

ORIGINAL RESEARCH

PAIN MANAGEMENT

Treatment algorithm of neuropathic pain in elderly population

Hanik Badriyah Hidayati ¹, Vania Ayu Puspamaniar ², Alexander Tikara Sugondo ³, Fajar Sena Firdausa ⁴

Author affiliations:

1. Hanik Badriyah Hidayati, Teaching Staff of Neurology Department, Faculty of Medicine Airlangga University – RSUD Dr. Soetomo, Surabaya
2. Vania Ayu Puspamaniar, Student of Faculty of Medicine Airlangga University – RSUD Dr. Soetomo, Surabaya
3. Alexander Tikara Sugondo, Student of Faculty of Medicine Airlangga University – RSUD Dr. Soetomo, Surabaya
4. Fajar Sena Firdausa, Education PersonPel of Faculty of Medicine Airlangga University, Surabaya

Correspondence: Hanik Badriyah Hidayati, E-mail: hanikhidayati@fk.unair.ac.id

ABSTRACT

Older persons are usually affected by neuropathic pain (NP). They typically have a number of comorbidities. Drug-drug interactions are more likely in elderly people since they frequently take multiple medications. These patients, particularly those who have cognitive issues, may also have limited communication skills, making it challenging to assess and treat their pain. To recognize and treat neuropathic pain as effectively as possible, clinicians and other healthcare professionals need a decision-making algorithm. We describe a decision-making algorithm created by a multidisciplinary team of experts that concentrates on pain evaluation and treatment options for the treatment of neuropathic pain, especially in the elderly.

Abbreviations: ECPA - Behavioral Scale for Elderly Persons; IASP - International Association for the Study of Pain; S-LANSS - Leeds Assessment of Neuropathic Symptoms and Signs pain scale; NP - neuropathic pain; NRS - numerical rating scale; PHN - Postherpetic neuralgia; PACSLAC - Pain Assessment Checklist for Seniors with Limited Ability to Communicate; PGIC - Patient Global Impression of Change; VRS - verbal rating scale; VAS - Visual analog scales;

Keywords: neuropathic pain, algorithm, treatment or management, elderly.

Citation: Hidayati HB, Puspamaniar VA, Sugondo AT, Firdausa FS. Treatment algorithm of neuropathic pain in elderly population. *Anaesth. pain intensive care* 2024;28(6): 1105-1112; DOI; [10.35975/apic.v28i6.2618](https://doi.org/10.35975/apic.v28i6.2618)

Received: October 04, 2023; **Reviewed:** October 23, 2023; **Accepted:** September 24, 2024

1. INTRODUCTION

Pain according to the definition of International Association for the Study of Pain (IASP) is an unpleasant sensory and emotional experience associated with actual and potential tissue damage.¹⁻³ One type of pain is neuropathic pain (NP). NP is defined by the IASP (International Association for the Study of Pain) as pain resulting from disease, dysfunction, damage or lesion in the somatosensory system, both in the peripheral and central nervous systems.⁴⁻⁷

Neuropathic pain (NP) has impacts on mood, activity daily living (ADL), work performance, function and

quality of life of patients.⁸⁻¹² NP is still a global burden.¹² It is estimated that the prevalence of pain in the community ranges from 3% using Berger's criteria to 9.8% using clinical examination (the gold standard). This depends on the method and population studied. The results of the postal survey in France show that the prevalence of pain is 6.9%, while surveys in the UK and France report that the prevalence of chronic pain with neuropathic characteristics in the general population is 7-8%. Using the independent report version of the Leeds Assessment of Neuropathic Symptoms and Signs pain scale (S-LANSS), reports in the UK show that the prevalence is 8.8%. Prevalence has been reported to be 9.3% in individuals aged 50-64 years in the general

population in the UK and France. Data are sparse showing prevalence in elderly and very elderly humans. Most of the methods used are approximate depending on the patient's ability to communicate and are not adapted for older people with cognitive impairment or communication difficulties.¹³

An increase in life expectancy increases the number of the elderly population which is a population that often experiences chronic pain such as NP. NP is difficult to treat, especially in the elderly who often have comorbidities and are in poly-medication. The medication error rate is high.¹³ Our paper will describe a treatment algorithm that will focus on pain assessment and treatment options for NP especially for the elderly.

2. ETIOLOGY

Neuropathic pain (NP) is caused by several things which are categorized as peripheral and central neuropathic pain.^{8,14,15} Toxic substances (e.g., chemotherapy-induced neuropathy), metabolic disorders (e.g., diabetic polyneuropathy), traumatic, leprosy (e.g., HIV-associated neuropathy, postherpetic neuralgia), compression (e.g., compression due to tumor, trigeminal neuralgia, cancer), ischemia (ischemic neuropathy), trauma (post-traumatic neuralgia), nutritional deficiencies (B12 deficiency), radicular pain, degenerative disorders, etc. can cause peripheral nerve lesions or dysfunction which is called peripheral neuropathic pain. Central nerve lesion or dysfunction, called central neuropathic pain, is caused by several etiologies such as stroke, multiple sclerosis and spinal cord injury, traumatic brain injury, epilepsy, abscess, Parkinson's disease, syringomyelia or syringobulbia.^{5,8,14,16-24}

3. NP Treatment Algorithms: A Focus for Elderly

The NP treatment algorithm includes 4 steps:

1. Detection and diagnosis of NP: pathological context and clinical signs.
2. Evaluation of NP and its impact: automated evaluation and assessment with behavioral tools.
3. General guidelines for the management of NP and treatment approaches.
4. Re-evaluation of pain and treatment.¹³

Step 1. Detection and Diagnosis of NP: Pathological Context and Clinical Signs.

Elderly people often do not report their NP complaints even though they are not experiencing communication

disorders. This makes doctors undertreat the pain of the elderly. NP can be masked by nociceptive pain. The clinician should look for signs of chronic pain with neuropathic characteristics.¹³

If there is a change in behavior, especially in the elderly with communication disorders, for example there is a change in facial expressions due to pain, the doctor must suspect that the patient has pain. The patient's file should be examined for a history of pathology that might underlie the occurrence of NP (Figure 1). Physicians should ask relatives of elderly patients about changes in expression due to pain, behavioral disturbances, and the patient's medical history.¹³

Observation and clinical examination are the essence of the diagnosis of NP. Covering certain parts of their body, taking an "analgesic position" in bed, paroxysmal screaming/sighing, or apathetic behavior can all lead to suspected breakthrough pain/NP features (eg: burning, tingling, electric shock) that the patient may not be able to describe. and distinguish. Physicians should look for clinical signs that can potentially cause NP (skin scars, skin disorders) and self-protection. The clinical examination should focus primarily on two main symptoms: allodynia (pain response to normally harmless stimuli) and hyperalgesia (increased pain response to painful stimuli). These symptoms often occur when the patient is being bathed or when mobilizing. Confirmation can be obtained by applying gentle stimulation with cotton and finger pressure on the suspected zone. Improvements/decreases in discomfort behavior can be detected by stimulation, massage/applying hot or cold stimuli.¹³

Step 2: Evaluation of NP and Its Impact: Automated Evaluation and Assessment with Behavioral Tools.

Self-report is the gold standard for pain assessment. Information may be difficult to obtain even if the patient is not cognitively impaired. Seniors may feel that pain is normal as they get older/ hesitate to complain because they are afraid of not being independent/ afraid to do additional tests and medical interventions. Elderly pain can be evaluated with a numerical rating scale (NRS) / verbal rating scale (VRS). Visual analog scales (VAS) are not recommended for the elderly. Seniors with mild to moderate dementia may still be able to report pain well. Open-ended questions without follow-up are elderly patients with cognitive impairment.¹³ The device can determine whether a patient has pain, but not whether the pain is neuropathic. Although the content of the tools varies, the items for identifying pain/discomfort overlap a lot. Specific scales for NP exist, but none are adapted for patients with communication disorders because all require

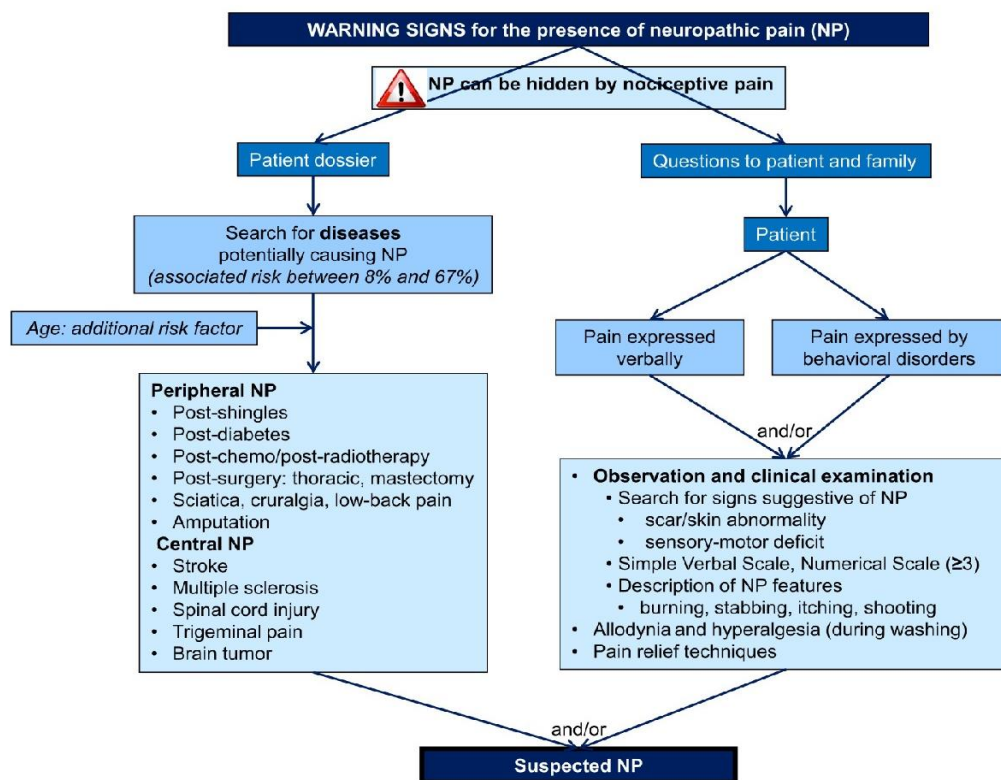


Figure 1: Algorithm Step 1. Detection and Diagnose of NP ¹³

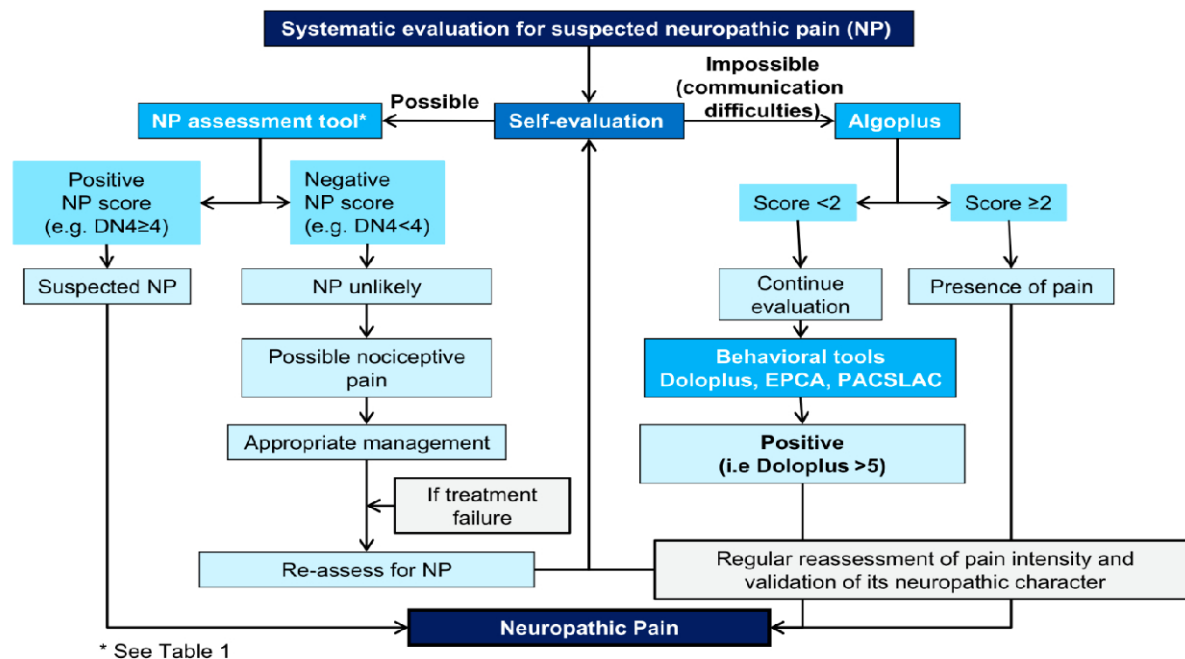


Figure 2: Algorithm part 2: Evaluation of neuropathic pain. DN4 pain questionnaire ‘Douleur Neuropathique 4’, EPCA Echelle Comportementale pour Personnes A’ge’es (Behavior Scale for Elderly Persons), PACSLAC Pain Assessment Checklist for Elderly with Limited Communication Skills.¹³

for participation (Table 1). Evaluation of quality of life and functional status, including cognitive psychological and depression/anxiety questionnaires, is also part of the global evaluation of geriatric patients (Figure 2).¹³

If self-evaluation allows, the elderly NP scale can be used (Table 1). If the NP scale results are negative while the previous evaluation showed pain, then the cause may be more nociceptive. Treatment of nociceptive pain should then be attempted, with re-evaluation.¹³

Among the behavioral scales, Doloplus—one of the first published scales—has been validated for the evaluation of pain in elderly people with communication disorders. Doloplus has 3 dimensions (somatic reaction, psychomotor, and psychosocial) which each consist of 10 items (rated 0-3). Algoplus focuses on the evaluation of acute pain and has 5 items (facial expressions, appearance, complaints, body position, atypical behavior); each item is scored 'yes' = 1 or 'no' = 0. Scores ≥ 2 for Algoplus and ≥ 5 for Doloplus indicates pain. If the Doloplus and Algoplus tools are combined, it will become the NP scale.¹³

If self-evaluation is not possible and NP is suspected, it is recommended to start the evaluation with the Algoplus scale. An Algoplus score ≥ 2 indicates pain and should be treated. Treatment should be attempted and pain reassessed regularly with re-evaluation of the neuropathic character of the pain. A score of < 2 on the Algoplus scale does not mean that the patient does not feel pain. Recent studies have shown that 17% of

patients with an Algoplus score < 2 have a positive Doloplus score. It is recommended that patients with an Algoplus score < 2 should be evaluated with Doloplus or another behavioral scale (eg Echelle Comportementale pour Personnes Aˆge'es [Behavioral Scale for Elderly Persons: ECPA] or Pain Assessment Checklist for Seniors with Limited Ability to Communicate [PACSLAC]) [Pain Assessment Checklist for Elderly with Limited Ability to Communicate [PACSLAC]]. A score of ≥ 5 on the Doloplus scale indicates pain and the patient should be treated, with further evaluation and reassessment.¹³

Step 3: General Guidelines for The Management of NP and Treatment Approaches.

Effective treatment of pain in the elderly begins with a comprehensive and accurate evaluation to select the most appropriate treatment strategy, including pharmacological and non-pharmacological approaches. Treatment efficacy and side effects should be evaluated and re-evaluated. Pharmacological treatment is usually the first line of treatment for NP. Non-pharmacological approaches should be added whenever possible. Guidelines for the treatment of elderly NP are generally based on international recommendations. Reports of drug efficacy in the elderly are limited. Data and research specifically for seniors are still lacking. NP should be managed in the specific setting of the geriatric patient. The choice of treatment depends on the clinical

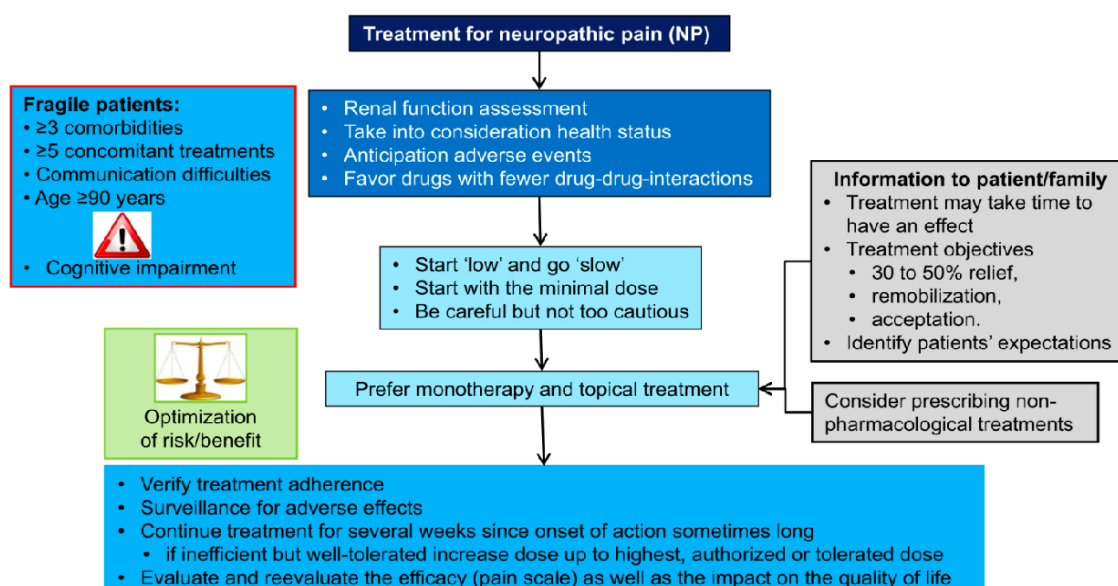


Figure 3: Algorithm Step 3. Neuropathic Pain Therapy.¹³

Table 1: Tools for assessing neuropathic pain

Tool name	Brief description
IDPain [34]	Five items 'yes' score = 1; sixth item 'yes' score = -1; all items 'no' score = 0, results displayed as a diagram to situate pain
Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) Self-report LANSS (S-LANSS)	LANSS: 5 items on neuropathic symptoms; 2 items on clinical examination S-LANSS: 7 items rated as present or absent; 2 items to evaluate pain distribution and intensity
Neuropathic Pain in 4 questions (NP4)	Four questions divided into 10 items: 'yes' score = 1; 'no' score = 0
Neuropathic Pain Questionnaire (NPQ)	Total 12 items: 10 items related to sensory or sensation responses; 2 items related to affect ^a
The Neuropathic Pain Scale (NPS)	Total 10 items: 7 items on pain characteristics (intensity, sharpness, hotness, dullness, coldness, skin sensitivity, and itchiness); 1 item on time when pain is present; 1 item on overall unpleasantness; 1 item on the intensity of deep and surface pain
Neuropathic Pain Symptom Inventory (NPSI)	Five parts (spontaneous burning pain, spontaneous deep pain, paroxysmal pain, evoked pain, and paresthesia/dysesthesia) divided into 10 pain descriptors
painDETECT	Nine items: 7 weighted sensory descriptor items and 2 items relating to the spatial and temporal characteristics of the individual pain pattern
^a NPQ Short-form comprising three items: numbness, tingling, and pain increase in response to touch [35]	

situation, comorbidities, renal function, other medications, and cognitive status (Figure 3).¹³

Elderly may have previous serious illness accompanied by significant pain. Polypharmacy-related comorbidities can complicate the evaluation, management, and treatment of NP, and patients are more likely to experience side effects. It has been reported that 31% of patients aged ≥ 85 years have four or more chronic comorbidities. Polypharmacy is common, and it has been reported that two-thirds of people living in the community aged 60 years are taking four or more drugs daily; frail elderly with various co-morbidities need an average of nine; and elderly hospital inpatients can take as many as 14 drugs. A number of physiological changes that can affect drug metabolism are also associated with aging, especially decreased kidney function. Adverse effects such as constipation, vomiting, or nausea should be anticipated in older patients, especially those taking opioids. Drugs with the least potential for drug-drug interactions should be preferred. In older patients, a 'start low' and a 'go slow' approach should be used, i.e start treatment at the lowest dose and titrate up depending on efficacy and tolerability. Monotherapy, local treatment, and the oral route over the intravenous route should be preferred.¹³

Optimizing the benefit or risk balance is important, therefore monitoring of drug overdose and efficacy should be planned. Treatment adherence should be verified even in patients who have no or only mild cognitive impairment. Beliefs about medication and its

cost, efficacy, or side effects can lead to non-adherence in 40-75% of older patients, who may take more than prescribed doses, forget to take, or discontinue medication. Patients should be advised that the onset of action of antidepressants for the treatment of NP may take up to 2 weeks and may require higher doses, and they should continue treatment for several weeks. The goals of treatment must be explained to patient, and they must understand that painless goals will rarely be achieved. Reassessment of pain should include evaluating its impact on quality of life using for example, Patient Global Impression of Change (PGIC). If the patient is cognitively impaired, the clinical team needs to reevaluate with the behavioral scale, observing all of the above points, and monitoring for side effects.¹³

Pain is difficult to diagnose in patients who are agitated and who show behavioral or psychological symptoms of dementia (BPSD); however medications for BPSD (including antipsychotics, anticonvulsants, antidepressants, anxiolytics, cholinesterase inhibitors, and N-methyl-D-aspartate receptor modulators) should only be used after pain has been eliminated as the cause of symptoms and after pharmacologic treatment has been tried.¹³

The pharmacological treatment of NP has been well described. Special consideration should be given to the elderly, especially those with cognitive impairment. The first line of NP treatment are antidepressants, antiepileptics, 5% lidocaine, and capsaicin patches. The efficacy of tricyclic antidepressants/TCA's

(amitriptyline, imipramine, clomipramine) for NP has been determined with a number needed to treat (NPT) of 3.6 and a number needed to harm (NPH) of 13.4. However, the anticholinergic effects of TCAs (visual, urinary, gastrointestinal) mean they should be used with caution in older patients as well as in those with cardiovascular and cardiac disease. Antidepressants also have many drug-drug interactions that need to be monitored. Gabapentinoids are also a first-line treatment (NPT 7.7, NPH 13.9) which has a better safety profile, with minimal concern for drug-drug interactions and no interference with liver enzymes; however, they cause central side effects, including sedation, ataxia, or edema. Although lidocaine patches have been shown to produce less cognitive impairment compared to antidepressants in older patients with post-herpetic neuralgia (PHN), recent publications indicate the quality of available evidence is too low to be considered a first-line treatment option. Other serotonin-norepinephrine reuptake inhibitor (SNRI) antidepressants (e.g., venlafaxine, duloxetine, milnacipran) have a better safety profile than TCAs (NPT 6.4, NPH 11.8). These drugs have the potential to cause side effects such as nausea, constipation, hot flashes, hyperhidrosis, palpitations, dry mouth, hypertension, and drug-drug interactions as well as the risk of serotonergic syndrome and therefore should be used with extreme caution in the elderly.¹³

Tramadol is an effective second-line analgesic for NP (NPT 4.7, NPH 12.6). Side effects are nausea,

constipation, drowsiness, and seizures and increased cognitive impairment. These drugs should not be taken in combination with antidepressants because when they are prescribed the elderly are at risk for serotonergic syndrome, which, although rarely fatal, increases the confusion and general health of the elderly. Capsaicin patches are effective for the second-line treatment of peripheral NPs, such as PHN, but the burning and stinging sensations may not be tolerated. Data on its use in the elderly is scanty. A recent study involving patients up to the age of 80 found that an onset capsaicin patch relieved their pain more quickly and overall satisfaction was higher than pregabalin.¹³

Strong opioids (morphine, oxycodone, methadone, tapentadol) have been shown to be efficacious in the treatment of peripheral NP (NPT 4.3, NPH 11.7) and are no longer considered solely end-of-life drugs. Some side effects, such as constipation, nausea or vomiting, should be monitored and treated in elderly patients, especially those with cognitive impairment. Sedation, cognitive impairment, respiratory depression, and psychomotor disturbances can be managed with an approach that includes slow titration and adequate patient hydration. These drugs are currently considered post-herpetic third-line treatment because of the potential risk of abuse, higher risk of death from overdose, diversion, misuse, and morbidity. However, these considerations may not be relevant for elderly patients with NP and communication difficulties in long-term care facilities. Other anti-epileptics, such as carbamazepine and sodium

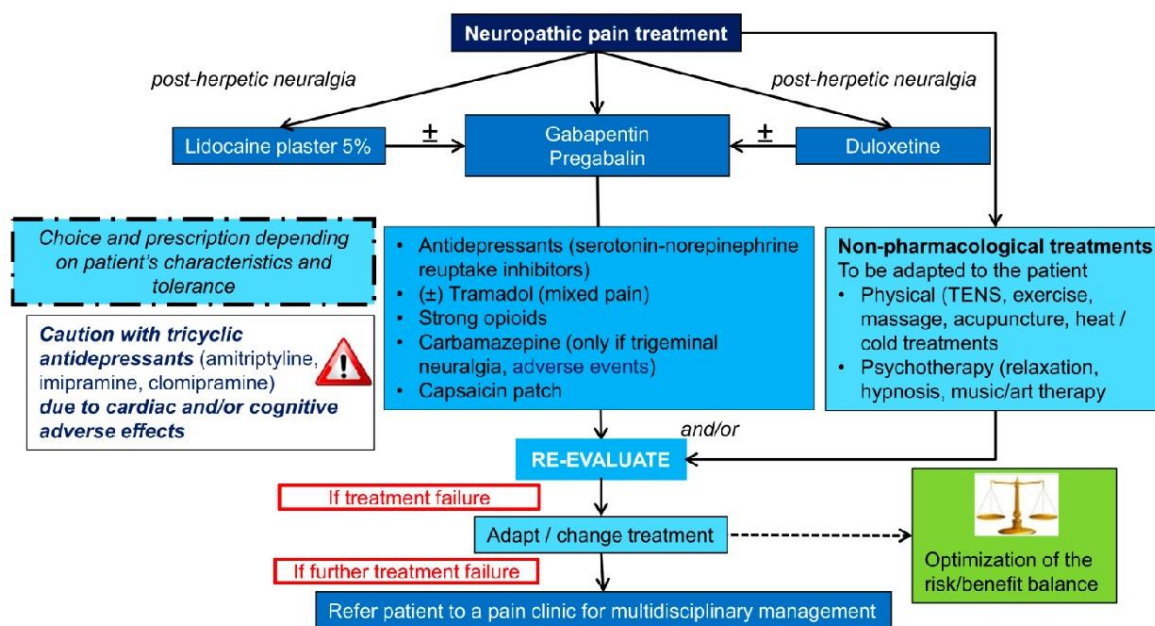


Figure 4: Algorithm Step 4. Therapy and Evaluation of NP. TENS= transcutaneous electrical nerve stimulation.¹³

valproate, which can be used for the treatment of third-line NP have many side effects and drug-drug interactions and should therefore be used with caution in the elderly.¹³

If a combination of drugs is needed, the drugs given must have a different mechanism of action. However, this approach should be used only when absolutely necessary and drugs should be hierarchized to reduce drug burden and risk of drug-drug interactions. A multimodal approach is recommended that includes both pharmacological and non-pharmacological treatments based on available evidence.¹³ The role of non-pharmacological treatment to treat pain in the elderly is becoming increasingly important because it is safe, can relieve pain, and can enhance the effect of pharmacological treatment.^{13,25} Many of the nonpharmacological treatments used for patients with cognitive impairment involve behavioral techniques and exercise and have been reported to reduce pain and result in improved function. Longer-term larger studies in the elderly are needed.¹³

Step 4. Re-evaluate Pain and Treatment¹³

The efficacy of treating pain in elderly with impaired communication and cognition should be regularly evaluated through pain assessment in collaboration with everyone involved in patient care. An important goal is to minimize the side effects of treatment and improve the benefit-risk ratio. The evaluation should be repeated frequently and discussed by the multidisciplinary health care team, who can decide what changes are needed in the therapeutic strategy. (Figure 4).¹³

This algorithm can be a practical tool that is useful in everyday practice. Its main limitation is that it has not been validated in real life. The Doloplus group plans to validate all four steps of the algorithm in a prospective study involving a large population of seniors with cognitive impairment in the near future. This validation will allow the tool to be disseminated to healthcare providers working with the geriatric population.¹³

4. CONCLUSION

Treatment of NP is a formidable challenge, especially in the elderly, especially in the elderly with communication disorders. Every important step and evaluation must be taken by the health care provider. The NP treatment algorithm is a useful tool for conducting clinical investigations for the elderly, especially those with cognitive impairment. Pharmacological treatment of the elderly must be carried out with caution considering the use of poly-medication can cause drug-drug interactions. Non-pharmacological treatment can be given, but evidence of efficacy is still limited. Periodic evaluation

and multidisciplinary team collaboration are important to provide the best quality of NP treatment. The algorithm for treating NP in the elderly with cognitive impairment shows that suspected NP can be diagnosed and managed effectively and efficiently.

5. Acknowledgement

The authors thankfully acknowledge sharing much of the information contained in this paper, as well the figures and a table, has been borrowed from a paper by Pickering G, Marcoux M, Chapiro S, David L, Rat P, Michel M, et al. An Algorithm for Neuropathic Pain Management in Older People. *Drugs and Aging*. 2016;33(8):575–83.

6. Author contribution

HBH: research, performed the analysis, manuscript editing
VAP, ATS, FSF: literature research, manuscript reviewing and revising

7. REFERENCES

1. Zarei M, Tabatabaee A, Roshan Ravan M. The effect of wet-cupping on the severity of migraine headaches: Randomized controlled clinical trial. *Biomed Res Ther*. 2019;6(2):2992–5.
2. Gebke KB, McCarberg B, Shaw E, Turk DC, Wright WL, Semel D. A practical guide to recognize, assess, treat and evaluate (RATE) primary care patients with chronic pain. *Postgrad Med [Internet]*. 2021;00(00):1–10. Available from: <https://doi.org/10.1080/00325481.2021.2017201>
3. Dagnino APA, Campos MM. Chronic Pain in the Elderly: Mechanisms and Perspectives. *Front Hum Neurosci*. 2022;16:1–11.
4. Serotonergic Receptors. In: *Pain Management Essential Topics for Examinations*. 1st ed. London: Springer; 2014. p. 11–2.
5. Szczudlik A, Dobrogowski J, Wordliczek J, St A, Przeklasa-muszy A, Kocot-k M, et al. ScienceDirect Review article Diagnosis and management of neuropathic pain : Review of literature and recommendations of the Polish Association for the Study of Pain and the Polish Neurological Society – Part one. 2014;8:2–11.
6. Cohen SP, Mao J. Neuropathic pain: mechanisms and their clinical implications. *Bmj [Internet]*. 2014;348(feb05 6):f7656–f7656. Available from: <http://www.bmj.com/cgi/doi/10.1136/bmj.f7656>
7. For G, Pharmacological THE, Of T, Pain N, The P, Note A, et al. Guidelines for the Pharmacological Treatment of Neuropathic Pain (2017). 2017; Available from: http://www.watag.org.au/watag/docs/Advisor_Note_Neuropathic_Pain_Guidelines.pdf
8. Casanova-García C, Lerma Lara S, Pérez Ruiz M, Ruano Domínguez D, Santana Sosa E. Non-pharmacological treatment for neuropathic pain in children with cancer. *Med Hypotheses*. 2015;85(6):791–7.
9. Cruccu G, Truini A. A review of Neuropathic Pain: From Guidelines to Clinical Practice. *Pain Ther [Internet]*. 2017;6(S1):35–42. Available from: <http://link.springer.com/10.1007/s40122-017-0087-0>

10. Murnion BP. Neuropathic pain: Current definition and review of drug treatment. *Aust Prescr*. 2018;41(3):60–3.
11. Lema MJ, Foley KM, Hausheer FH. Types and epidemiology of cancer-related neuropathic pain: the intersection of cancer pain and neuropathic pain. *Oncologist*. 2010;15 Suppl 2(suppl 2):3–8.
12. Nickel FT, Seifert F, Lanz S, Maihöfner C. Mechanisms of neuropathic pain. *Eur Neuropsychopharmacol* [Internet]. 2012;22(2):81–91. Available from: <http://dx.doi.org/10.1016/j.euroneuro.2011.05.005>
13. Pickering G, Marcoux M, Chapiro S, David L, Rat P, Michel M, et al. An Algorithm for Neuropathic Pain Management in Older People. *Drugs and Aging*. 2016;33(8):575–83.
14. Kessler TL. Treatments for neuropathic pain. *Clin Pharm*. 2017;9(12):1–16.
15. Hansson P. Difficulties in stratifying neuropathic pain by mechanisms. *Eur J Pain* [Internet]. 2003;7(4):353–7. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/12821406>
16. Abrecht CR, Nedeljkovic SS. Neuropathic pain. *Pain Med An Essent Rev* [Internet]. 2017;3:541–3. Available from: <http://dx.doi.org/10.1038/nrdp.2017.2>
17. Miranda CCV, Seda Junior L de F, Pelloso LRC do A. New physiological classification of pains: current concept of neuropathic pain. *Rev Dor* [Internet]. 2016;17(Suppl 1):3–5. Available from: <http://www.gnresearch.org/doi/10.5935/1806-0013.20160037>
18. Practice C. Neuropathic pain – pharmacological management The pharmacological management of neuropathic pain in adults in. NICE clinical guideline 173. <http://guidance.nice.org.uk/CG173>. 2013.
19. Baron R, Binder A, Wasner G. Neuropathic pain: Diagnosis, pathophysiological mechanisms, and treatment. *Lancet Neurol* [Internet]. 2010;9(8):807–19. Available from: [http://dx.doi.org/10.1016/S1474-4422\(10\)70143-5](http://dx.doi.org/10.1016/S1474-4422(10)70143-5)
20. Colloca L, Ludman T, Bouhassira D, Baron R, Dickenson A, Yarnitsky D, Freeman R, Truini A, Attal N FN. HHS Public Access - Neuropathic Pain. *Nat Rev Dis Prim*. 2017;3 (doi:10.1038/nrdp.2017.2):1–45.
21. Stein C. Opioids, sensory systems and chronic pain. *Eur J Pharmacol* [Internet]. 2013;716(1–3):179–87. Available from: <http://dx.doi.org/10.1016/j.ejphar.2013.01.076>
22. Alles SRA, Smith PA. Etiology and Pharmacology of Neuropathic Pain. *Pharmacol Rev* [Internet]. 2018;70(2):315–47. Available from: <http://pharmrev.aspetjournals.org/lookup/doi/10.1124/pr.117.014399>
23. Mu A, Frcpc M, Weinberg E, Moulin DE, Clarke H. Pharmacologic management of chronic neuropathic pain. *Can Fam Physician* [Internet]. 2017;63(11):844–52. Available from: <http://www.cfp.ca/content/cfp/63/11/844.full.pdf>
24. Hung AL, Lim M, Doshi TL. Targeting cytokines for treatment of neuropathic pain. *Scand J Pain*. 2017;
25. Gulistan Bahat Ozturk RI, Asli Tufan TSA. Approach to Pain in the Elderly. *J Gerontol Geriatr Res*. 2013;02(03).