classification by DN4 and identifying the numerical intensity of pain in the various daily activities by BPI (validation articles of the citation scales). By the studies included in this research, it was possible to select review, validation and intervention about use of several validated questionnaires used for screening neuropathic pain and DN, making it possible to design a program and build a protocol based on the prevalence of these in the research, through the predictive, sensitivity and specificity values of each instrument important in the physical therapy area described for DM [67-70].

The screening DN and neuropathic pain is a challenge for multiprofessional teams in public health, because there are no specific instruments or protocols for DM. This problem hinders the evolution of physical therapy treatment, and this study made it possible to highlight instruments and build a protocol with the most prevalent, validated ones, with positive predictive value, percentage of reliability, percentage of sensitivity, specificity, cut-off point, alpha Cronbach and roc curve. Thus, neuropathic pain needs to be assessed in a comprehensive and specific way in DM in order to guide, direct and treat these people in a more appropriate and early manner, preventing the rapid onset of major complications and damage to quality of life, reflecting on professional and daily life activities[69-72].

With the increase in the prevalence of DM in Brazil and in the world, epidemic proportions of PDN will make neuropathic pain much more disabling at even higher levels, today with a prevalence of 25%, requiring an easy-to-apply screening to guide treatment. Neuropathic pain is a significant complication of DM, disability and severe, due to its complex natural history, unknown etiology and ineffective response to standard physiotherapeutic treatments, so a multimodal neuropathic pain management plan is essential, directing treatment through a protocol screening procedure being applied as early as possible[1,3,6,73].

Aiding the most appropriate and targeted treatment and physiotherapeutic guidance, the early detection of neuropathic pain allows greater awareness of the problem, with habit changes occurring to improve glycemic control with diet, physical activity and continuity of treatment, preventing further complications such as ulcers and amputations. New diagnostic techniques are available, which would complement the clinical evaluation and assist in early detection to boost treatments for neuropathic pain that are currently very limited[9,73,74].

In this way, the evaluation and creation of an effective screening protocol is fundamental to outline physiotherapeutic objectives and conduct the qualification of professionals in the area of DM. Thus, it will provide a greater professional involvement with people affected in an attempt to reduce greater risks and weaknesses such as amputations and ulcerations, in addition to provide psychological and biomechanical improvements.

Current researches discuss the innovative potential of physical rehabilitation in treatment of neuropathic pain, new reflections on therapeutic options are being studied from a thorough assessment of the problem, providing a parallel between the specific pathological mechanism of some neuropathic pain conditions and the neurophysiological mechanism of the proposed therapeutic modality focusing on biomechanical improvement with psychosocial reflex[15,16,73].

The limitations of this study are the scarcity of specific instruments for screening in DM that guide clinical practice for the treatment of neuropathic pain, requiring further studies to bring greater benefits and clinical developments in DM.

CONCLUSION

The development of studies to define the best screening instruments is a crucial point for a greater evolution of clinical studies, diagnosis and physiotherapeutic treatment of neurological complications of DM, contributing to improve the quality of life of the patients through biomechanical and emotional improvements.

Therefore, this integrative review revealed that the instruments most used in recent years and that can direct physiotherapeutic treatment for DN and neuropathic pain by building a screening protocol are MNSI, BPI, LANNS and DN4.

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