

Neuropathic pain in diabetic polyneuropathy: comparison of first-line drugs.

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Abstract

Painful diabetic peripheral neuropathy (PDPN) is a common complication of diabetes and a leading cause of chronic neuropathic pain, sleep disturbance, and reduced quality of life. Modern guidelines converge on a small set of first-line pharmacologic options—most commonly duloxetine (SNRI), pregabalin or gabapentin (gabapentinoids), and amitriptyline (TCA)—selected according to comorbidities, contraindications, and tolerability. A major contemporary insight is that these first-line agents often show similar average analgesic efficacy, and if monotherapy is insufficient, combination strategies (e.g., adding pregabalin to duloxetine or amitriptyline) can provide additional benefit, as demonstrated in the OPTION-DM trial.

This review summarizes how to differentiate first-line choices in practice (efficacy, onset, adverse effects, and patient phenotypes) and highlights a stepwise strategy to reduce pain while minimizing harms, especially medication burden and inappropriate opioid use.

Keywords

painful diabetic peripheral neuropathy; diabetic polyneuropathy; neuropathic pain; duloxetine; pregabalin; gabapentin; amitriptyline; first-line therapy; combination therapy; option-dm; adverse effects; sleep disturbance

Introduction

Painful diabetic peripheral neuropathy arises from diabetes-related nerve injury (typically length-dependent, distal symmetric neuropathy). Pain is often described as burning, electric shocks, tingling, stabbing, or deep aching, frequently

worsening at night and strongly affecting sleep and mood. Because neuropathic pain is driven by altered peripheral and central pain processing, common “simple analgesics” are usually insufficient, and evidence-based first-line therapy relies on neuromodulating agents (antidepressants and anticonvulsants) rather than opioids.

International guidance generally recommends choosing among four core first-line drugs—amitriptyline, duloxetine, pregabalin, and gabapentin—then switching class or combining if response is incomplete. Best fit when: pain + depression/anxiety, widespread pain, or when you prefer a non-sedating option. Strengths: Strong guideline support and widely used as an initial choice; helpful when mood symptoms coexist; generally straightforward once-daily dosing. Common limitations: nausea, dry mouth, dizziness, insomnia or somnolence; avoid/monitor carefully with certain hepatic conditions (and follow local labeling for renal thresholds). Clinical “tip”: If the patient’s main complaint is daytime pain with comorbid depression, duloxetine is often a logical first pick; if the main complaint is nocturnal pain and insomnia, you may prefer a more sedating option. Painful diabetic peripheral neuropathy (PDPN) is a common and disabling complication of diabetes, producing burning, electric-shock pain, tingling, and allodynia—often worse at night and strongly affecting sleep and mood. Contemporary guidelines consistently recommend non-opioid “neuromodulating” medicines as first-line therapy, most commonly duloxetine (SNRI), pregabalin or gabapentin (gabapentinoids), and tricyclic antidepressants (TCAs) such as amitriptyline; some guidance also includes sodium-channel blockers as effective options.

Recent head-to-head pathway evidence (OPTION-DM) shows that treatment pathways based on amitriptyline, duloxetine, and pregabalin have similar average analgesic efficacy, and that combination therapy (adding a second first-line agent when monotherapy is insufficient) can provide additional pain relief and is generally well tolerated. Diabetic distal symmetric polyneuropathy develops through metabolic and microvascular injury to peripheral nerves and typically

progresses in a length-dependent “stocking” pattern. When neuropathy becomes painful, patients describe burning or stabbing pain, “pins and needles,” hypersensitivity to touch, and nocturnal worsening that disrupts sleep and daily functioning. Because neuropathic pain reflects abnormal peripheral nerve signaling and central sensitization, simple analgesics alone are often inadequate, and modern evidence-based care prioritizes targeted agents that modulate neurotransmission (serotonin/noradrenaline pathways, calcium channel signaling, and related mechanisms). A second, very practical point is that PDPN is frequently accompanied by comorbidities that influence medication choice—depression/anxiety, insomnia, obesity, edema, renal impairment, and polypharmacy. Guidelines therefore support several “first-line” options and encourage individualized selection and stepwise adjustments.

In practice, the “best” first-line drug is usually determined less by large efficacy differences and more by patient-specific factors: sleep disturbance, depression/anxiety, renal function, frailty/age, drug interactions, and adverse-effect vulnerability.

Conclusion

For neuropathic pain in diabetic polyneuropathy, modern evidence and guidelines consistently support a small set of first-line options—duloxetine, pregabalin, gabapentin, and amitriptyline—with selection driven mainly by comorbidities (mood, sleep), contraindications (renal/hepatic/cardiac considerations), and side-effect tolerance rather than major differences in average efficacy.

Head-to-head pathway evidence from OPTION-DM indicates that these approaches can be similarly effective, and that combination therapy is a rational next step when monotherapy is insufficient—while opioids should generally be avoided due to unfavorable risk-benefit in PDPN.

Literature:

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