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Scales of valoration of neuropathic pain in patients with cancer: science, reality or applicability?

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Introduction

Pain is the reason for 40% of patient´s consultations in primary care. It is also a very frequent symptom in the oncological patient, being described in some study in up to 70% with metastatic cancer, in which up to 30-40% of the pain is not well controlled due to lack or ineffectiveness of the prescription. For this reason, the American Pain Society has defined it as the "fifth vital sign". Neuropathic pain (NP) is defined as that pain created as a direct result of an injury or illness that affects the somatosensory system, produced from the damage of nerve pathways at any point (from peripheral nociceptors to cortical neurons). The incidence of NP increases worldwide, as a consequence of the life expectancy, diabetes, HIV infection, cancer, exposure to toxic substances and traumatisms. In cancer patients it appears in 1 in 3 patients, and is independently associated with chemotherapy, surgery, recent analgesics,breakthrough pain, concomitant medication or tumor location. It differs from nociceptive or non-neuropathic pain in that it is not usually described as burning, lacerating or allodynia, as NP does. It responds well to opioids, while NP does it in a variable way, needing more doses of opioids, anti-inflammatory analgesics and even antidepressants, anticonvulsants or local anesthesics.

Therefore we are facing an increasing pain in which as we now describe, we do not have effective scales to assess it in a multidimensional way, since the pain impacts in various spheres of life such as social relationships,mood, physical...Some authors recommend that in daily clinical practice, in addition to general scales such as the visual analogue scale (VAS) that does not differentiate NP from nociceptive, other more specific ones should be used, such as the Mc Gill questionnaire (specific por NP assessment), Edmonton Symptom Assessment System (defines pain of good and worse prognosis, including in the second to breakthrough pain and NP), the Mini Mental scale and the CAGE questionnaire recommended by several European guidelines.

Analgesic valuation

The scales also have their limitations and must be individualized on the type of patient to perform, since for example that VAS is not a good scale in patients with dementia, as it is difficult to assess the degree of pain they present and be able to compare it between visits (which is its most useful) for the lack of memory. In patients with dementia, it is recommended to use the Folstein MMSE questionnaire. Thus, it has to be invidualized and in elderly patients, for example, the Mc Gill questionnaire and 4 one-dimensional scales are recommended, of which we will detail later. As we wsee, pain is not an easy symptom to evaluate because of the subjectivity that of it is derived and especially by the scarce time that we have in Consultation. While it is true that scales can help us, in no case should replace the medical history and physical examination. Ideally, we should collect the intensity, location, length pattern (paroxysmal, permanent), frequency and type of pain. Paresthesias, spontaneous pain and evoked pain (hyperalgesia, allodynia) are considered as positive symptoms, while negative ones are sensory deficits in all their modalities (hypo/anesthesia, hypo/analgesia), symptoms that help us and are included in the previous questionnaires. Also a good physical examination should be performed at each visit to the specialist, however this is not feasible, except before a very striking worsening. It must include an assessment of the sensitive nervous system using a tuning fork to assess vibratory stimuli or pick up those painful areas, if there is allodynia (pain sensation in the presence of a non-painful situation) or hyperalgesia (pain more expected than normal after mechanical stimuli such as a puncture. or touch). Imaging techniques such as PET may have an interest in the study of the neurological pathways involved, however, they are impractical to evaluate the treatment and titration in oncological patients in which we must periodically increase the treatment especially when it is due to the tumor progression.

In patients undergoing Palliative Care, pain appears between 40-70%, but other symptoms such as depression appear in 33-40%, anxiety 57-68%, nausea 24-68%, constipation 65%, dyspnea 12-58% and asthenia in up to 90%. Therefore, we should evaluate all these symptoms since it has been seen that some of them can affect other ones; and that if we control them, we can improve the quality of life.[1] Within the evaluation of NP, there are several mechanisms that justify it and allow a classification into 4 groups: ectopic discharges, loss of inhibition, peripheral and central sensitization. However, this classification is not practical for day to day. Depending on the location, we divide it into peripheral (radiculopathy, postherpetic neuralgia, trigeminal) or central (cerebrovascular accident, multiple sclerosis, phantom limb pain), which are of interest when directing treatment. Although this may seem useful, research lines and clinical trials collect "screeening" questionnaires with the objective of differentiating NP from nociceptive pain.

Screening neuropathic pain

Mc Gill questionnaire is the most specific form although it has not been evaluated for acute pain.[2] Each aspect that is valued fits into four subscales: 1 to 10, sensitive subscale; 11 to 15, affective subscale; 16, evaluative subscale; 17 to 20, diverse items (Figure 1). A more abbreviated questionnaire has been developed with 15 items (Short Form Mc Gill Pain Questionnaire or SF-MPQ) that have high profitability and takes less time to complete. Its disadvantage is that both were not developed to assess the characteristics of NP, and the

abbreviated form does not include serious symptoms that are very frequent in NP. To improve it and be able to differentiate it from non-neuropathic pain, to the abbreviated questionnaire 7 relevant symptoms were added, with a numbering of the symptoms from 1 to 10 not being verbal anymore, and being called SF-MPQ2. It has been translated into more than 35 languages and is used in several clinical trials to assess the analgesic response. Other screening questionnaires include DN4, which has a sensitivity of 83%, specificity of 90%, positive predictive value of 89.5%.[3] and is also translated and validated in oncological patients (sensitivity of 87.5%). (Burning, pain, tingling...) and 3 on physical signs (hypesthesia to the touch or prick, pain to rubbing), being one of the few that includes the itch in its assessment. (Figure 2) There are other 4 tools, not yet translated and therefore not validated in our country such as Neuropathic pain scale of Gallery & Jensen[4] and the second most used in Spain LANSS pain scale of Bennett[5] Neuropathic Pain Questionnaire of Krause & Backonja[6] and Neuropathic pain symptom inventory of Bouhassira & Attal[7] other validated for low-back pain is PAIN DETECT, that found by chance that difference very well patients with DN.[8] Note all scale LANSS (Leeds Assessment of Neuropathic Symptoms and Signs), which was evaluated in a study of 112 patients with chronic pain and cancer and where scale had a correlation with the physical examination of up to 94%. The scale is divided into two parts, the first with 5 items (wind chill, autonomic changes, dysesthesia, paroxysmal and evoked pain) and sensory, checking allodynia. Each item is valued as a yes/no with a maximum of 24, resulting in the study population (which included patients with lung cancer, breast, gynecological, pancreas and prostate), an average of 16 for DN while it descended to 5.5 in nociceptive pain.[9] So the next question is and which one we choose? In a recent systematic review that analyzed the differences between the physical examination and screening tools such as LANSS and DN4 and PAINDETECT in patients with cancer, all of them target a good correlation. Although studies are not comparable to each other, it seems that DN4 (82-87%) is the most sensitive followed by LANSS (79-86%) and PAINDETECT (53%) while the more specific is LANSS (100%), followed by DN4 (88%) and PAINDETECT (77%).[10] In Table 1 we describe the differences evaluated in both scales. It is important to reflect, that although it is important that focus scales to assess DN, also they should be focused in cancer population, because it is very different to evaluate a diabetic neuropathy or a post herpetic neuralgia. Oncological population should also highlight the pain produced by the own chemotherapy (drugs such as Platinum or taxane, used in most of the tumors in advanced stage). Given that this is a very common symptom and where several specialists need to be involved, because of its high frequency in primary care, has created a consensus on how to assess the NP in primary care.[11]

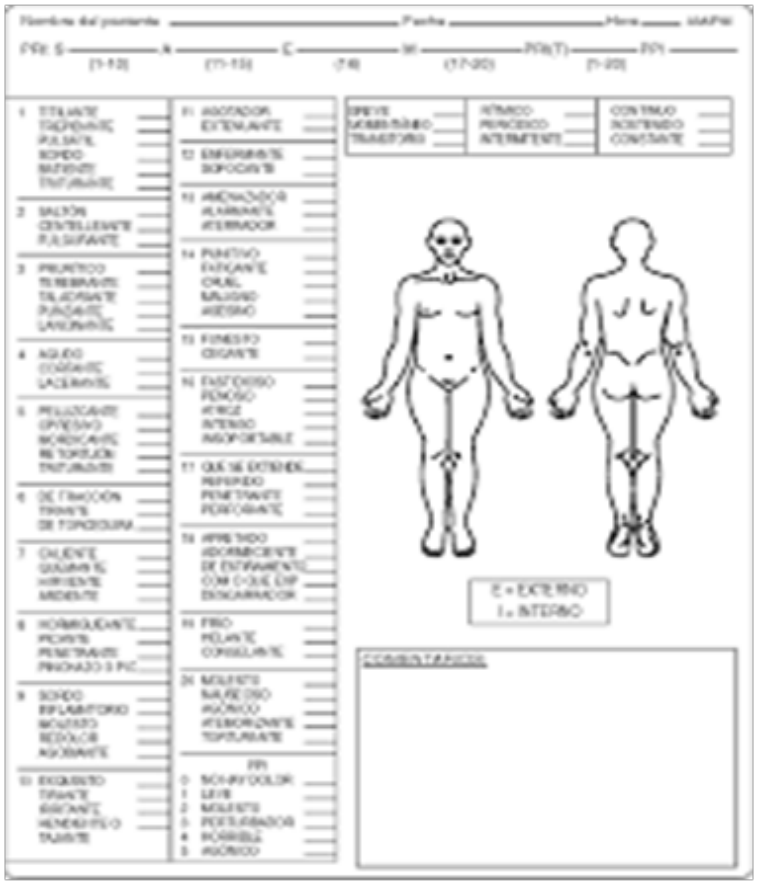

Figure 1 Mc Gill Questionnaire.

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Table 1 Differences between the most commonly used screening questionnaires for neuropatic pain

	LANSS	DN4	NPQ	Paindetect	ID pain
Stabbing, tingling	X	X	X	X	X
Electric shock, shot	X	X	X	X	X
Hot	X	X	X	X	X
Numbness		X	X	X	X
Pain created by soft touch	X		X	X	X
Painful cold		X	X		
Autonomic changes	X				
Allodynia	X	X			
Threshold increased to soft touch		X			
Threshold increased to prick	X	X			

Classification of neuropathic pain

Therefore, if we felt not enough with the difficulty in making a good clinical history, physical examination and the variety of available scales, another issue to discuss is that NP is not always 'pure' as such and usually appears with nociceptive component at the same time. So we need more specific tests that seek to classify as possible, probable and definite NP based on clinical history, physical examination and tests. Therefore with screening tools that have commented such as DN4, LANSS or Pain Detect should be graded as maximum in pain as possible (never definitive), and it must also be taken into account if they were on oncology population. Thus arises the study collecting that NeuPSIG (Neuropathic Pain Special Interest Group) is the best tool to really classify NP in cancer patients. There are 4 criteria. The first reflects that pain has a characteristic neuroanatomical distribution. The second step confirms a history of relevant injury or disease affecting the somatosensory system. These first two can corroborate the interview and physical examination. The third step is to have confirmatory tests showing the presence of positive and negative signs, confined to the innervation of the damaged nerve structure (vibration, heat, cold...). And the 4th criterion includes more specific diagnostic tests that confirm the injury or illness under the term of NP, such as imaging such as CT or MRI tests. Ideal method would be the sensory assessment of the sural and radial nerve, so sometimes electroneurograms or electromyelograms, though actually most sought to rule out causes of loss of sensitivity when they are very striking or unexplained. If the criteria 1 and 2 are met we would talk about possible DN. If the criterion number 3 or 4 is added to them, it would be likely, while if all are met, we would talk about definitive DN.[12]

New scales

Pain greatly influences within the assessment of the quality of life, so it should be equally valued this too. We therefore set ourselves new variables when defining if the patient presents a type of pain or not and what impact does the same. Currently, there is no specific scale to assess quality of life and NP, but there are some performed on pain and quality of life, being the most used of MOS SF-36, MOS SF-12 (but simplified), WHOQOL-BREF or Nottingham Health Profile, assessing the social, physical, emotional and cognitive spheres.[13] At the end of 2017 is published an article on the NP and the effect of the chemotherapy, with the aim of preventing or discontinuing drugs that create it, defining new questionnaires such as L-BASIC (location based assessment of sensory symptoms in cancer), CIPN-R-ODS (Rasch built overall disability scale for Cancer induced neuropathy pain), NPS-CIN (assesses pain neuropathic, chemotherapy and cancer) or CIPNAT (assesses pain and interference with the activities of daily living), pending of being valued in new clinical trials.[14] The one that can be more useful in cancer patients is CIPN-R-ODS because it assesses the effect of chemotherapy on pain, including also questions like if the patient is able to go out with friends, running, load weight, fix..., so it assesses in a multidisciplinary way (Table 2). The problem is as they are still underdeveloped, not having a clear cut-off point to define NP (Figure 2).

Table 2 CIPN-R-ODS Questionnaire

Are you able of…?	Not able	Able but with difficulty	Possible without difficulty
Getting up from the bed			
Visit family			
Washer			
Use knife or fork			
Sit			
Go to the hospital			
Rinse			
Move a chair			
Get money out of ATM			
Pick something			
Cooking			
Throw an object			
Use brush teeth			
Shopping			
Clean the bathroom			

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1. Does your pain have any of these characteristics?
A) burning YES/NO
B) YES/NO painful cold feeling
C) electric shock YES/NO

2 Do you have in the area where it hurts any of these symptoms?
D) tingling YES/NO
E) puncture YES/NO
F) numbness YES/NO
G) stinging YES/NO

3. What is evidenced in exploring any of these signs in the painful area?
H) Hypoaesthesia touch YES/NO
I) Hypesthesia to prick YES/NO

4. Pain is caused or intensified by...?
J) the YES/NO friction

Figure 2 DN4 questionnaires (≥4 points, neuropathic pain).

Neuropathic pain treatment

Finishing up, and without being the objective of the review, NP treatment must include several strategies, not only pharmacological. Within the drugs, both antidepressants and anticonvulsants relieve up to 50% of the cases, being less effective opioid drugs. Tapentadol is a suitable drug for NP,primarily as a second tier when it did not work the first line with antidepressants or anticonvulsants. It is also used in cases of severe pain due to its delayed formulation that can help avoid that increase both the dose of opioid and avoid side effects Table 3 & (Figure 3). Its mechanism of action lies in its dual action on the receiver or (agonist) and inhibitor of the reuptake of noradrenaline, similar to antidepressants. It has a good tolerance, standing out like the rest of opioid side effects an increase in nausea, drowsiness, dizziness, vomiting and weakness. The incidence of gastrointestinal effects is lower than the opioids. Initially the dose should be 50mg every 12hours, but this dose can be increased in other 50mg every week, being the maximum dose of 500mg every 24hours. Tapentadol is contraindicated in patients with creatinine clearance less than 0.5ml/s/m^2 and Child Pugh Class C. Finally, note that the NP evaluation is complex (joint pain in a high percentage of patients) and needs a good medical history and physical examination which may be supplemented by screening tools such as the aforementioned questionnaires. Also we have individualized studies and rely on the oncology population or even only in patients receiving chemotherapy, since they need to specifically evaluate its toxicity or other items such as quality of life and depression that can influence the optimal analgesic control. Tapentadol is a good drug in cancer patients, also showing an improvement by the scales of quality of life although they need more prospective studies.[15] It has recently published a study of 38 patients which demonstrate the effectiveness of tapentadol in opioids refractory NP, so are such studies that reflect clinical practice who also need.[16]

Table 3 Recommended treatments for DN in guides and algorithm proposed by the guides European Federation of Neurological Societies (EFNS) and the Special Interest Group on Neuropathic Pain (NEUPSIG)

Treatment	NeuPSIG	EFNS
Anticonvulsivants		
Pregabalin	1st line NP	1st line NP except the V neuralgia
Gabapentin	1st line NP	1st line NP except the V neuralgia
Antidepressants		
Tricyclic antidepressants	1st line NP	1st line NP except neuralgia of the V and caution the elderly
Duloxetine	1st line NP	1st line Mellitus Diabetes painful neuropathy
Venlafaxine	1st line NP	1st line Mellitus Diabetes painful neuropathy
Opioids		
Tramadol	2nd line NP	2nd line NP except certain situations
Strong Opioids	3rd line NP	2nd-3rd line NP

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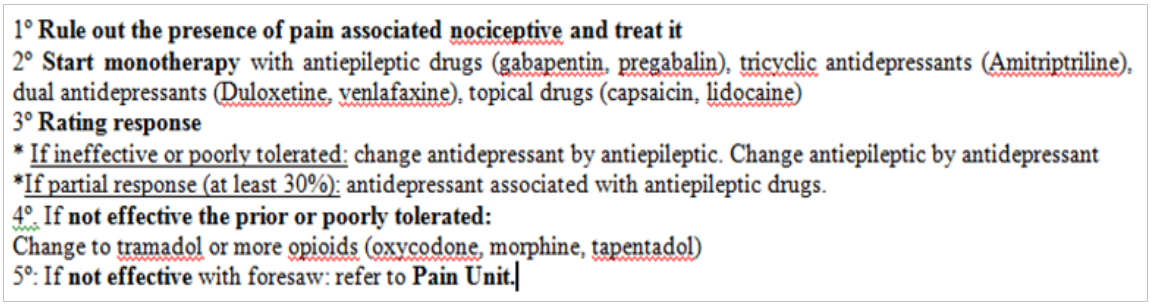

Figure 3 Algorithm for DN in primary care (reproduced from Rafael Galvez et al 2016).

Conclusion

i. Ideally the assessment of pain should be done with a general scale (VAS), a NP scale (Mc Gill) and assessment of quality of life.

ii. A practical evaluation for every day consists on reflecting the most important features of the clinical history, finding etiology aiming to improve treatment and reevaluate frequently.

iii. Scales of "screening" (LANSS, DN4, DETECT PAIN) should not replace the clinical and physical examination and the scales that classify NP as definitive (NeuPSIG) need neurological tests or tests image difficult to achieve in every day. They are useful to differentiate joint pain (neuropathic and nociceptive), but little applicable in clinical practice.

iv. Specific and multidimensional in patients with cancer, scales are needed since also own chemotherapy produces NP and are associated more frequently to other symptoms as anxiety that also has to be treated.

v. Treatment must include pharmacological (anticonvulsants, antidepressants, tapentadol) and non-pharmacological strategies.

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Conflict of interest

The author declares there is no conflict of interest.

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