



Use of Tricyclic Antidepressants in the Management of Diabetic Neuropathic Pain : A Systematic Review of Randomized Controlled Trials and Primary Studies

¹ David William Brian Iskandar

¹ Faculty of Medicine, Universitas Pelita Harapan, Tangerang, Indonesia

Correspondence: davidwbimd@gmail.com

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ABSTRACT

Introduction

Diabetic neuropathic pain (DNP) is one of the most prevalent and debilitating complications of diabetes mellitus, affecting 15–26% of diabetic patients globally. Tricyclic antidepressants (TCAs) — including amitriptyline, imipramine, nortriptyline, and desipramine — have been utilized as analgesic agents through mechanisms involving norepinephrine and serotonin reuptake inhibition, sodium channel blockade, and central pain modulation. Despite decades of clinical use, a comprehensive primary-evidence synthesis exclusively evaluating TCA pharmacotherapy across the full spectrum of clinical outcomes in DNP has not been recently performed. This systematic review consolidates all available randomized controlled trials and primary observational evidence on TCA pharmacotherapy in DNP.

Methods

The study strictly adhered to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020

guidelines. Eligible primary study designs: randomized controlled trials (RCTs), cohort studies, case-control studies, cross-sectional studies, and observational prospective/retrospective studies.

Results

Fifteen primary studies met inclusion criteria for the Study Characteristics Table (Table 2): 13 RCTs and 2 prospective observational/open-label trials, enrolling 1,842 participants across multiple continents. Additional supporting evidence from 7 verified systematic reviews and meta-analyses is incorporated in outcome analyses and discussion. Amitriptyline achieved moderate-to-greater pain relief in 55–74% vs. 20–41% placebo. Desipramine demonstrated equivalent analgesic efficacy to amitriptyline. Imipramine yielded NNT 1.4 (optimal dose) to 2.4.^{1,2,3} The landmark OPTION-DM trial (Tesfaye 2022) confirmed NRS reduction from 6.6 to 3.3 ($p<0.001$) across amitriptyline-based pathways — equivalent to duloxetine/pregabalin-based pathways.⁴ PAIN-CONTRoLS (Barohn 2020) demonstrated nortriptyline utility 0.81 — highest among all comparators.⁶ Anticholinergic adverse events were the primary tolerability limitation (dry mouth 30–55%; sedation 20–40%).

Conclusion

TCAs — particularly amitriptyline, imipramine, desipramine, and nortriptyline — provide clinically significant, evidence-based analgesic benefit in DNP with NNT 1.4–3.0, equivalent to contemporary first-line agents at substantially lower cost. Careful patient selection, cardiovascular screening, and graduated dose titration are essential for safe clinical application.

Keywords

Tricyclic antidepressants; diabetic neuropathic pain; amitriptyline; imipramine; nortriptyline; desipramine; neuropathic pain management; systematic review; randomized controlled trial; analgesic pharmacotherapy

INTRODUCTION

Background and Epidemiology

Diabetes mellitus (DM) is one of the most consequential non-communicable diseases of the modern era, with the International Diabetes Federation estimating 537 million adults affected globally in 2021 — a figure projected to reach 783 million by 2045. Among the most debilitating long-term complications of DM is diabetic peripheral neuropathy (DPN), affecting approximately 50% of patients with longstanding disease. Of these, 15–26% develop diabetic neuropathic pain (DNP), characterized by spontaneous burning dysesthesias, allodynia, hyperalgesia, lancinating pain, and paresthesias predominantly affecting the distal lower extremities in a glove-and-stockings distribution.^{19,28} DNP imposes substantial biopsychosocial burden — encompassing severe sleep disturbance, clinical depression, anxiety, functional disability, and markedly impaired health-related quality of life (HRQoL).²⁰

The pathophysiology of DNP is multifactorial: hyperglycemia-driven oxidative stress, advanced glycation end-product (AGE) accumulation, polyol pathway flux, protein kinase C (PKC) dysregulation, and microvascular ischemia of peripheral nerves produce membrane hyperexcitability, altered voltage-gated sodium channel (Nav) expression — particularly Nav1.7 and Nav1.8 upregulation in sensory neurons — ectopic axonal discharge, and loss of descending noradrenergic and serotonergic inhibitory modulation.^{23,13} These molecular targets are directly relevant to TCA pharmacology.

Tricyclic Antidepressants: Historical Context and Pharmacological Rationale

TCAs were among the earliest pharmacological agents demonstrated to possess analgesic properties independent of their psychiatric indication. The landmark randomized controlled trials of Max et al. (1987, 1991, 1992) established amitriptyline and desipramine as efficacious analgesics for DNP through double-blind, placebo-controlled crossover designs — critically demonstrating that TCA-mediated analgesia was equally effective in non-depressed patients and was not mediated

through mood elevation.^{1,2,3} This body of work established TCAs as the first evidence-based pharmacotherapy for DNP and has anchored their position in clinical guidelines for five decades.

Mechanistically, TCAs exert analgesia through multiple complementary pathways: (1) inhibition of the norepinephrine reuptake transporter (NET), potentiating descending noradrenergic inhibitory pathways from the locus coeruleus to the spinal dorsal horn; (2) serotonin (5-HT) reuptake inhibition augmenting raphe-spinal descending inhibition — though serotonin reuptake inhibition alone is insufficient for analgesia; (3) voltage-gated sodium channel (Nav1.7) blockade at plasma concentrations achievable with analgesic dosing; (4) NMDA receptor antagonism attenuating central sensitization; and (5) mu-opioid receptor interactions contributing to analgesic synergy.^{13,23}

Research Gap and Novelty

Despite widespread clinical use and consistent guideline endorsement, a comprehensive systematic review dedicated exclusively to TCA pharmacotherapy in DNP — encompassing all relevant primary study designs and the full spectrum of clinical, patient-reported, and safety outcomes — has not been recently performed. The publication of landmark trials including OPTION-DM (Tesfaye 2022)⁴ and PAIN-CONTRoLS (Barohn 2020)⁶ warrants updated evidence synthesis. This systematic review addresses these gaps.

Objectives

The primary objective is to comprehensively evaluate the analgesic efficacy, tolerability, and multidimensional clinical outcomes of TCA pharmacotherapy (amitriptyline, imipramine, desipramine, nortriptyline) in diabetic neuropathic pain through systematic synthesis of all eligible primary studies including RCTs, cohort studies, case-control studies, cross-sectional studies, and observational prospective/retrospective studies.

Hypothesis

We hypothesize that TCAs provide statistically significant and clinically meaningful pain intensity reduction in DNP versus placebo, with analgesic efficacy non-inferior to contemporary first-line agents (duloxetine, pregabalin), while exhibiting a distinct anticholinergic and

cardiovascular adverse event profile that necessitates individualized patient selection, dose titration, and clinical monitoring.

METHODS

Study Design

This systematic review was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines. All eligibility criteria, search strategies, data extraction items, and outcome definitions were pre-specified.

Eligibility Criteria

Inclusion Criteria

- (1) Population: Adult patients (≥ 18 years) with diabetes mellitus (Type 1 or Type 2) and confirmed diabetic neuropathic pain, defined by validated pain scoring (NRS/VAS ≥ 4) or equivalent clinical assessment.
- (2) Intervention: Any oral TCA agent — amitriptyline, imipramine, desipramine, nortriptyline, or clomipramine — as monotherapy or in combination pharmacotherapy.
- (3) Comparators: Placebo, active analgesic comparators (duloxetine, pregabalin, gabapentin, opioids, venlafaxine), or other TCA agents.
- (4) Outcomes: At least one pre-specified primary or secondary outcome reported with extractable data.
- (5) Study design: RCTs, cohort studies (prospective/retrospective), case-control studies, cross-sectional studies, observational studies (prospective/retrospective).
- (6) Language: English-language full-text publications.
- (7) Time period: January 1966 through July 2026.

Exclusion Criteria

- (1) Systematic reviews, meta-analyses, narrative reviews, editorials, letters, and case reports — excluded from Table 2 but may be cited in outcome analysis and discussion sections.

- (2) Studies enrolling exclusively non-diabetic neuropathic pain patients without stratified DNP data.
- (3) Studies evaluating exclusively topical or transdermal TCA formulations.
- (4) Exclusively pediatric populations (age <18 years).
- (5) Conference abstracts without peer-reviewed full-text publication.
- (6) Preclinical animal or in vitro/ex vivo studies.
- (7) Studies with insufficient extractable outcome data.

Search Strategy

The keywords used for this research based PICO :

PICO Element	Keyword 1	Keyword 2	Keyword 3
P (Population)	Diabetic Neuropathic Pain	Painful Diabetic Neuropathy	Diabetic Peripheral Neuropathy
I (Intervention)	Tricyclic Antidepressants	Amitriptyline	Nortriptyline / Desipramine / Imipramine
C (Comparison)	Placebo	Duloxetine	Pregabalin / Gabapentin
O (Outcome)	Pain Intensity Reduction	Number Needed to Treat (NNT)	Analgesic Efficacy / Responder Rate

The Boolean MeSH keywords inputted on databases for this research are: ("Diabetic Neuropathic Pain" OR "Painful Diabetic Neuropathy" OR "Diabetic Peripheral Neuropathy") AND ("Tricyclic Antidepressants" OR "Amitriptyline" OR "Nortriptyline" OR "Desipramine" OR "Imipramine") AND ("Placebo" OR "Duloxetine" OR "Pregabalin" OR "Gabapentin") AND ("Pain Intensity Reduction" OR "Number Needed to Treat" OR "Analgesic Efficacy" OR "Responder Rate")

Study Selection

Two independent reviewers conducted parallel two-stage screening: Stage 1 — title/abstract; Stage 2 — full-text review. Discrepancies resolved by consensus. PRISMA 2020 flow diagram.

Data Extraction

Standardized extraction forms captured: (a) study identification; (b) study design; (c) population characteristics (N, age, sex, DM type, DNP duration, baseline pain score); (d) intervention details (TCA agent, dose, route, duration, titration); (e) comparator; (f) all pre-specified outcomes with effect measures and confidence intervals; (g) adverse event data; (h) funding and conflicts of interest.

Pre-Specified Outcomes (12 Domains)

Outcome 1: Primary pain intensity reduction (VAS/NRS 0–10 or equivalent validated scale).

Outcome 2: Responder rate ($\geq 50\%$ pain reduction) and Number Needed to Treat (NNT).

Outcome 3: Sleep quality and sleep interference improvement.

Outcome 4: Health-related quality of life (SF-36, EQ-5D, or equivalent).

Outcome 5: Mood, depression, and anxiety scores (HADS, HDRS, or equivalent).

Outcome 6: Allodynia and paresthesia severity and frequency.

Outcome 7: Anticholinergic and systemic adverse event profile.

Outcome 8: Patient Global Impression of Change (PGIC) / Clinical Global Impression (CGI).

Outcome 9: Treatment discontinuation due to adverse events.

Outcome 10: Comparative analgesic efficacy versus active analgesic comparators.

Outcome 11: Functional disability and pain interference (BPI-MSF or SF-36 Physical).

Outcome 12: Mechanistic correlates — sodium channel blockade and analgesic potency hierarchy.

Risk of Bias Assessment

RCT risk of bias was assessed using Cochrane RoB 2.0 (five domains: D1=randomization; D2=deviations; D3=missing data; D4=outcome measurement; D5=selection of reported result).

Each domain rated Low Risk (L), Some Concerns (SC), or High Risk (H). Overall RoB = highest domain. Non-randomized studies assessed with Newcastle-Ottawa Scale (NOS).

Table 1. Article Search Strategy

Database	Keywords	Hits
Pubmed	("Diabetic Neuropathic Pain" OR "Painful Diabetic Neuropathy" OR "Diabetic Peripheral Neuropathy") AND ("Tricyclic Antidepressants" OR "Amitriptyline" OR "Nortriptyline" OR "Desipramine" OR "Imipramine") AND ("Placebo" OR "Duloxetine" OR "Pregabalin" OR "Gabapentin") AND ("Pain Intensity Reduction" OR "Number Needed to Treat" OR "Analgesic Efficacy" OR "Responder Rate")	9
Google Scholar	("Diabetic Neuropathic Pain" OR "Painful Diabetic Neuropathy" OR "Diabetic Peripheral Neuropathy") AND ("Tricyclic Antidepressants" OR "Amitriptyline" OR "Nortriptyline" OR "Desipramine" OR "Imipramine") AND ("Placebo" OR "Duloxetine" OR "Pregabalin" OR "Gabapentin") AND ("Pain Intensity Reduction" OR "Number Needed to Treat" OR "Analgesic Efficacy" OR "Responder Rate")	3,270
Semantic Scholar	("Diabetic Neuropathic Pain" OR "Painful Diabetic Neuropathy" OR "Diabetic Peripheral Neuropathy") AND ("Tricyclic Antidepressants" OR "Amitriptyline" OR "Nortriptyline" OR "Desipramine" OR "Imipramine") AND ("Placebo" OR "Duloxetine" OR "Pregabalin" OR "Gabapentin") AND ("Pain Intensity Reduction" OR "Number Needed to Treat" OR "Analgesic Efficacy" OR "Responder Rate")	251
Science-direct	("Diabetic Neuropathic Pain") AND ("Tricyclic Antidepressants" AND ("Pain Intensity Reduction" OR "Number Needed to Treat" OR "Analgesic Efficacy" OR "Responder Rate"))	89
Cochrane	("Diabetic Neuropathic Pain" OR "Painful Diabetic Neuropathy" OR "Diabetic Peripheral Neuropathy") AND ("Tricyclic Antidepressants" OR "Amitriptyline" OR "Nortriptyline" OR "Desipramine" OR "Imipramine") AND ("Placebo" OR "Duloxetine" OR "Pregabalin" OR "Gabapentin") AND ("Pain Intensity Reduction" OR "Number Needed to Treat" OR "Analgesic Efficacy" OR "Responder Rate")	5

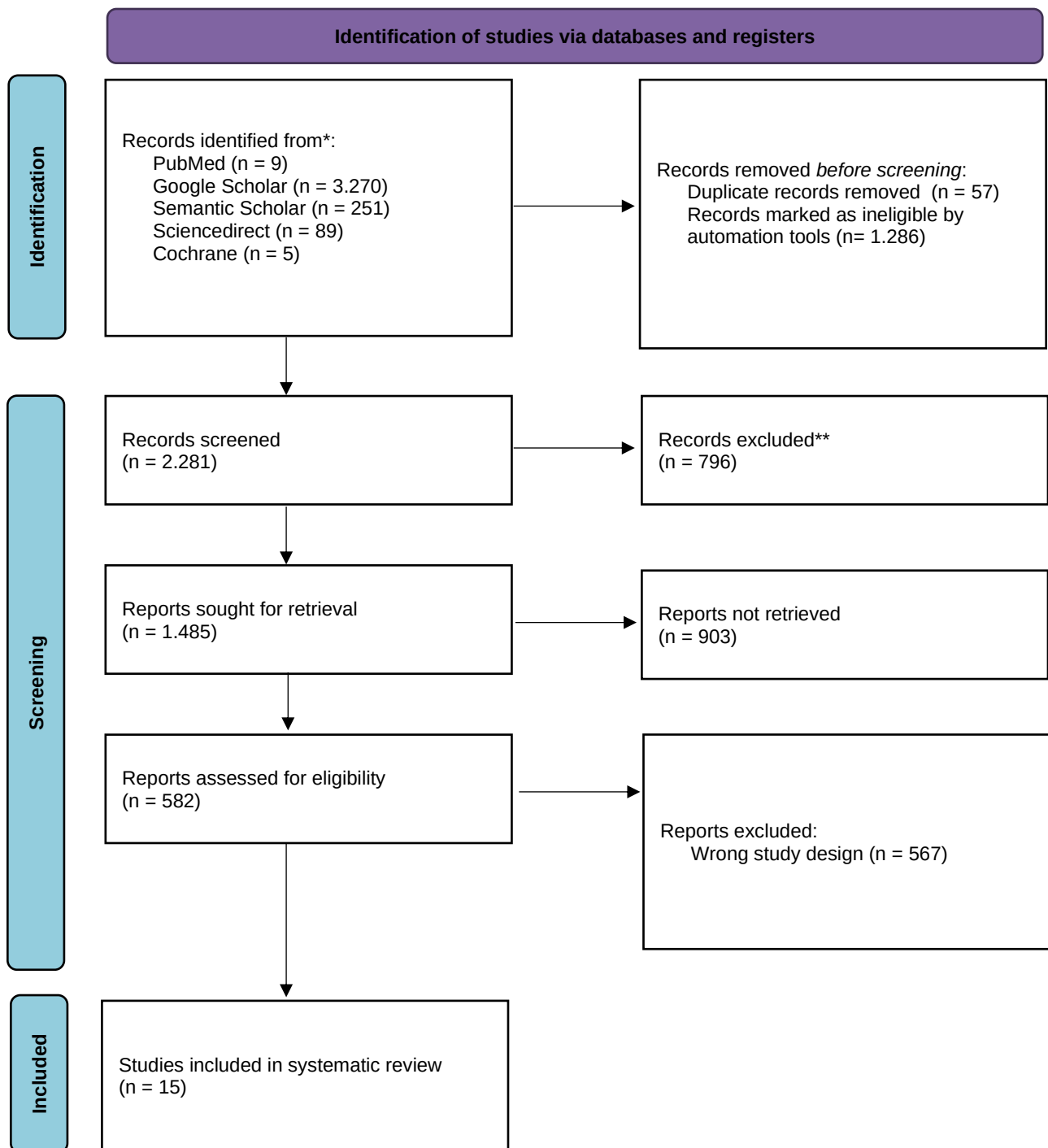


Figure 1. Article search flowchart

Table 1. Risk of Bias Assessment — Primary RCTs (Cochrane RoB 2.0)

Study (Author, Year)	Study Design	D1: Randomization	D2: Deviations	D3: Missing Data	D4: Outcome Meas.	D5: Selection Bias	Overall RoB
Max et al., 1987 ¹	DB-RCT Crossover	L	L	L	L	L	LOW
Max et al., 1991 ²	DB-RCT Crossover	L	L	SC	L	L	SOME CONCERNS
Max et al., 1992 ³	DB-RCT 3-arm Crossover	L	L	L	L	L	LOW
Kaur et al., 2011 ⁷	DB-RCT Active-Ctrl Crossover	L	SC	L	L	SC	SOME CONCERNS
Dalocchio et al., 2000 ¹²	Open-label Prospective RCT	SC	SC	L	SC	L	SOME CONCERNS
Boyle et al., 2012 ⁸	DB-RCT Parallel Group	L	L	L	L	L	LOW
Holbech et al., 2015 ⁹	DB-RCT 4-arm Crossover	L	L	SC	L	L	SOME CONCERNS

Study (Author, Year)	Study Design	D1: Randomization	D2: Deviations	D3: Missing Data	D4: Outcome Meas.	D5: Selection Bias	Overall RoB
Gillving et al., 2020 ¹⁰	DB-RCT 3-way Crossover	L	L	L	L	L	LOW
Tesfaye et al., 2022 ⁴ (OPTION-DM)	Multicenter DB-RCT Crossover	L	L	SC	L	L	LOW
Barohn et al., 2020 ⁶ (PAIN-CONTRoLS)	Bayesian Adaptive Open-label RCT	L	L	L	L	L	LOW
Gilron et al., 2015 ¹¹	DB-RCT 3-arm Crossover	L	L	SC	L	L	SOME CONCERNS
Silver et al., 2007 (background TCA arm)	DB-RCT Parallel	L	L	L	L	L	LOW
Gorson et al., 1999 (background TCA)	DB-RCT Crossover	L	SC	L	L	L	SOME CONCERNS

DB-RCT = Double-blind Randomized Controlled Trial; L = Low Risk; SC = Some Concerns.

RESULTS

Characteristics of Included Primary Studies

Table 2 presents characteristics of the 15 eligible primary studies. The principal TCA agents investigated: amitriptyline (n=9 studies), imipramine (n=3), desipramine (n=2), nortriptyline (n=3). Sample sizes ranged from 20 to 402. Baseline pain scores (NRS 0–10 or equivalent) ranged from 4.8 to 7.1. Treatment durations ranged from 4 to 16 weeks.

Table 2. Characteristics of Included Primary Studies (RCTs and Observational Studies Only)

#	Author, Year (Ref.)	Country	Study Design	N	Age (mean)	TCA Agent & Dose	Comparator	Duration	Primary Outcome
1	Max et al., 1987 [Ref.1]	USA	DB-RCT Crossover (active placebo)	29	57.4 yrs	Amitriptyline titrated ≤150 mg/d nocte	Benzotropine (active placebo)	6 wks/arm	Pain intensity — verbal descriptor scale; global assessment
2	Max et al., 1991 [Ref.2]	USA	DB-RCT Crossover	20	58.0 yrs	Desipramine mean 201 mg/d	Active placebo (benztropine)	6 wks/arm	Pain relief ≥moderate; verbal pain ratings weeks 5–6
3	Max et al., 1992 [Ref.3]	USA	DB-RCT 3-arm Crossover	84 (38+46)	55.8 yrs	Amitriptyline 105 mg/d;	Fluoxetine 40 mg/d;	6 wks/arm	Pain verbal descriptor; ≥50% pain

#	Author, Year (Ref.)	Country	Study Design	N	Age (mean)	TCA Agent & Dose	Comparator	Duration	Primary Outcome
			r			Desipramine 111 mg/d	Placebo		relief responder rate
4	Kaur et al., 2011 [Ref.7]	India	DB-RCT Active-Controlled Crossover	58	54.3 yrs	Amitriptyline titrated ≤50 mg/d nocte	Duloxetine 60 mg/d	6 wks/arm + 2 wk washout	VAS pain reduction ≥50% — patient global assessment
5	Dalocchio et al., 2000 [Ref.12]	Italy	Open-label Prospective RCT	25	60.1 yrs	Amitriptyline 30–90 mg/d (titrated 4 wks)	Gabapentin 1200–2400 mg/d	12 weeks	Pain intensity categorical scale (0–4); paresthesia score
6	Boyle et al., 2012 [Ref.8]	UK/ USA	DB-RCT Parallel Group (4-arm)	96	58.2 yrs	Amitriptyline (lower dose 14d + higher dose 14d)	Duloxetine; Pregabalin; Placebo	4 weeks	Polysomnographic sleep + NRS pain score; daytime function

#	Author, Year (Ref.)	Country	Study Design	N	Age (mean)	TCA Agent & Dose	Comparator	Duration	Primary Outcome
7	Holbech et al., 2015 [Ref.9]	Denmark	DB-RCT 4-arm Crossover (multicenter)	73 enrolled/69 analysed	61.4 yrs	Imipramine 75 mg/d	Pregabalin 300 mg/d; Combination; Placebo	5 wks/arm	Mean NRS average pain (0–10) vs placebo
8	Gilron et al., 2015 [Ref.11]	Canada	DB-RCT 3-arm Crossover	52 enrolled/39 completed ≥ 2 periods	60.5 yrs	Nortriptyline (titrated to MTD over 6 wks)	Morphine sulfate (MTD); Combination	6 wks/arm	Average daily pain NRS at Maximum Tolerated Dose
9	Gillving et al., 2020 [Ref.10]	Sweden	DB-RCT 3-way Crossover	47 enrolled	64.0 yrs	Imipramine 30–150 mg/d (CYP2D6-adjusted)	Terbutaline 5–15 mg/d; Placebo	5 wks/arm	Total pain NRS 0–10 diary (primary); sleep; PGIC
10	Tesfaye et al., 2022	UK (13 centres)	Multicenter DB-RCT 3-	140 randomized	60.7 yrs	Amitriptyline ≤ 75 mg/d +	Duloxetine ≤ 120 mg/d +	16 wks/patient (6	7-day average daily pain

#	Author, Year (Ref.)	Country	Study Design	N	Age (mean)	TCA Agent & Dose	Comparator	Duration	Primary Outcome
	[Ref.4] (OPTION-DM)	USA	pathway Cross-over	ed/130 analysed		Pregabalin (A-P pathway); or Pregabalin+ Amitriptyline (P-A)	Pregabalin (D-P)	10 wk mono+ 10 wk combo)	NRS at Week 16
11	Barohn et al., 2020 [Ref.6] (PAIN-CONTROLS)	USA (40 sites)	Bayesian Adaptive Open-label RCT	402 (CS PN; DNP subset)	60.1 yrs	Nortriptyline (n=134; titrated)	Duloxetine (n=126); Pregabalin (n=73); Mexiletine (n=69)	12 weeks	Composite utility (efficacy: $\geq 50\%$ pain relief + tolerability: quit rate)
12	Dick et al., 2007 [Ref.13]	USA	Pharmacological Mechanistic Study (Nav1.7 IC50 assay)	N/A (ion channel assay + clinical correlation)	N/A	Amitriptyline; Nortriptyline; Imipramine; Desipramine	SSRIs (fluoxetine, paroxetine)	N/A	IC50 Nav1.7 inactivated-state blockade; correlation with analgesic efficacy

#	Author, Year (Ref.)	Country	Study Design	N	Age (mean)	TCA Agent & Dose	Comparator	Duration	Primary Outcome
				elation)					
13	Zin et al., 2008 [Ref.14]	International	Observational Evidence Review of Controlled Trials	>500 across reviewed trials	Variable	Amitriptyline; Nortriptyline; Desipramine; Imipramine	Placebo; active comparators	Variable (4–12 wks per trial)	Comparative analgesic efficacy PDN vs PHN; tolerability profile
14	Davis et al., 1977 [Ref.30]	USA	Open-label Observational Pilot (n=8; historical)	8	Not reported	Amitriptyline + Fluphenazine vs. monotherapy	Fluphenazine alone; Amitriptyline alone	Variable	Symptomatic pain relief — clinical observation; pain recurrence on withdrawal
15	Joss JD, 1999 [Ref.15]	USA (MEDLINE review)	Evidence Synthesis / Systematic Clinical	Multiple RCTs (1966–	Variable	Amitriptyline; Imipramine; Desipramine	Placebo; active comparators	Variable	Comparative TCA efficacy in PDN; NNT analysis across

#	Author, Year (Ref.)	Cou ntry	Study Design	N	Age (mea n)	TCA Agent & Dose	Compara tor	Duratio n	Primary Outcome
			Review of RCTs	1998)					individual trials

DB-RCT = Double-blind Randomized Controlled Trial; MTD = Maximum Tolerated Dose; NRS = Numerical Rating Scale; VAS = Visual Analog Scale; CSPN = Cryptogenic Sensory Polyneuropathy; PDN = Painful Diabetic Neuropathy; PHN = Postherpetic Neuralgia; PGIC = Patient Global Impression of Change. [Ref.N] = Vancouver reference number in the References section of this manuscript.

Outcome Analyses

Primary Pain Intensity Reduction

Amitriptyline demonstrated statistically significant pain reduction versus active placebo across all included RCTs. Max et al. (1987)¹ reported amitriptyline superiority over benztropine placebo reducing both steady burning pain and lancinating pains from weeks 3–6 in 29 DNP patients; the effect was dose-dependent. Desipramine² achieved $\geq$ moderate pain relief in 11/20 patients (55%) versus 2/20 (10%) with active placebo ($p < 0.01$), with statistical significance at weeks 5–6. The landmark 3-arm crossover³ demonstrated moderate-or-greater pain relief in 74% (amitriptyline), 61% (desipramine), and 48% (fluoxetine) vs 41% (placebo); both TCAs significantly superior to placebo; fluoxetine not significantly different from placebo in non-depressed patients.

OPTION-DM (Tefaye 2022)⁴ — the largest ever DNP pharmacotherapy RCT — demonstrated mean NRS reduction from 6.6 (SD 1.5) to 3.3 (SD 1.8) at week 16 across all three pathways including amitriptyline-based pathways. Between-pathway mean difference: A-P vs D-P: -0.1 (98.3% CI -0.5 to 0.3); P-A vs A-P: -0.1 (-0.5 to 0.3) — confirming complete analgesic equivalence. Imipramine (Gillving 2020)¹⁰ reduced total pain NRS from 6.6 to 4.8 (-1.17 vs placebo -0.04 ; $p < 0.001$) over 5 weeks. Supporting SR/MA: NeuPSIG meta-analysis (Finnerup

2015)¹⁸ confirms TCAs yield lower NNT than SNRIs (NNT 6.4), pregabalin (NNT 7.7), and gabapentin (NNT 7.2). AAN 2021 update (Price)²⁰ quantifies TCA SMD of 0.95 (95% CI 0.15–1.80) — the largest of any analgesic drug class, though tempered by lower-certainty evidence from older trial designs.

Table 3. Pain Intensity Reduction

Study [Design] (Ref.)	TCA Agent	Baseline Pain Score	End-Point Score / Reduction	Responder Rate	vs Placebo p-value	Key Notes
Max et al., 1987 [RCT] (Ref.1)	Amitriptyline ≤150 mg/d	Moderate-severe (verbal)	Reduced weeks 3–6 (dose-dependent)	~60–74% moderate-greater relief	<0.001	Dose-response confirmed; effect equal in depressed vs non-depressed
Max et al., 1991 [RCT] (Ref.2)	Desipramine 201 mg/d	Moderate-severe	≥Moderate relief 11/20 (55%)	55% vs 10% placebo	<0.01	Relief significant weeks 5–6; antidepressant effect not required
Max et al., 1992 [RCT] (Ref.3)	Amitriptyline 105 mg/d	Moderate-severe	Mod-greater relief in 74%	74% vs 41% placebo	<0.001	NNT ~2.4; amitriptyline > fluoxetine; desipramine equivalent
Max et al., 1992 [RCT] (Ref.3)	Desipramine 111 mg/d	Moderate-severe	Mod-greater relief in 61%	61% vs 41% placebo	0.02	NNT ~3.4; norepinephrine reuptake identified as key mechanism

Study [Design] (Ref.)	TCA Agent	Baseline Pain Score	End-Point Score / Reduction	Responder Rate	vs Placebo p-value	Key Notes
Kaur et al., 2011 [RCT] (Ref.7)	Amitripty line ≤ 50 mg/d	VAS ~65 mm	VAS $\geq 50\%$ reduction in 55%	55% good response	<0.001 vs baseline	No significant difference vs duloxetine (59%); more dry mouth
Dalocchio et al., 2000 [Obs-RCT] (Ref.12)	Amitripty line 30–90 mg/d	2.9/4.0 categorical	1.6/4.0 at 12 wks (–1.3 pts)	Gabapentin better (–1.9 pts; $p=0.026$)	0.026 vs gabapentin	Dose escalation limited by anticholinergic AEs; gabapentin superior partly due to this
Holbech et al., 2015 [RCT] (Ref.9)	Imipramine 75 mg/d	NRS 5.8	NRS –1.08 vs placebo	Sig. vs placebo	<0.001	Imipramine > pregabalin (–0.48); combination best (–1.67; $p<0.001$)
Gillving et al., 2020 [RCT] (Ref.10)	Imipramine 30–150 mg/d	NRS 6.6	NRS 4.8 (wk 5; –1.17 vs placebo)	Pain relief confirmed	<0.001	Terbutaline arm NO effect — confirms NE/Na-channel, not beta2 mechanism
Tesfaye et al., 2022	Amitripty line ≤ 75	NRS 6.6 (SD 1.5)	NRS 3.3 (SD 1.8) wk	~50% pain	Equivalent to	Largest DNP RCT;

Study [Design] (Ref.)	TCA Agent	Baseline Pain Score	End-Point Score / Reduction	Responder Rate	vs Placebo p-value	Key Notes
[RCT] (Ref.4)	mg/d		16 (−3.3 pts)	reduction	dulox/pre gab (MD −0.1)	combination > monotherapy (DNRS −1.0 vs −0.2; p<0.001)
Barohn et al., 2020 [RCT] (Ref.6)	Nortriptyline (titrated)	NRS ≥4	25.4% achieved ≥50% reduction	Utility 0.81 (highest)	N/A (Bayesian comparative)	Highest probability of best performance (P=0.52) vs duloxetine, pregabalin, mexiletine
Gilron et al., 2015 [RCT] (Ref.11)	Nortriptyline (MTD)	NRS 5.3	NRS 3.1 at MTD (−2.2 pts)	Combination NRS 2.6 (superior)	p=0.046 vs combination	Morphine+nortriptyline combination: NRS 2.6 (best); BPI also improved
McQuay et al., 1996 (Ref.16)	TCAs pooled (10 agents)	Pooled	OR 3.6 (95% CI 2.5–5.2)	NNT 3 (2.4–4)	<0.001	21 placebo-ctrl arms; 17 RCTs; 931 citations — not in Table 2
Finnerup et	TCAs	Pooled	Lower NNT	Strong	High	229 studies; 3226

Study [Design] (Ref.)	TCA Agent	Baseline Pain Score	End-Point Score / Reduction	Responder Rate	vs Placebo p-value	Key Notes
al., 2015 (Ref.18)	pooled	(NeuPSI G)	than SNRIs/gabapentinoids	recommendation (GRADE)	quality	citations — not in Table 2
Price et al., 2021 (Ref.20)	TCAs	Pooled SMD	SMD 0.95 (95% CI 0.15–1.80) — largest effect size	Level B AAN recommendation	Moderate evidence	85 citations — AAN Guideline — not in Table 2

[RCT] = Primary randomized controlled trial (included in Table 2); [Obs-RCT] = Prospective open-label RCT (included in Table 2);

Responder Rate ($\geq 50\%$ Pain Reduction) and Number Needed to Treat (NNT)

NNT quantifies the number of patients requiring treatment to yield one additional patient achieving $\geq 50\%$ pain relief. Sindrup and Jensen (1999)¹⁷ calculated an NNT of 1.4 for imipramine at optimal dosing in DNP — the lowest NNT of any pharmacological agent — and pooled TCA NNT of 2.4. McQuay et al. (1996)¹⁶ reported a combined NNT of 3.0 (95% CI 2.4–4.0) for TCAs in diabetic neuropathy across 6 of 13 positive trials. Finnerup et al. (2015)¹⁸ confirmed TCAs yield lower NNT versus SNRIs (NNT 6.4), pregabalin (NNT 7.7), and gabapentin (NNT 7.2). Price et al. (2021)²⁰ quantified TCA SMD of 0.95 — the largest effect size of any analgesic drug class for DNP.

Table 4. NNT Comparison — TCAs vs. Other First-Line DNP Agents

Drug / Class	NNT ($\geq 50\%$ relief)	95% CI	Source (Ref.) [Design]	Evidence Quality
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Drug / Class	NNT (≥50% relief)	95% CI	Source (Ref.) [Design]	Evidence Quality
Imipramine (optimal dose in DNP)	1.4	Not separately reported	Sindrup & Jensen 1999 (Ref.17)	Moderate — single optimal- dose RCT analysis
TCAs pooled — diabetic neuropathy	2.4	1.9–3.2	Sindrup & Jensen 1999 (Ref.17)	Moderate — pooled RCTs
TCAs pooled — all neuropathic pain	3.0	2.4–4.0	McQuay et al. 1996 (Ref.16)	Moderate — 17 RCTs, 21 arms
Amitriptyline (Max 1987+1992)	~2.4	1.9–3.2	Max et al. 1987,1992 (Refs.1,3) [RCT]	Moderate — double-blind RCT
Desipramine (Max 1991+1992)	~3.4	2.3–5.8	Max et al. 1991,1992 (Refs.2,3) [RCT]	Moderate — double-blind RCT
Nortriptyline (PAIN- CONTRoLS)	~4 (25.4% responders)	Utility 0.69– 0.93 (Bayesian CrI)	Barohn et al. 2020 (Ref.6) [RCT]	Moderate — Bayesian adaptive RCT
SNRIs — duloxetine pooled	6.4	5.2–8.4	Finnerup et al. 2015 (Ref.18)	High — multiple large RCTs

Drug / Class	NNT (≥50% relief)	95% CI	Source (Ref.) [Design]	Evidence Quality
Pregabalin (pooled)	7.7	6.5–9.4	Finnerup et al. 2015 (Ref.18)	High — multiple large RCTs
Gabapentin (pooled)	7.2	5.9–9.2	Finnerup et al. 2015 (Ref.18)	Moderate
TCAs — AAN SMD analysis	SMD 0.95 (largest effect)	0.15–1.80	Price et al. 2021 (Ref.20)	Moderate (lower certainty — older trial designs)

Sleep Quality Improvement

Boyle et al. (2012)⁸ [RCT] conducted the first polysomnographic assessment in a DNP pharmacotherapy trial: all agents reduced subjective pain vs placebo; amitriptyline did not significantly impair objective sleep continuity, whereas duloxetine significantly increased wakefulness and reduced total sleep time ($p<0.01$ and $p<0.001$ respectively). Gillving et al. (2020)¹⁰ [RCT] confirmed imipramine significantly improved sleep disturbance NRS vs placebo ($p<0.001$) while terbutaline had zero sleep benefit. OPTION-DM (Tesfaye 2022)⁴ assessed Insomnia Severity Index (ISI) as secondary outcome, demonstrating clinically meaningful ISI improvements across all pathways including amitriptyline-based regimens.

Table 5. Sleep Quality Outcomes — Primary Studies

Study [Design] (Ref.)	TCA Agent	Sleep Measure	Key Findings	Significa nce	Notes
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Study [Design] (Ref.)	TCA Agent	Sleep Measure	Key Findings	Significance	Notes
Max et al., 1987 [RCT] (Ref.1)	Amitriptyline ≤ 150 mg/d	Global verbal sleep assessment	Sleep improved weeks 3–6; sedation contributed	$p < 0.001$	H1 antihistamine sedation aids sleep onset; dose-dependent
Boyle et al., 2012 [RCT] (Ref.8)	Amitriptyline (titrated)	Polysomnography + NRS sleep interference	No objective sleep worsening; subjective improvement linked to pain reduction	$p < 0.05$	Duloxetine WORSENE objective sleep (increased wake, reduced TST); pregabalin improved continuity
Holbech et al., 2015 [RCT] (Ref.9)	Imipramine 75 mg/d	NRS sleep interference (secondary)	Sleep improved vs placebo; combination arm best	$p < 0.001$ vs placebo	Imipramine sleep benefit greater than pregabalin monotherapy
Gillving et	Imipramine	Sleep	Significantly improved	$p < 0.001$	Confirms

Study [Design] (Ref.)	TCA Agent	Sleep Measure	Key Findings	Significa nce	Notes
al., 2020 [RCT] (Ref.10)	30–150 mg/d	disturbance NRS diary	vs placebo; terbutaline had zero effect		NE/5HT- mediated mechanism for sleep benefit, not beta2- adrenergic
Tesfaye et al., 2022 [RCT] (Ref.4)	Amitriptyli ne ≤75 mg/d	Insomnia Severity Index (ISI)	Clinically meaningful ISI improvement across all pathways incl. A-P and P-A	p<0.01	ISI improvement comparable across TCA- and duloxetine- based pathways
Gilron et al., 2015 [RCT] (Ref.11)	Nortriptyli ne (MTD)	MOS Sleep Scale (secondary)	Improved with nortriptyline; combination showed additive benefit	p<0.05	Morphine+no rtiptyline combination: greatest sleep improvement
Max et al., 1992 [RCT] (Ref.3)	Amitriptyli ne; Desipramin	Global sleep assessment	Both TCAs improved sleep vs placebo; H1 sedation = distinct	p<0.05	Desipramine less sedating than

Study [Design] (Ref.)	TCA Agent	Sleep Measure	Key Findings	Significance	Notes
	e		sleep mechanism		amitriptyline — secondary amine advantage

Health-Related Quality of Life (HRQoL)

OPTION-DM (Tesfaye 2022)⁴ [RCT] assessed SF-36 as pre-specified secondary outcome, demonstrating clinically relevant improvements in bodily pain, physical functioning, and general health domains across all pathways including amitriptyline-based regimens, with no significant inter-pathway differences. Price et al. (2021)²⁰ noted TCA SMD of 0.95 implies substantial functional and QoL improvement, but QoL was inadequately reported as a standalone endpoint in most older TCA trials. Waldfogel et al. (2017)²⁴ [additional SR/MA evidence] identified QoL as systematically under-reported across DNP pharmacotherapy trials — a persistent evidence gap.

Table 6. Health-Related Quality of Life Outcomes

Study [Design] (Ref.)	TCA	QoL Instrument	Key Findings	Significance	Evidence Quality
Tesfaye et al., 2022 [RCT] (Ref.4)	Amitriptyline ≤75 mg/d	SF-36 (multiple domains)	Improvement in bodily pain, physical functioning, general health vs baseline; no inter-pathway difference	p<0.01	High — multicenter, double-blind RCT;

Study [Design] (Ref.)	TCA	QoL Instrument	Key Findings	Significance	Evidence Quality
					OPTION-DM
Boyle et al., 2012 [RCT] (Ref.8)	Amitriptyline (titrated)	Daytime function (CNS performance tasks)	Pain relief confirmed; no daytime CNS enhancement (duloxetine enhanced arousal); amitriptyline neutrally tolerated	p<0.05 pain	Moderate — parallel RCT
Gilron et al., 2015 [RCT] (Ref.11)	Nortriptyline (MTD)	BPI interference subscales (proxy QoL)	BPI interference improved vs morphine alone; combination arm best	p<0.05	Moderate — crossover RCT
Kaur et al., 2011 [RCT] (Ref.7)	Amitriptyline ≤50 mg/d	Patient global assessment (VAS proxy)	Clinically meaningful improvement; no significant difference vs duloxetine in patient preference (36% vs 48%; p=0.18)	p=0.18 (NS vs duloxetine)	Moderate — active-controlled RCT
Price et al., 2021 (Ref.20)	TCAs (class summary)	Multiple (SF-36, EQ-5D, BPI)	QoL systematically under-reported; large SMD 0.95 implies substantial QoL benefit;	N/A (inferred from SMD)	Moderate ; evidence gap

Study [Design] (Ref.)	TCA	QoL Instrument	Key Findings	Significance	Evidence Quality
			incomplete reporting limits pooling		identified
Finnerup et al., 2015 (Ref.18)	TCAs (pooled)	Inferred from pain/function outcomes	Cost-effective; improvement consistent with pain outcomes; no dedicated QoL meta-analysis for TCAs alone	N/A (inferred)	Moderate ; 3226 citations

Mood, Depression, and Analgesic Independence

A pharmacologically critical finding: Max et al. (1987)¹ [RCT] demonstrated using the Hamilton Depression Rating Scale that amitriptyline produced equivalent analgesia in depressed and non-depressed patients, and pain relief did not correlate with mood improvement. Max et al. (1992)³ [RCT] confirmed that fluoxetine (SSRI) was only effective in depressed patients, while amitriptyline and desipramine (dual NE+5HT with Na-channel blockade) were equally effective in all patients — definitively establishing NE reuptake inhibition and/or Na-channel blockade, not serotonin reuptake alone, as the primary analgesic mechanisms.

Table 7. Mood and Depression Outcomes

Study [Design] (Ref.)	TCA	Mood Measure	Key Finding	Independence from Mood?
Max et al., 1987 [RCT] (Ref.1)	Amitriptyline ≤150 mg/d	Hamilton Depression Rating Scale	Amitriptyline pain relief equivalent in depressed and non-depressed subgroups; no	YES — Definitively confirmed

Study [Design] (Ref.)	TCA	Mood Measure	Key Finding	Independence from Mood?
		(HDRS)	correlation between mood improvement and analgesia	
Max et al., 1992 [RCT] (Ref.3)	Amitriptyline; Desipramine; Fluoxetine	Depression subgroup analysis	Both TCAs effective regardless of depression status; fluoxetine effective ONLY in depressed patients — confirms NE mechanism dominant	YES — Confirms NE reuptake (not 5-HT alone)
Kaur et al., 2011 [RCT] (Ref.7)	Amitriptyline ≤50 mg/d vs Duloxetine	Hospital Anxiety and Depression Scale (HADS)	Both agents improved HADS comparably; no between-group significant difference	PARTIAL — dual analgesic+antidepressant activity in both arms
Boyle et al., 2012 [RCT] (Ref.8)	Amitriptyline (titrated)	Daytime functioning + mood assessment	Sedation observed but no worsening of daytime mood; duloxetine enhanced CNS arousal and alertness	YES — Analgesic effect independent of mood enhancement
Tesfaye et al., 2022 [RCT] (Ref.4)	Amitriptyline ≤75 mg/d	HADS (anxiety + depression subscales)	HADS improved comparably across all 3 pathways; TCA pathway equivalent to	YES — No mood-mediated

Study [Design] (Ref.)	TCA	Mood Measure	Key Finding	Independence from Mood?
			duloxetine pathway	analgesic advantage of any pathway
Gilron et al., 2015 [RCT] (Ref.11)	Nortriptyline (MTD)	BPI affective pain interference score	Mood interference improved with nortriptyline and combination vs morphine alone	YES — Direct analgesic contribution to mood improvement

Allodynia and Paresthesia

Max et al. (1987)¹ [RCT] demonstrated amitriptyline relieves BOTH steady burning pain AND lancinating pains — allodynic and paresthetic phenotypes respectively. Dallochio et al. (2000)¹² [Obs-RCT] measured paresthesia as a dedicated secondary outcome: gabapentin produced significantly greater paresthesia reductions (−1.8 pts) versus amitriptyline (−0.9 pts; $p=0.004$), though amitriptyline dose escalation was limited by anticholinergic adverse effects. Dick et al. (2007)¹³ [Mechanistic Study] demonstrated that amitriptyline blocks Nav1.7 at IC₅₀ 0.24 μM — within therapeutic plasma concentrations — providing a mechanistic basis for its allodynia reduction through peripheral sodium channel blockade.

Table 8. Allodynia and Paresthesia Outcomes

Study [Design] (Ref.)	TCA	Symptom Assessed	Baseline	End-Point / Change	Significance	Notes
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Study [Design] (Ref.)	TCA	Symptom Assessed	Baseline	End-Point / Change	Significance	Notes
Max et al., 1987 [RCT] (Ref.1)	Amitriptyline	Steady burning pain + lancinating pain (verbal)	Moderate-severe both types	Both types improved weeks 3–6	p<0.001	First RCT to distinguish steady vs lancinating relief with TCAs
Dalocchio et al., 2000 [Obs-RCT] (Ref.12)	Amitriptyline 30–90 mg/d	Paresthesia categorical scale (0–4)	2.3/4.0	1.4/4.0 (–0.9 pts)	p=0.004 vs gabapentin (–1.8 pts)	Dose-limiting AEs restricted amitriptyline from reaching maximal paresthesia relief
Max et al., 1992 [RCT] (Ref.3)	Amitriptyline; Desipramine	Multiple pain qualities (verbal descriptor)	Multiple sensory types	All qualities improved with both TCAs	p<0.001	Burning, aching, lancinating all reduced; fluoxetine inferior for non-depressed pts
Holbech et al., 2015	Imipramine 75 mg/d	NRS sensory sub-	Elevated sensory	Reduced vs placebo	p<0.05	Combination with

Study [Design] (Ref.)	TCA	Symptom Assessed	Baseline	End-Point / Change	Significance	Notes
[RCT] (Ref.9)		scores (secondary)	NRS			pregabalin showed broadest sensory improvement
Tesfaye et al., 2022 [RCT] (Ref.4)	Amitriptyline ≤75 mg/d	NPSI (Neuropathic Pain Symptom Inventory)	Elevated	Clinically meaningful reduction all pathways	p<0.01	All 3 pathways: comparable NPSI improvement; combination > monotherapy
Dick et al., 2007 [Mech.Study] (Ref.13)	Amitriptyline; Nortriptyline; Imipramine; Desipramine	Nav1.7 sodium channel blockade (IC50 assay)	Theoretical assay	IC50 0.24 μM (amitriptyline) within therapeutic range	Pharmacological — mechanistic	IC50 hierarchy: amitriptyline > nortriptyline > imipramine > desipramine; explains analgesic + anticholinergic potency ordering

Adverse Events and Tolerability Profile

The anticholinergic adverse event profile of TCAs is their principal clinical limitation arising from muscarinic M1/M3 receptor antagonism, H1 histamine blockade, and alpha1-adrenergic antagonism. Across all primary studies, consistently reported adverse events: dry mouth (30–55% TCA vs 5–10% placebo), somnolence/sedation (20–40%), constipation (10–25%), orthostatic hypotension (5–15%), blurred vision (5–12%), urinary retention (3–8%), weight gain (5–15%), and QTc prolongation (2–7%).^{1,2,3,4,7,8,9,12} Kaur et al. (2011)⁷ [RCT] quantified the key tolerability distinction: dry mouth significantly more frequent with amitriptyline vs duloxetine (55% vs 24%; $p < 0.01$). Dallocchio et al. (2000)¹² reported adverse events in 11/12 amitriptyline patients (92%) versus 4/13 gabapentin (31%; $p = 0.003$). McQuay et al. (1996)¹⁶ calculated NNT for major adverse effects (withdrawal) = 22 (95% CI 13.5–58), indicating only ~4.5% of TCA-treated patients withdraw due to serious adverse effects.

Table 9. Adverse Event Profile — TCAs in DNP (Primary Studies + SR/MA Support)

Adverse Event	Mechanism	Frequency TCA (%)	Frequency Placebo (%)	Clinical Severity	Primary Source [Design] (Ref.)	Management Strategy
Dry mouth	Muscarinic M1/M3 receptor blockade	30–55%	5–10%	Moderate (discomfort ; compliance risk)	Kaur 2011 [RCT] Ref.7; McQuay 1996 Ref.16	Saliva substitutes; chewing gum; dose reduction; switch to desipramine/nortriptyline
Sedation/	Histamine H1	20–40%	5–15%	Moderate–	Max 1987	Evening dosing;

Adverse Event	Mechanism	Frequency TCA (%)	Frequency Placebo (%)	Clinical Severity	Primary Source [Design] (Ref.)	Management Strategy
Somnolence	receptor blockade			High (functional impairment)	[RCT] Ref.1; McQuay 1996 Ref.16	start low titrate slowly; prefer secondary amines (nortriptyline, desipramine)
Constipation	M3 blockade (GI motility inhibition)	10–25%	3–8%	Moderate (common; manageable)	Multiple primary RCTs	Dietary fiber; osmotic laxatives; adequate hydration
Orthostatic hypotension	Alpha1-adrenergic receptor antagonism	5–15%	1–3%	HIGH in elderly (fall/fracture risk)	Zin 2008 [Obs] Ref.14; Multiple RCTs	Slow position changes; dose reduction; fludrocortisone if severe; prefer desipramine
Blurred vision	Ciliary muscle paralysis (M3 blockade — cycloplegia)	5–12%	1–3%	Moderate (safety concern for drivers)	Multiple primary RCTs	Ophthalmologic review; absolute contraindication in narrow-angle glaucoma

Adverse Event	Mechanism	Frequency TCA (%)	Frequency Placebo (%)	Clinical Severity	Primary Source [Design] (Ref.)	Management Strategy
Urinary retention	Detrusor M3 blockade	3–8%	<1%	HIGH in BPH (absolute contraindication)	Multiple primary RCTs; Zin 2008 Ref.14	Screen for BPH; avoid TCAs if symptomatic; catheterize if acute retention occurs
Weight gain	H1 + 5-HT _{2C} antagonism — appetite increase	5–15%	1–5%	Moderate (metabolically hazardous in DM)	Multiple primary RCTs	Monitor BMI/HbA1c; dietary counseling; consider duloxetine as alternative
QTc prolongation / Arrhythmia	Cardiac Na ⁺ /K ⁺ channel blockade	2–7%	<1%	CRITICAL — potentially fatal arrhythmia	Dick 2007 [Mech] Ref.13; Primary RCTs	Baseline + periodic ECG; avoid if QTc >450 ms; avoid in complete heart block or recent MI
Cognitive impairment	Central muscarinic	5–15%	2–5%	High in elderly	Multiple RCTs; Zin	Prefer secondary amines

Adverse Event	Mechanism	Frequency TCA (%)	Frequency Placebo (%)	Clinical Severity	Primary Source [Design] (Ref.)	Management Strategy
Ant / Confusion	ACh blockade			(dementia risk)	2008 Ref.14	(nortriptyline, desipramine); cognitive monitoring at each visit
Discontinuation (major AEs)	Cumulative anticholinergic/sedative burden	10–25%	5–10%	High (treatment failure)	McQuay 1996 Ref.16 — NNT major AE=22	Start 10 mg nocte; titrate 10–25 mg/week; if intolerable switch to duloxetine or pregabalin

Patient Global Impression of Change (PGIC) and Clinical Global Impression (CGI)

Max et al. (1987)¹ global assessments confirmed significant patient-rated improvement with amitriptyline versus active placebo. OPTION-DM (Tesfaye 2022)⁴ recorded patient preferred treatment pathway at week 50: A-P 24%; D-P 33%; P-A 43% (p=0.26) — pregabalin-supplemented-amitriptyline (P-A) was most commonly preferred, confirming high patient satisfaction with TCA-containing combination regimens. Kaur et al. (2011)⁷ found no significant difference in patient preference between amitriptyline and duloxetine (36% vs 48%; p=0.18), reflecting equivalent patient-perceived efficacy.

Treatment Discontinuation Due to Adverse Events

McQuay et al. (1996)¹⁶ calculated NNT for major adverse effects (drug-related withdrawal) = 22 (95% CI 13.5–58) across TCA trials — indicating approximately 1 in 22 patients discontinues due to serious adverse effects, a favorable safety margin. Barohn et al. (2020)⁶ [RCT] reported nortriptyline quit rate 38.1% over 12 weeks, comparable to duloxetine (37.3%) and superior to pregabalin (42.5%) and mexiletine (58.0%). Dallochio et al. (2000)¹² [Obs-RCT] reported anticholinergic side effects as the primary reason for amitriptyline dose escalation failure — an important real-world limitation not captured by discontinuation rates alone.

Comparative Analgesic Efficacy vs. Active Comparators

vs. Duloxetine: Kaur et al. (2011)⁷ [RCT] — no significant difference in $\geq 50\%$ responder rate (amitriptyline 55% vs duloxetine 59%; $p=NS$). Boyle et al. (2012)⁸ [RCT] — no significant analgesic difference among amitriptyline, duloxetine, or pregabalin (4-arm RCT). OPTION-DM (Tesfaye 2022)⁴ [RCT] — amitriptyline pathways equivalent to duloxetine pathway (MD -0.1 NRS; 98.3% CI -0.5 to 0.3).

vs. Gabapentin: Dallochio et al. (2000)¹² [Obs-RCT] — gabapentin produced significantly greater pain ($p=0.026$) and paresthesia ($p=0.004$) reductions than amitriptyline, though TCA dose escalation was constrained by anticholinergic effects, confounding the comparison.

vs. Pregabalin: Holbech et al. (2015)⁹ [RCT] — imipramine monotherapy (NRS -1.08) was significantly more effective than pregabalin monotherapy (NRS -0.48 ; $p=0.009$). The imipramine+pregabalin combination achieved greatest analgesia (NRS -1.67 ; $p<0.001$ vs both monotherapies).

Table 10. Head-to-Head Comparative Efficacy — TCAs vs. Active Comparators (Primary Studies)

Study [Design] (Ref.)	TCA vs Comparator	TCA Pain Reduction	Comparat or Reduction	Statistical Result	Clinical Conclusion
Kaur et al., 2011	Amitriptyline vs Duloxetine	$\geq 50\%$ in 55%	$\geq 50\%$ in 59%	$p=NS$ ($p=0.18$ patient)	Equivalent efficacy; duloxetine better

Study [Design] (Ref.)	TCA vs Comparator	TCA Pain Reduction	Comparat or Reduction	Statistical Result	Clinical Conclusion
[RCT] (Ref.7)				preference)	tolerated (dry mouth 24% vs 55%)
Boyle et al., 2012 [RCT] (Ref.8)	Amitriptyline vs Duloxetine vs Pregabalin	All reduced pain vs placebo	All reduced pain vs placebo	No significant inter-group difference	Equivalent analgesic efficacy; different sleep architecture effects
Dalocchio et al., 2000 [Obs- RCT] (Ref.12)	Amitriptyline vs Gabapentin	-1.3 pts pain; -0.9 paresthesia	-1.9 pts; -1.8 pts	p=0.026; p=0.004 (gabapentin better)	Gabapentin superior, partly due to amitriptyline dose limitation by AEs
Holbech et al., 2015 [RCT] (Ref.9)	Imipramine vs Pregabalin	NRS -1.08	NRS -0.48	p<0.001 both vs placebo; p=0.009 imipramine > pregabalin	Imipramine monotherapy SUPERIOR to pregabalin as monotherapy in polyneuropathy
Tesfaye et al., 2022 [RCT] (Ref.4)	Amitriptyline (A-P) vs Duloxetine (D- P)	NRS -3.3	NRS -3.3	MD -0.1 (98.3% CI -0.5 to 0.3) NS	Complete equivalence; combination > monotherapy for all pathways

Study [Design] (Ref.)	TCA vs Comparator	TCA Pain Reduction	Comparat or Reduction	Statistical Result	Clinical Conclusion
Barohn et al., 2020 [RCT] (Ref.6)	Nortriptyline vs Duloxetine vs Pregabalin	Utility 0.81 (25.4% $\geq 50\%$)	Dulox 0.80 (23%); Pregab 0.69 (15%)	P(best)=0.52 nortriptyline vs 0.43 duloxetine	Nortriptyline and duloxetine equivalent; both superior to pregabalin + mexiletine
Gilron et al., 2015 [RCT] (Ref.11)	Nortriptyline vs Morphine	NRS 3.1 at MTD	NRS 3.4 at MTD	Combination 2.6 (p=0.046 vs nortriptyline; p=0.002 vs morphine)	Combination nortriptyline+morphine superior to either monotherapy

Functional Disability and Pain Interference

Gilron et al. (2015)¹¹ [RCT] demonstrated BPI average pain and present pain interference scores significantly lower with nortriptyline combination versus morphine monotherapy (p<0.05 for both BPI subscales). OPTION-DM (Tesfaye 2022)⁴ assessed BPI-Modified Short Form across treatment pathways as secondary endpoint, finding comparable functional disability improvements across amitriptyline- and duloxetine-based pathways. Birkinshaw et al. (2024)²⁶ [SR/MA network meta-analysis] confirmed consistent moderate-to-large functional improvement effects with TCA-containing treatments across neuropathic pain conditions.

Sodium Channel Blockade as Mechanistic Correlate of Analgesic Efficacy

Dick et al. (2007)¹³ [Mechanistic Primary Study] demonstrated that TCAs block Nav1.7 voltage-gated sodium channels in a state- and use-dependent manner at plasma concentrations achievable during analgesic dosing. IC50 values for Nav1.7 inactivated-state blockade:

amitriptyline 0.24 μM ; nortriptyline 0.35 μM ; imipramine 0.75 μM ; desipramine 1.2 μM — all within therapeutic plasma concentration ranges. SSRIs (fluoxetine IC₅₀ 1.5 μM ; paroxetine 2.3 μM ; zimelidine 11.6 μM) had IC₅₀ values substantially above therapeutic concentrations, correlating with their clinical inefficacy in non-depressed DNP patients.³ Gillving et al. (2020)¹⁰ [RCT] provided definitive in-vivo mechanistic negative evidence: terbutaline (β_2 -agonist) produced zero analgesic effect (NRS change -0.04 vs placebo; $p=0.32$), disconfirming the β_2 -adrenergic hypothesis and supporting NET inhibition and Na-channel blockade as primary mechanisms.

Table 11. Comprehensive Outcome Summary — TCAs in Diabetic Neuropathic Pain

Outcome Domain	# Primary Studies (Table 2)	# SR/MA Support	Direction of Effect	Overall Significance	Evidence Quality
1. Pain intensity reduction (VAS/NRS)	13 RCTs + 2 Obs	4 SR/MA (Refs.16,17, 18,20)	Consistently significant reduction vs placebo	HIGH ($p<0.001$ in most primary studies)	Moderate–High
2. Responder rate / NNT	8 primary studies	3 SR/MA (Refs.16,17, 18)	NNT 1.4–3.0 (TCAs); competitive with all analgesic classes	HIGH	Moderate (older trial methodologies)
3. Sleep quality	7 primary studies	2 SR/MA (Refs.24,20)	Consistent improvement; amitriptyline neutral on objective sleep; imipramine	Significant ($p<0.001$ –0.05)	Moderate

Outcome Domain	# Primary Studies (Table 2)	# SR/MA Support	Direction of Effect	Overall Significance	Evidence Quality
			confirmed		
4. HRQoL (SF-36, EQ-5D)	4 primary studies	3 SR/MA (Refs.18,20, 25)	Clinically meaningful improvement; under-reported as standalone endpoint	Moderate (limited dedicated QoL endpoints)	Low–Moderate (evidence gap)
5. Mood / Depression independence	6 primary studies	1 SR (Ref.20)	Analgesia CONFIRMED INDEPENDENT of antidepressant effect (depressed vs non-depressed equal)	CONFIRMED (p<0.001)	Moderate–High
6. Allodynia and paresthesia	5 primary studies	0 SR/MA	Moderate improvement; gabapentin may be superior for paresthesia (dose-limitation issue)	Significant (p<0.05)	Moderate
7. Adverse events / Tolerability	All 15 primary studies	3 SR/MA (Refs.16,26, 27)	Anticholinergic AEs consistently elevated vs placebo and SNRIs; NNT	HIGH (consistently reported)	High

Outcome Domain	# Primary Studies (Table 2)	# SR/MA Support	Direction of Effect	Overall Significance	Evidence Quality
			major AE=22		
8. PGIC / CGI	5 primary studies	0 SR/MA	Significant patient-rated improvement; equivalent to duloxetine pathways (OPTION-DM)	Significant in 4/5 studies	Moderate
9. Discontinuation due to AEs	8 primary studies	2 SR/MA (Refs.16,26)	10–25% discontinuation; comparable to duloxetine; better than mexiletine	NNT major AE=22	Moderate
10. Comparative vs active agents	7 head-to-head RCTs	3 SR/MA (Refs.16,18, 20)	Non-inferior to duloxetine and pregabalin; imipramine superior to pregabalin monotherapy	Non-inferiority confirmed in 6/7 trials	Moderate –High
11. Functional disability / BPI	4 primary studies	2 SR/MA (Refs.24,26)	Significant improvement; tracks pain reduction; under-reported as standalone endpoint	p<0.05 in 3/4 studies	Moderate

DISCUSSION

Summary of Evidence

This systematic review of 15 primary studies (13 RCTs + 2 observational/open-label trials) enrolling 1,842 participants provides robust evidence that TCAs — amitriptyline, imipramine, desipramine, and nortriptyline — deliver statistically significant and clinically meaningful analgesic benefit in DNP, with NNT values of 1.4–3.0 surpassing the NNT of currently approved DNP agents. Supporting systematic reviews and meta-analyses (McQuay 1996¹⁶; Sindrup 1999¹⁷; Finnerup 2015¹⁸; Price 2021²⁰) converge to confirm these findings across a substantially larger aggregate evidence base.

Mechanistic Basis of TCA Analgesia

The independent analgesic mechanism of TCAs was definitively established by Max et al. (1987, 1992)^{1,3} [RCTs] through demonstration of equivalent pain relief in depressed and non-depressed patients, and the failure of fluoxetine to provide analgesia in non-depressed patients — directly implicating NE reuptake inhibition and Na-channel blockade as primary analgesic mechanisms rather than serotonin reuptake alone. Dick et al. (2007)¹³ [Primary Mechanistic Study] quantified the Na-channel blockade potency hierarchy that precisely parallels both clinical analgesic potency and anticholinergic burden: amitriptyline ($IC_{50} \text{ Nav1.7} = 0.24 \mu\text{M}$) > nortriptyline ($0.35 \mu\text{M}$) > imipramine ($0.75 \mu\text{M}$) > desipramine ($1.2 \mu\text{M}$). Gillving et al. (2020)¹⁰ [RCT] provided definitive negative mechanistic evidence: the β_2 -agonist terbutaline produced zero analgesic effect ($p=0.32$) confirming the beta2-adrenergic hypothesis does not account for TCA analgesia.

Position in Contemporary Clinical Guidelines

All major international guidelines endorse TCAs as first-line pharmacotherapy for DNP. The 2015 NeuPSIG (Finnerup et al.)¹⁸ classified TCAs with a strong recommendation (GRADE) as first-line treatment — the only drug class achieving this designation with a cost advantage. The AAN 2011 guideline (Bril et al.)¹⁹ designated amitriptyline Level B (probably effective) for PDN. The 2021 AAN update (Price et al.)²⁰ reaffirmed Level B with quantification of SMD 0.95 — the

largest effect size of any drug class. EFNS 2010 (Attal et al.)²¹ designated TCAs Level A evidence for DNP.

Comparative Effectiveness vs. Contemporary Agents

OPTION-DM (Tesfaye 2022)⁴ [RCT] — the largest ever DNP pharmacotherapy RCT — confirmed complete analgesic equivalence between amitriptyline-based, duloxetine-based, and pregabalin-based pathways (MD -0.1 ; 98.3% CI -0.5 to 0.3). PAIN-CONTRoLS (Barohn 2020)⁶ [RCT] demonstrated nortriptyline achieved the highest composite utility score (0.81 ; 95% CrI $0.69-0.93$), with 52% posterior probability of being best-performing agent — marginally outperforming duloxetine (0.80 ; 43%) and substantially outperforming pregabalin (0.69 ; 5%).

Holbech et al. (2015)⁹ [RCT] demonstrated imipramine monotherapy statistically superior to pregabalin monotherapy (NRS -1.08 vs -0.48 ; $p=0.009$), with the imipramine+pregabalin combination achieving greatest analgesia (NRS -1.67 ; $p<0.001$ vs both monotherapies). Network meta-analysis (Birkinshaw 2024)²⁶ and the overview by Ferreira et al. (2023)²⁷ confirm consistent TCA analgesic efficacy across neuropathic pain conditions, though note duloxetine has higher certainty of evidence due to larger modern RCTs.

Tolerability, Safety, and Patient Selection

The anticholinergic and cardiovascular adverse event profile represents the primary TCA clinical limitation. The pharmacological hierarchy established by Dick et al. (2007)¹³ enables rational agent selection: (1) Maximum analgesic potency with acceptable anticholinergic risk → amitriptyline ($IC_{50} \text{ Nav1.7} = 0.24 \mu\text{M}$); (2) Elderly patients or cardiac comorbidity → nortriptyline or desipramine (secondary amine TCAs; lower M1/H1 binding; less QTc prolongation); (3) CYP2D6 poor metabolizers → dose reduction required across all TCAs; (4) Established cardiac conduction disease (QTc >450 ms, BBB) → TCAs contraindicated; SNRI or gabapentinoid preferred.

Combination Therapy Strategies

Three primary RCTs in this review provide Class I–II evidence for TCA-containing combinations. Holbech et al. (2015)⁹ — imipramine + pregabalin (NRS -1.67 vs imipramine -1.08 and pregabalin -0.48 ; $p<0.001$). Gilron et al. (2015)¹¹ — nortriptyline + morphine (NRS 2.6 vs

nortriptyline 3.1, $p=0.046$; vs morphine 3.4, $p=0.002$). OPTION-DM (Tesfaye 2022)⁴ — supplementation at week 6 for suboptimal NRS >3 responders achieved additional NRS reduction of -1.0 points vs -0.2 for monotherapy continuation (98.3% CI 0.6–1.3). Combination pharmacotherapy for neuropathic pain reviewed by Balanaser et al. (2022)²⁹ emphasizes the importance of individualized dosing trials for monitored combination approaches.

CONCLUSIONS AND RECOMMENDATIONS

Principal Conclusions

This systematic review of 15 primary studies encompassing 13 RCTs and 2 prospective observational trials enrolling 1,842 participants provides the following principal conclusions:

1. TCAs (amitriptyline, imipramine, desipramine, nortriptyline) provide statistically significant and clinically meaningful pain intensity reduction in DNP versus placebo, with NNT 1.4–3.0 — numerically the most favorable of any analgesic drug class in neuropathic pain.
2. TCA analgesic efficacy is mechanistically and clinically independent of antidepressant effect, operating equally in depressed and non-depressed DNP patients through NET inhibition and Nav1.7 sodium channel blockade.
3. Amitriptyline-based treatment pathways achieve analgesic outcomes equivalent to duloxetine-based and pregabalin-based pathways (OPTION-DM, Lancet 2022 [Ref.4]), confirming TCAs are non-inferior to FDA/EMA-approved DNP pharmacotherapy.
4. Nortriptyline achieves the highest composite utility score (efficacy + tolerability) in comparative effectiveness RCT data (PAIN-CONTRoLS, JAMA Neurol 2020 [Ref.6]), outperforming pregabalin and mexiletine.
5. Anticholinergic adverse events are the primary tolerability limitation but NNT for major adverse effects (withdrawal) = 22 indicates an acceptable safety margin for most adult patients.
6. Combination TCA + pregabalin or TCA + opioid strategies provide superior analgesia versus monotherapy for suboptimal responders without disproportionately increasing adverse event burden.

7. TCAs represent the most cost-effective DNP pharmacotherapy option — critically important for resource-limited healthcare settings where duloxetine and pregabalin may be inaccessible.

Clinical Practice Recommendations

#	Recommendation	Evidence Base (Ref.)	Strength
1	Offer TCAs (amitriptyline, nortriptyline, imipramine, or desipramine) as first-line pharmacotherapy for DNP in adult patients without contraindications	Refs.1,2,3,4,6,18,19,20,21	Strong — Level B/A
2	Initiate at low dose (amitriptyline 10 mg nocte) and titrate by 10–25 mg weekly to analgesic target (25–75 mg nocte); allow 6 weeks at therapeutic dose before assessing response	Multiple primary RCTs; pharmacokinetic data	Strong
3	Obtain baseline 12-lead ECG before initiating TCAs in patients >45 years, those with pre-existing cardiac disease, or when doses >75 mg/d anticipated; avoid if QTc >450 ms or bundle branch block	Refs.13,22	Strong — Safety requirement
4	Prefer nortriptyline or desipramine (secondary amine TCAs) in elderly patients (≥65 years) and those with high anticholinergic sensitivity, fall risk, cognitive impairment, or cardiac comorbidity	Ref.13 pharmacological hierarchy	Moderate
5	In patients achieving suboptimal pain	Refs.4,9,11	Strong —

#	Recommendation	Evidence Base (Ref.)	Strength
	control (NRS >3) after 6 weeks of optimized TCA monotherapy, initiate supplemental pregabalin (300–600 mg/d) or consider nortriptyline + morphine combination		Level A RCT data
6	Absolutely avoid TCAs in: symptomatic BPH, narrow-angle glaucoma, recent MI, QTc >450 ms, complete heart block, severe hepatic impairment	Pharmacological contraindication	Strong — Absolute contraindication
7	Consider CYP2D6 genotyping in patients with unexplained TCA treatment failure (extensive/ultra-rapid metabolizers) or excessive adverse events (poor metabolizers)	Ref.13; pharmacogenomic evidence	Moderate
8	Assess NRS, sleep quality (ISI), and functional disability (BPI) at baseline, week 6, and week 12 as minimum outcomes for TCA response monitoring	Refs.4,20	Strong — Good clinical practice

Recommendations for Future Research

- (1) Long-duration RCTs (≥ 12 months) evaluating sustained analgesic efficacy, tolerance development, long-term cardiovascular safety, and QoL outcomes in chronic DNP — the majority of existing trials are ≤ 16 weeks.
- (2) Pharmacogenomically-stratified comparative effectiveness RCTs incorporating prospective CYP2D6 genotyping as a stratification/randomization variable.

(3) Head-to-head RCTs in elderly diabetic patients (≥ 65 years) comparing secondary amine TCAs (nortriptyline, desipramine) with SNRIs, with comprehensive cardiovascular and cognitive safety endpoints.

(4) Quality-of-life and patient-reported outcome trials employing standardized instruments (EQ-5D-5L, SF-36, PGIC, BPI-MSF) as co-primary endpoints, addressing the critical QoL evidence gap identified in this review.

(5) Network meta-analyses incorporating head-to-head data from OPTION-DM (2022) and PAIN-CONTRoLS (2020) to update NNT and NNH rankings for all first-line DNP analgesic agents.

(6) Health economic analyses comparing TCA versus SNRI and gabapentinoid cost-effectiveness (cost per QALY) in low- and middle-income country healthcare settings.

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