

Diagnosis & Treatment of Neuropathic Pain

Neuropathic pain is characterized by burning, tingling, or sharp, stabbing pain. If a patient has these symptoms, consider the following diagnoses:

Painful peripheral neuropathy:

- Most common presentation is symmetric and distal, involving the toes and/or balls of the feet
- Over time, symptoms often progress slowly up the legs and may also involve the hands (stocking–glove distribution)
- Can be accompanied by hyperalgesia (increased sensitivity to pain), allodynia (pain from touch or from other stimuli that do not usually cause pain), sensory impairment, and/or slight weakness

or

Postherpetic neuralgia:

- Neuropathic pain involving 1 or 2 (rarely ≥ 3) adjacent dermatomes, not crossing midline
- Most commonly involves thoracic dermatomes but may occur elsewhere
- Diagnosis is often clinical and can be made when dermatomal pain persists for >30 days after resolution of the typical rash of herpes zoster.
- The pain from postherpetic neuralgia typically persists for several months after the rash resolves and can be accompanied by allodynia (pain from touch or from other stimuli that do not usually cause pain) and/or sensory impairment to the affected area.

Does the patient have an atypical presentation or one of the following red flags?

- ▶ Rapid onset
- ▶ Unilateral or asymmetric distribution
- ▶ Significant weakness
- ▶ Systemic symptoms

yes

Refer to a neurologist for further diagnostic workup

no

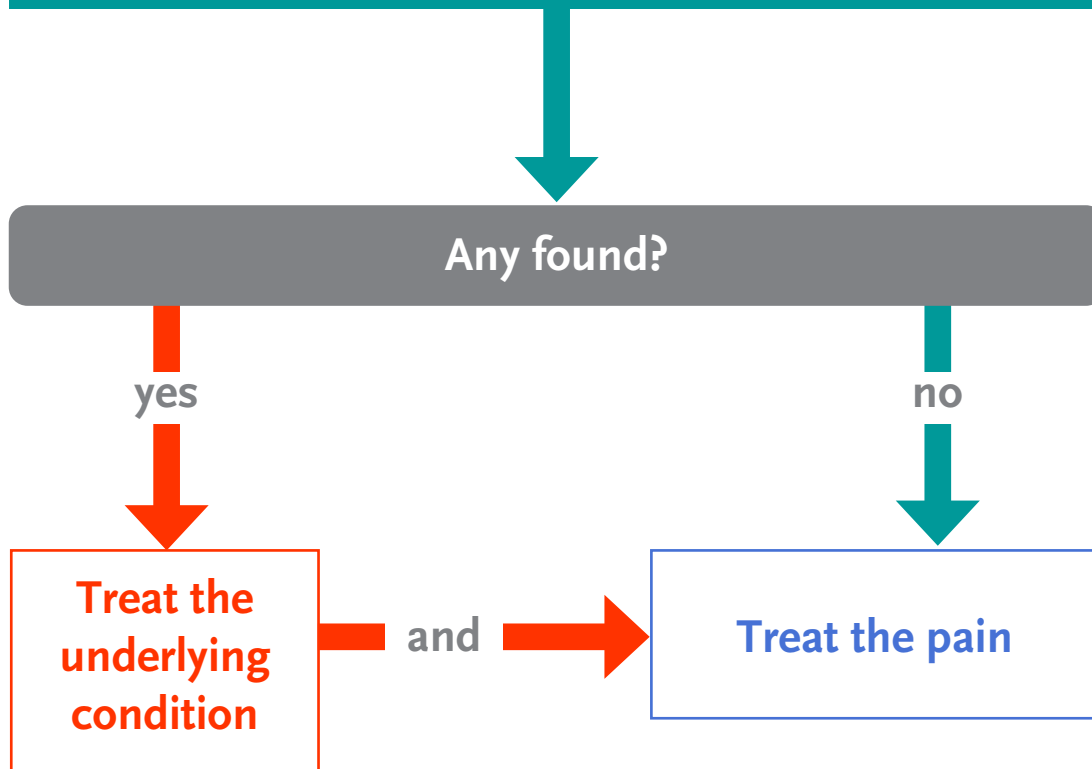
Evaluate and treat

Evaluation for Underlying Conditions

- Postherpetic neuralgia → no testing needed
- Painful peripheral neuropathy → test for the following underlying conditions:

- **Diabetes or prediabetes** → measurement of glycated hemoglobin, and if normal, glucose tolerance testing*
- **Vitamin B₁₂ deficiency** → metabolites such as methylmalonic acid can help confirm a physiologic effect of vitamin B₁₂ deficiency
- **Thyroid dysfunction** → measurement of thyroid-stimulating hormone
- **HIV infection**
- **Multiple myeloma or other paraproteinemias** → serum and urine protein electrophoresis with immunofixation
- **Uremic polyneuropathy** → measurement of blood urea nitrogen and creatinine

* In patients with impaired glucose tolerance, even without diabetes, neuropathic pain may be responsive to tight glycemic control.



Options for Treating Neuropathic Pain

When moving forward with a trial of pharmacologic therapy, take the following factors into account:



- Nature of the symptoms*
- Comorbidities (e.g., depression, insomnia, headaches)
- Risk of adverse effects with medication (e.g., in older patients, those with renal failure)
- Drug interactions with other medications
- Location of pain
- Functional impact of pain

*Note: Medications help reduce paresthesias and pain but do not help pure numbness (the lack of sensation), which may also occur in peripheral neuropathy. For sensory impairment, treatment should focus on management of any underlying cause and on physical therapy for improving balance.

Choose either a trial of topical medications, or go directly to systemic medications.



Try one of the following TOPICAL medications.

These medications are primarily approved for and used in patients with postherpetic neuralgia whose pain is in an accessible area. They can also be considered in other forms of neuropathy, especially if the patient prefers topical interventions or if the patient is at high risk for adverse effects of oral medications (e.g., older adults, those with multiple comorbidities).

Medication	 Pros	 Cons
Lidocaine 5% patch	<ul style="list-style-type: none">• Convenient to apply• Best for large, flat, hairless areas without a lot of movement (e.g., thorax, abdomen)	<ul style="list-style-type: none">• May be expensive• Systemic absorption may lead to adverse effects if overused
Capsaicin 0.075% cream	<ul style="list-style-type: none">• Can be used on areas with a lot of movement (e.g., extremities, joints)	<ul style="list-style-type: none">• May cause topical adverse effects (erythema, burning)• Requires repeated administration• Messy to apply (wash hands well afterwards)• May take several weeks to take effect

No clinically meaningful effect with one of the above?

Try one of the following **ORAL** medications:

Medication	 Pros	 Cons
Gabapentinoids	<ul style="list-style-type: none">• Good efficacy in neuropathic pain	<ul style="list-style-type: none">• May cause adverse effects (e.g., fatigue, imbalance)
Pregabalin		<ul style="list-style-type: none">• Expensive
Gabapentin	<ul style="list-style-type: none">• Less expensive than pregabalin• Wide dose range	<ul style="list-style-type: none">• Must be taken three times daily (although long-acting forms do exist)
Serotonin–norepinephrine reuptake inhibitors (SNRIs) e.g., duloxetine, venlafaxine	<ul style="list-style-type: none">• May help with comorbid depression or anxiety	<ul style="list-style-type: none">• Potential for adverse effects (e.g., hypertension with venlafaxine, sedation with duloxetine)
Tricyclic antidepressants (TCAs) e.g., nortriptyline, amitriptyline	<ul style="list-style-type: none">• May help with comorbid depression or anxiety (though often given in lower doses than indicated for depression)• Can be taken at nighttime so that the sedating effects can help with insomnia	<ul style="list-style-type: none">• Risk of adverse effects (e.g., anticholinergic [dry mouth and urinary retention], antihistaminic, cardiac conduction abnormalities)

Opioids do not have a role in the initial management of neuropathic pain.

No clinically meaningful effect with one of the above?

- Try a **different option** from the above list
- Try **combining** a gabapentinoid with either a TCA or an SNRI
- Try **second-line therapy** with valproic acid (a sodium channel blocker)
 - Should be avoided in people of childbearing potential
 - Requires frequent monitoring of blood levels and dose adjustments
 - Has many drug interactions

No clinically meaningful effect?

**Refer to a neurologist
or pain clinic**

References:

1. Pop-Busui R et al. Diabetic neuropathy: a position statement by the American Diabetes Association. *Diabetes Care* 2017; 40:136.
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3. Snyder MJ et al. Treating painful diabetic peripheral neuropathy: an update. *Am Fam Physician* 2016 Aug 1; 94:227.
4. Barohn RJ et al. Patient assisted intervention for neuropathy: comparison of treatment in real life situations (PAIN-CONTRoLS): Bayesian adaptive comparative effectiveness randomized trial. *JAMA Neurol* 2021 Jan 1; 78:68.
5. Price R et al. Oral and topical treatment of painful diabetic polyneuropathy: practice guideline update. *Neurol* 2022 Jan 4; 98:31

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