Neuropathic Pain:
Treatment Options, Cost Considerations, & Current Limitations

featuring **Brian Callaghan, MD**

July 10, 2025

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Today's moderator:

Lindsay Colbert
Executive Director
the Foundation *for* Peripheral Neuropathy

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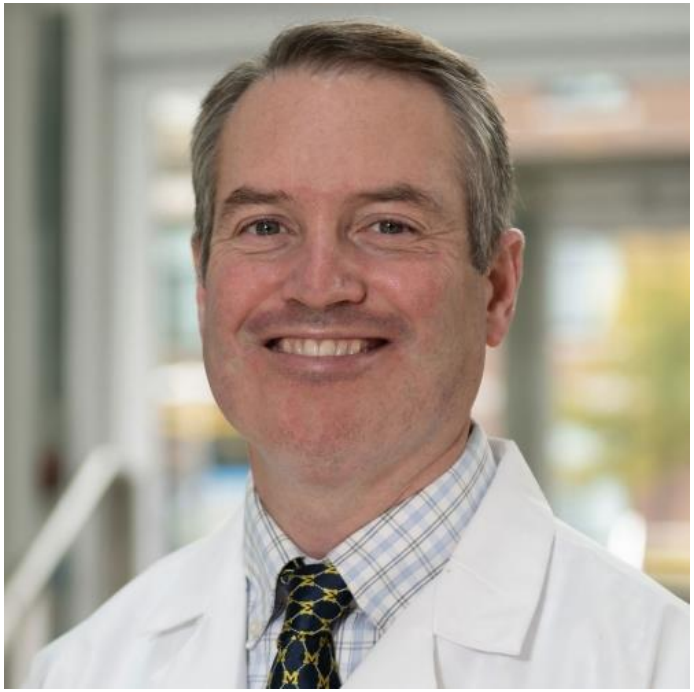
Today's expert:



Brian Callaghan, MD
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Professor of Neurology

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Neuropathic Pain

Treatment Options, Cost Considerations, & Current Limitations

June 19, 2025

Brian Callaghan

University of Michigan Health System

Outline

- What is it?
- How is it different from other pain?
- How do you treat it?
- How much does it cost?
- What are the unique challenges?
- What are the promising future options?

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Neuropathic pain

- Neuropathic pain is pain from an injury or disease affecting nerves.
- Context- Often accompanied by numbness, tingling, pins and needles, itching
- Allodynia-non painful becomes painful
- Type of pain- Burning, electric, painful cold

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Differences with other pain

- Anatomy- nerve vs skin, joints, bones, central pain (fibromyalgia)
- Context- history and exam findings
- Characteristic of pain-burning, electric vs other

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Neuropathic pain treatments

Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis

Nanna B Finnerup*, Nadine Attal*, Simon Haroutounian, Ewan McNicol, Ralf Baron, Robert H Dworkin, Ian Gilron, Maija Haanpää, Per Hansson, Troels S Jensen, Peter R Kamerman, Karen Lund, Andrew Moore, Srinivasa N Raja, Andrew S C Rice, Michael Rowbotham, Emily Sena, Philip Siddall, Blair H Smith, Mark Wallace

EFNS GUIDELINES

EFNS guidelines on the pharmacological treatment of neuropathic pain: 2010 revision

N. Attal[a,b], G. Cruccu[a,c], R. Baron[a,d], M. Haanpää[a,e], P. Hansson[a,f], T. S. Jensen[a,g] and T. Nurmikko[a,h]

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Evidence-based guideline: Treatment of painful diabetic neuropathy: Report of the American Academy of Neurology, the American Association of Neuromuscular and Electrodiagnostic Medicine, and the American Academy of Physical Medicine and Rehabilitation

V. Bril, J. England, G.M. Franklin, et al.

Neurology 2011;76:1758-1765 Published Online before print April 11, 2011
DOI 10.1212/WNL.0b013e3182166ebe

Annals of Internal Medicine | REVIEW

Pharmacologic Interventions for Painful Diabetic Neuropathy

An Umbrella Systematic Review and Comparative Effectiveness Network Meta-analysis

Marcio L. Griebeler, MD; Oscar L. Morey-Vargas, MD; Juan P. Brito, MD; Apostolos Tsapas, MD, PhD; Zhen Wang, PhD; Barbara G. Carranza Leon, MD; Olivia J. Phung, PharmD; Victor M. Montori, MD; and M. Hassan Murad, MD, MPH

VIEWS & REVIEWS

Pharmacotherapy for diabetic peripheral neuropathy pain and quality of life

A systematic review

SPECIAL ARTICLE Level of Recommendation

Oral and Topical Treatment of Painful Diabetic Polyneuropathy: Practice Guideline Update Summary

Report of the AAN Guideline Subcommittee

Raymond Price, MD, Don Smith, MD, Gary Franklin, MD, MPH, Gary Gronseth, MD, Michael Pignone, MD, MPH, William S. David, MD, PhD, Carmel Armon, MD, MSc, MHS, Bruce A. Perkins, MD, MPH, Vera Bril, MD, Alexander Rae-Grant, MD, John Halperin, MD, Nicole Licking, DO, Mary Dolan O'Brien, MLIS, Scott R. Wessels, MPS, ELS, Leslie C. MacGregor, PhD, VMD, JD, Kenneth Fink, MD, MPH, Lawrence B. Harkless, DPM, Lindsay Colbert, MA, and Brian C. Callaghan, MD, MS

Correspondence
American Academy of Neurology
guidelines@aan.com

Neurology® 2022;98:31-43. doi:10.1212/WNL.0000000000013038

- Look at drug classes
- Combine studies
- Penalize studies without placebo response
- Address opioids

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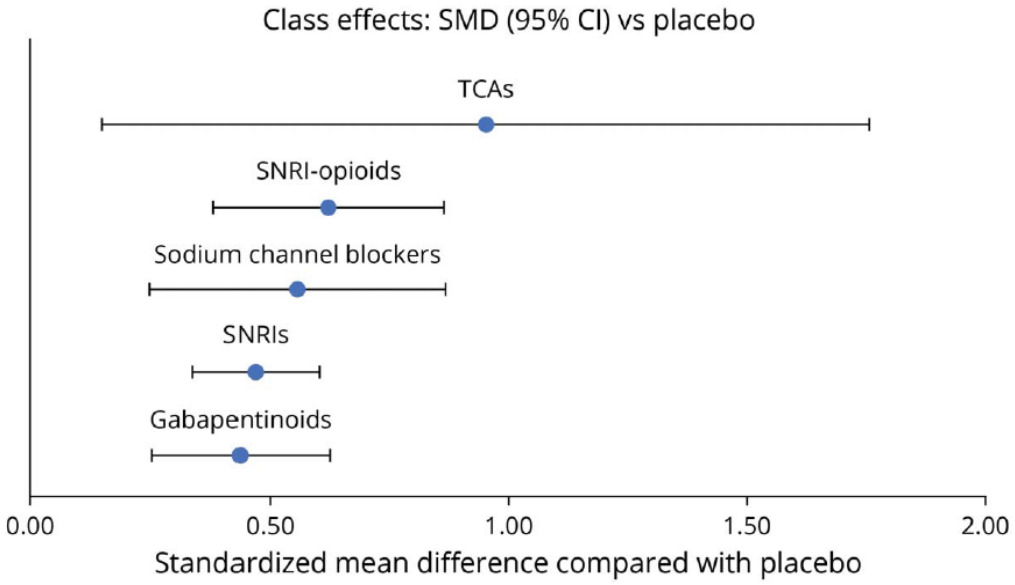
All work about the same

Figure Class Effects for the Most Well-Studied Oral Treatments of Painful Diabetic Polyneuropathy



The effects of different oral medication classes on painful diabetic neuropathy including gabapentinoids, serotonin-norepinephrine reuptake inhibitors (SNRIs), sodium channel blockers, SNRI/opioid dual mechanism agents, and tricyclic antidepressants (TCAs). CI = confidence interval; SMD = standardized mean difference.

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Many studies in many patients

Table 3 Efficacy of Oral Medications for Painful Diabetic Neuropathy by Class Effect

Medication class	SMD[a]	LCL	UCL	Number of articles	Number of patients	Conclusion	Confidence
Gabapentinoids	0.44	0.25	0.63	16	3,550	Probably more likely than placebo to improve pain	Moderate
Sodium channel blocker	0.56	0.25	0.87	5	566	Probably more likely than placebo to improve pain	Moderate
SNRI	0.47	0.34	0.60	9	1,884	Probably more likely than placebo to improve pain	Moderate
SNRI-opioid	0.62	0.38	0.86	4	775	Probably more likely than placebo to improve pain	Moderate
TCA	0.95	0.15	1.75	3	139	Possibly more likely than placebo to improve pain	Low

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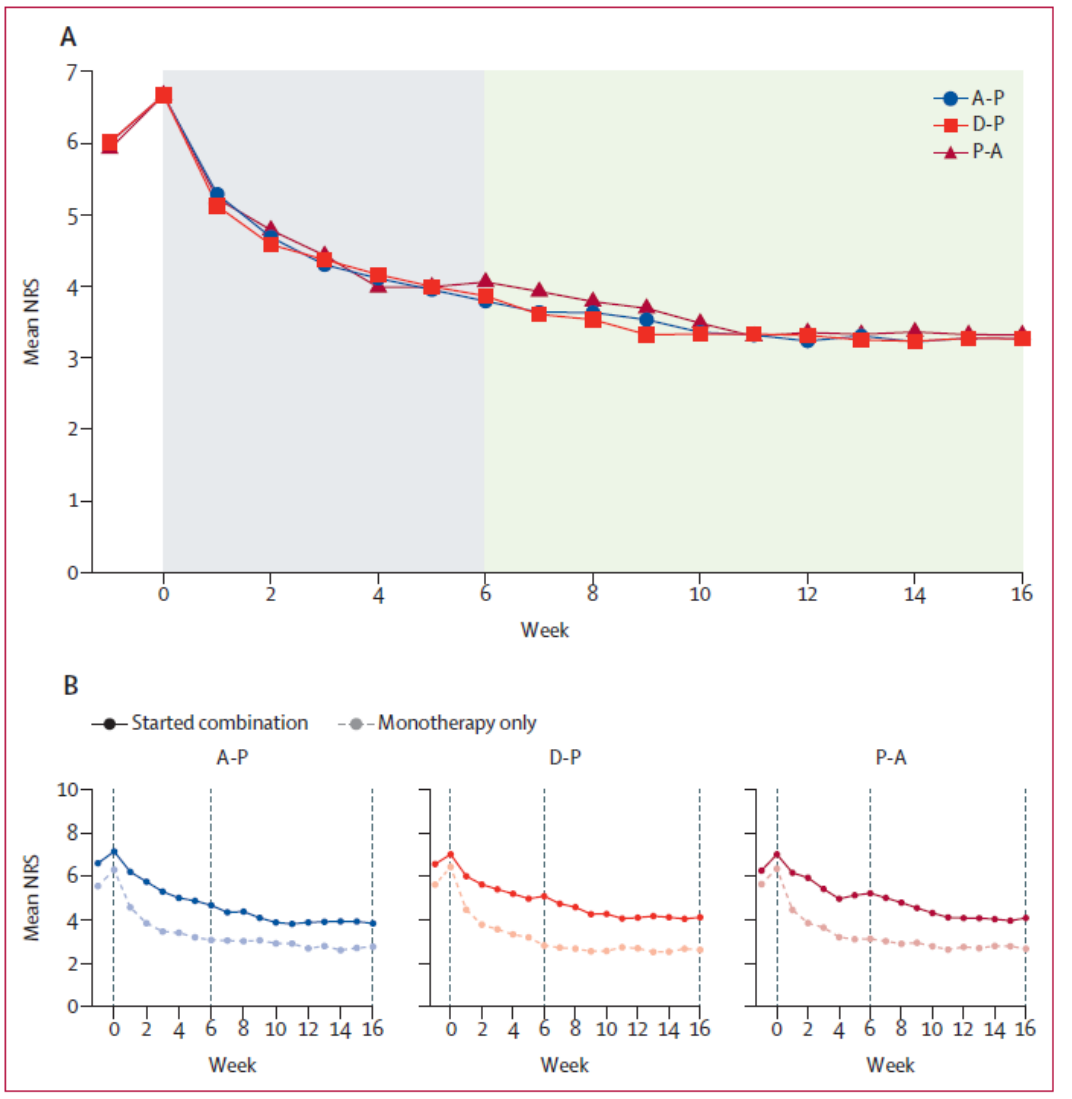
All work the same and two is better than one



- Amitripyline, pregabalin, and duloxetine have similar efficacy
- Combination therapy is helpful

Tesfaye et al, Lancet 2022

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Insurance and side effects important

Table 2. Study Outcomes

Outcome	Nortriptyline (n = 134)	Duloxetine (n = 126)	Pregabalin (n = 73)	Mexiletine (n = 69)
Week 12 outcome, No. (%)[a]				
Efficacious and nonquit	34 (25.4)	29 (23.0)	11 (15.1)	14 (20.3)
Nonefficacious and nonquit	49 (36.6)	50 (39.7)	31 (42.5)	15 (21.7)
Quit	51 (38.1)	47 (37.3)	31 (42.5)	40 (58.0)

- *Nortriptyline and duloxetine superior to pregabalin and mexilitene*
- Pregabalin had insurance issues
- Mexilitene had tolerability issues

Barohn et al, JAMA Neuro 2020

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Topical capsaicin

- 2 studies that both demonstrated a small positive effect
- Good for patients that prefer topical
- Inexpensive
- Hard to apply for patients with more diffuse involvement
- 8% patch by medical personnel
- Creams 0.025%, 0.075%, 0.1%

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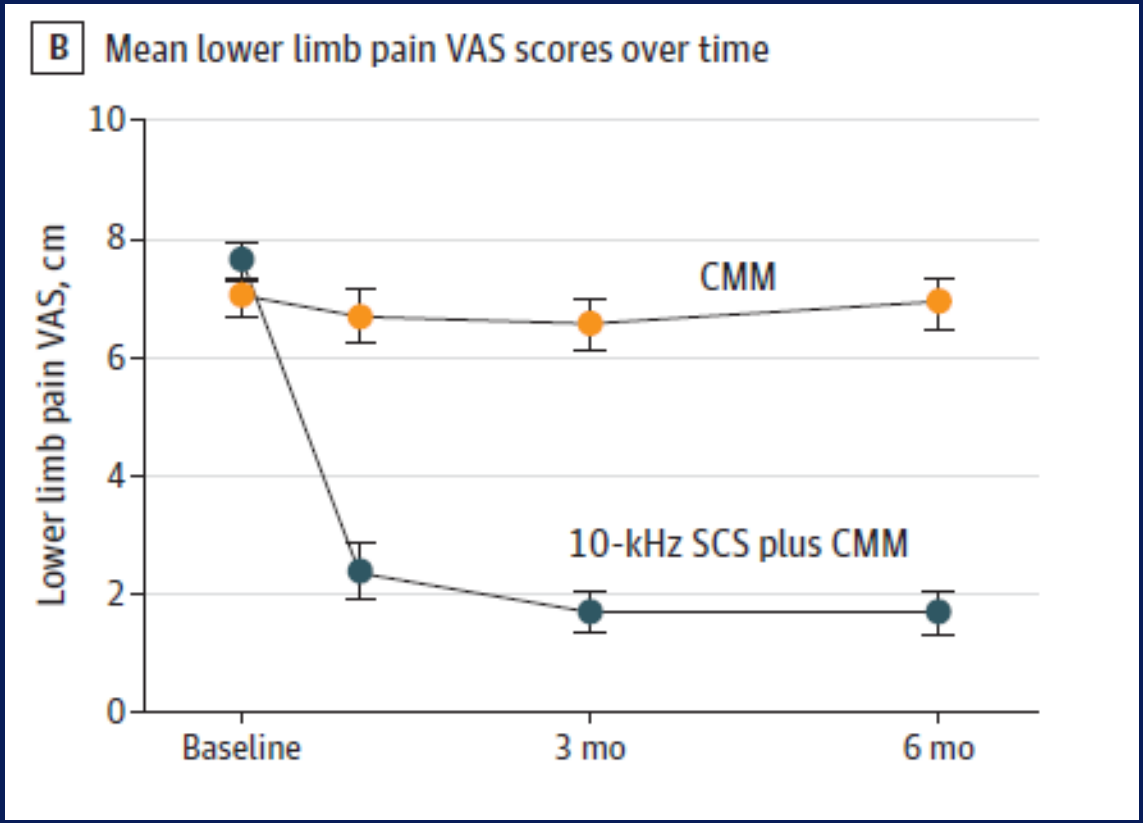
Spinal cord stimulator



- No sham control
- Petersen et al JAMA Neuro 2021

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Spinal cord stimulator
Chronic radicular pain after surgery

Table 2. Effect of Spinal Cord Burst Stimulation on Primary and Secondary Outcomes

	Mean score (95% CI)				
	At baseline	Spinal cord burst stimulation	Placebo stimulation	Between-group difference	*P* value
No. of stimulation periods		91	89		
Primary outcome					
Oswestry Disability Index, points[a]	44.7 (41.4 to 47.9)	34.0 (30.0 to 38.1)	35.4 (31.3 to 39.4)		
Change from baseline		−10.6 (−14.1 to −7.2)	−9.3 (−12.7 to −5.9)	−1.3 (−3.9 to 1.3)	.32
Secondary outcomes					
Numerical Rating Scale[b]					
Leg pain	7.3 (6.8 to 7.7)	5.9 (5.3 to 6.4)	6.1 (5.6 to 6.6)	−0.2 (−0.7 to 0.2)	.32
Back pain	6.8 (6.4 to 7.3)	5.7 (5.2 to 6.2)	6.1 (5.6 to 6.6)	−0.4 (−0.8 to 0.04)	.07
5-Dimension EuroQol index[c]	0.21 (0.13 to 0.28)	0.48 (0.39 to 0.56)	0.44 (0.35 to 0.53)	0.04 (−0.03 to 0.11)	.32
Physical activity level[d]					
No. of steps per day	6775 (5651 to 7899)	7561 (6411 to 8710)	7155 (6006 to 8305)	405 (−422 to 1233)	.34
Time spent standing or walking, h/d	3.8 (3.3 to 4.3)	4.0 (3.5 to 4.4)	4.0 (3.6 to 4.4)	−0.02 (−0.4 to 0.3)	.89

- Sham control
- Hara et al, JAMA 2022

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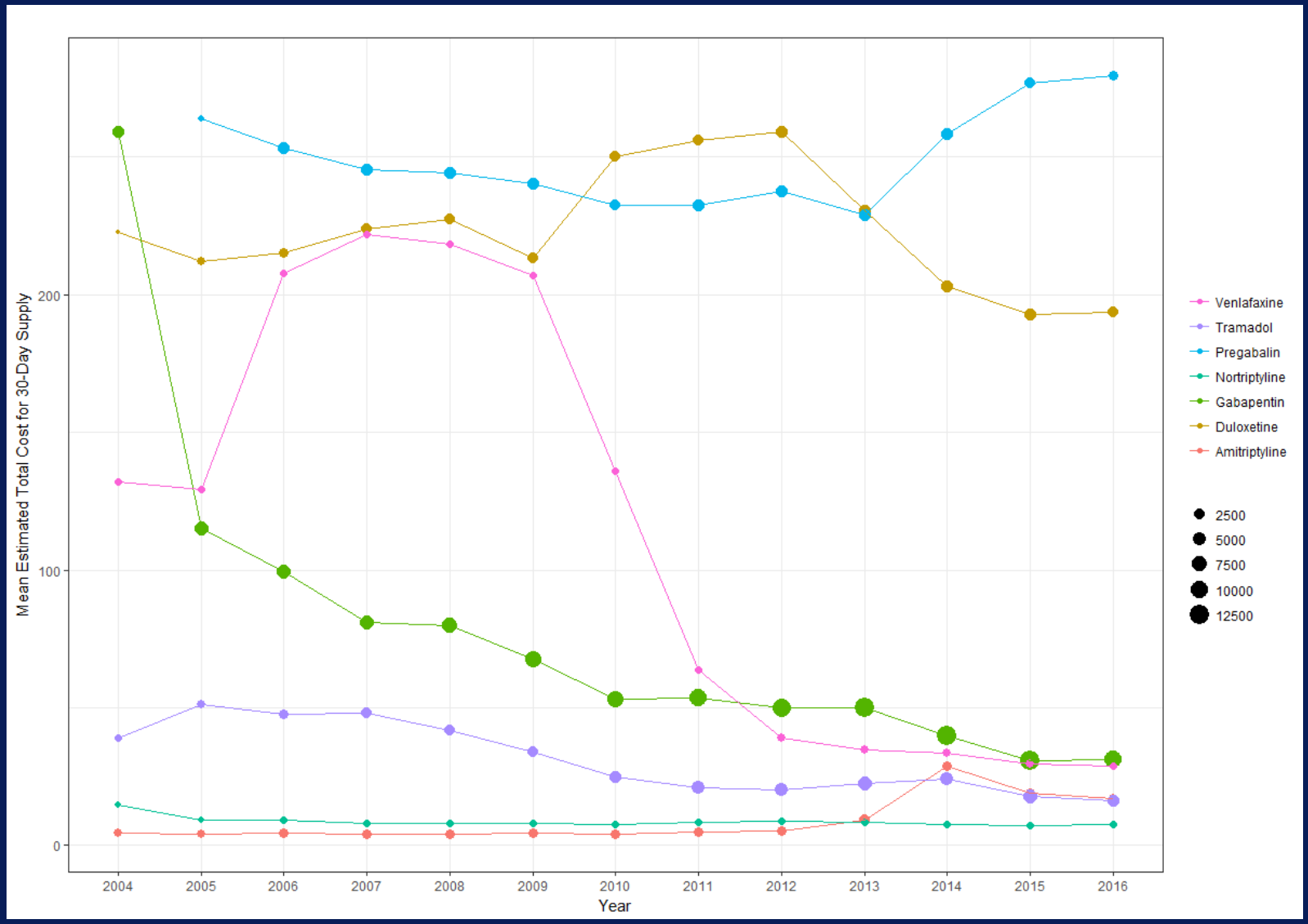
Total costs are high



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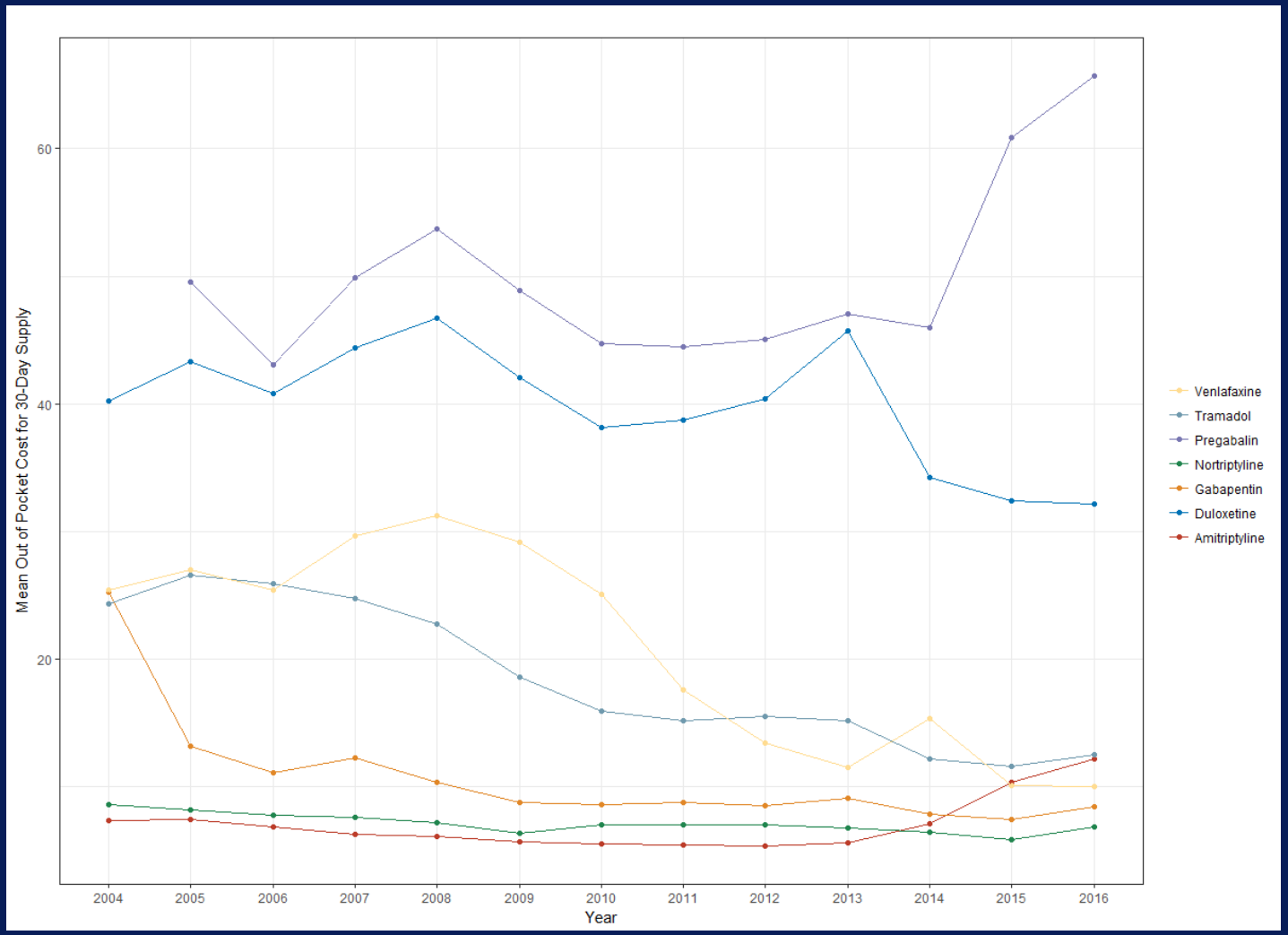
Costs to patients vary a lot



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Advice

- No need for brand medications
- Cheap pills available in all classes
- Two cheap topical options (lidocaine 4% patch and capsaicin creams)
- Other interventions highly variable (acupuncture, cognitive behavioral therapy, mindfulness)

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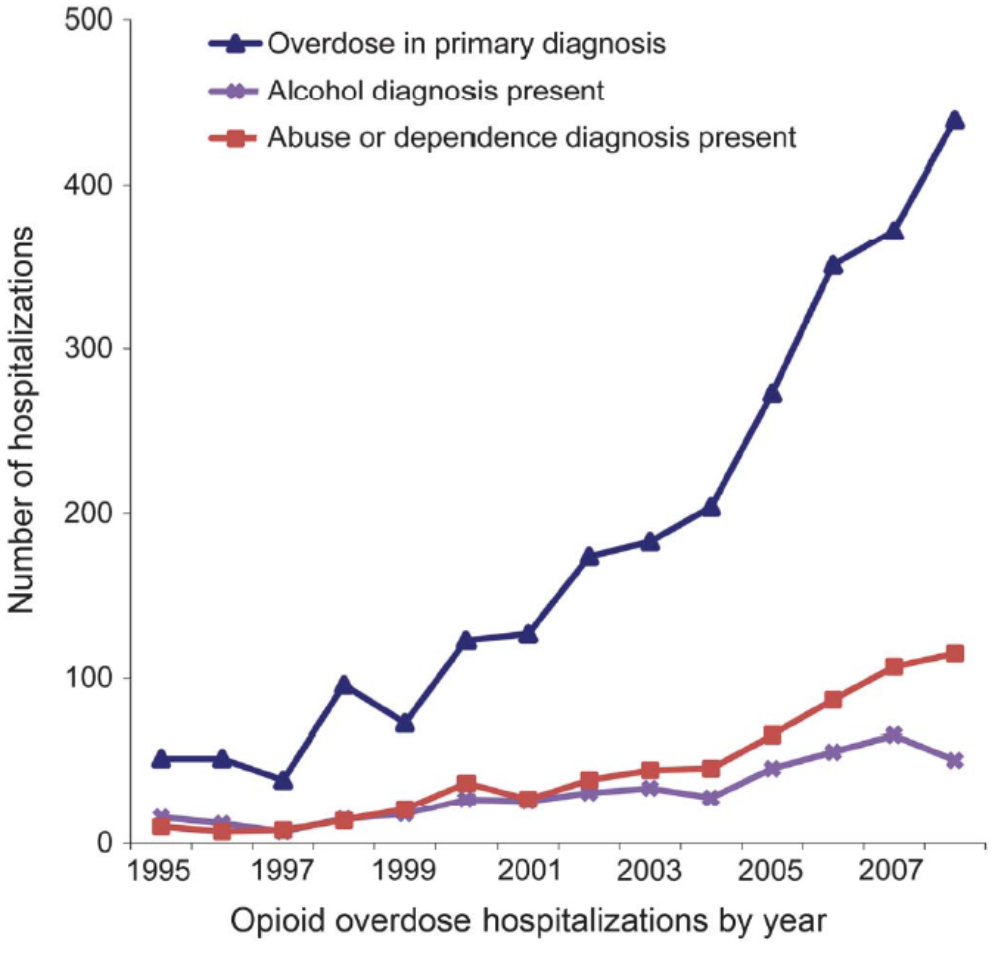
Don't use opioids

Figure 1 Hospitalizations from opioid overdose (Washington State, 1987–2008)



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Opioids for chronic noncancer pain: A position paper of the American Academy of Neurology

Gary M. Franklin

Neurology 2014;83:1277-1284

DOI 10.1212/WNL.0000000000000839

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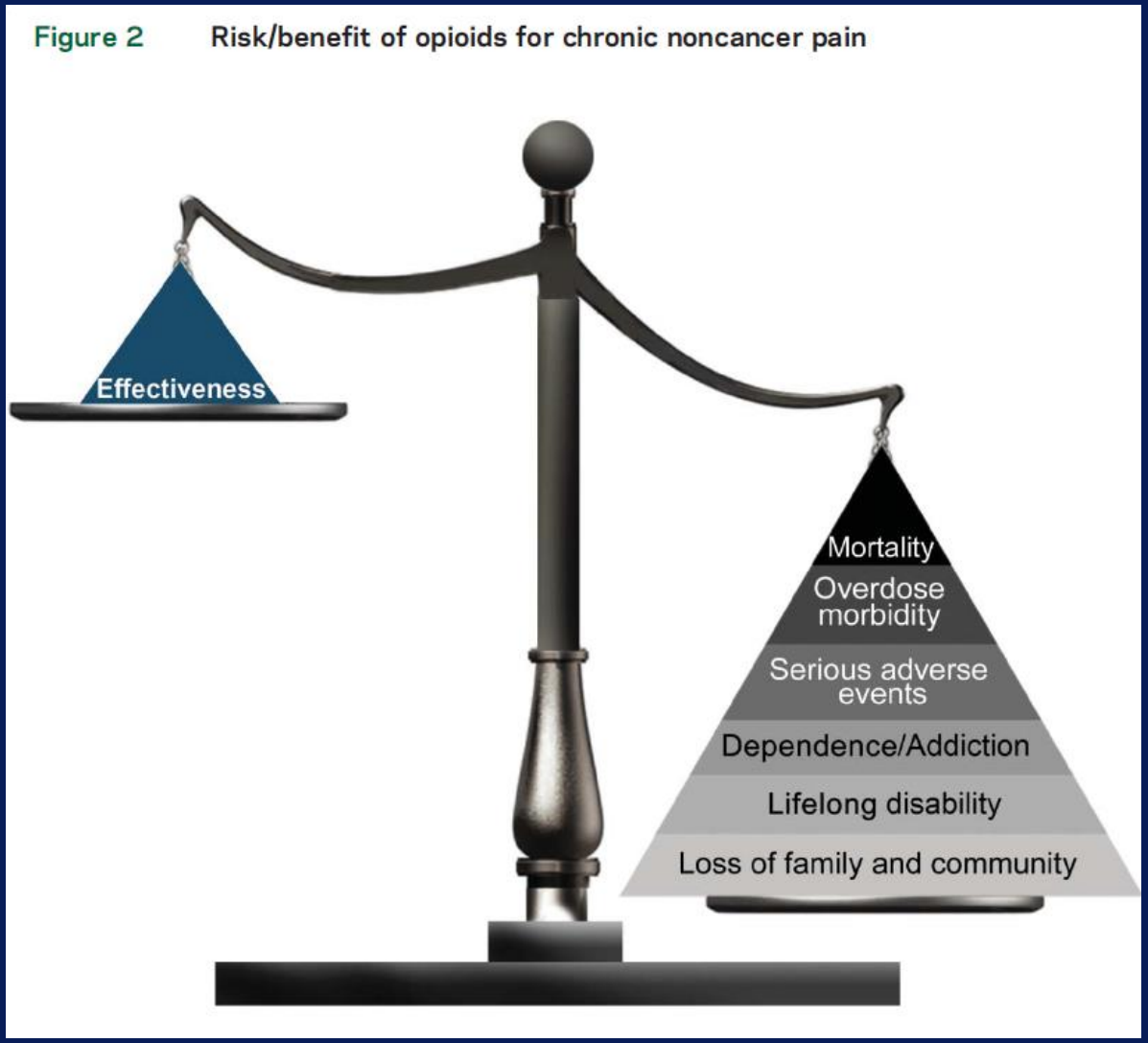
Don't use opioids

Figure 2 Risk/benefit of opioids for chronic noncancer pain



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No long-term evidence

Clinical Review & Education

Special Communication

CDC Guideline for Prescribing Opioids for Chronic Pain—United States, 2016

Table 1. GRADE Ratings of the Evidence for the Key Clinical Questions[a]

Outcome	Studies	Limitations	Inconsistency	Imprecision	Type of Evidence[b]	Other Factors	Estimates of Effect or Findings
Effectiveness and Comparative Effectiveness (Key Question 1)							
Effectiveness of long-term opioid therapy vs placebo or no opioid therapy for long-term (≥1 y) outcomes							
Pain, function, and quality of life	None	NA	NA	NA	Insufficient	NA	No evidence.

Dowell et al, JAMA 2016

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Big downsides

Harms and Adverse Events (Key Question 2)							
Risks of opioids vs placebo or no opioids on opioid abuse, addiction, and related outcomes; overdose; and other harms							
Abuse or addiction	1 cohort study (n = 568 640)	Serious limitations	Unknown (1 study)	No imprecision	3	None identified	One retrospective cohort study found long-term use of prescribed opioids was associated with an increased risk of abuse or dependence diagnosis vs no opioid use (adjusted OR range, 14.9-122.5, depending on dose).
Abuse or addiction	10 uncontrolled studies (n = 3780)	Very serious limitations	Very serious inconsistency	No imprecision	4	None identified	In primary care settings, prevalence of opioid abuse ranged from 0.6%-8%; prevalence of dependence, 3%-26%. In pain clinic settings, prevalence of misuse, 8%-16%, and addiction, 2%- 14%. Prevalence of aberrant drug-related behaviors, 6%-37%.
Overdose	1 cohort study (n = 9940)	Serious limitations	Unknown (1 study)	Serious imprecision	3	None identified	Current opioid use associated with increased risk of any overdose events, adjusted HR, 5.2 (95% CI, 2.1-12), and serious overdose events, adjusted HR, 8.4 (95% CI, 2.5-28) vs current nonuse.
Fractures	1 cohort study (n = 2341) 1 case-control study (n = 21 739 case patients)	Serious limitations	No inconsistency	No imprecision	3	None identified	Opioid use associated with increased risk of fracture in 1 cohort study, adjusted HR, 1.28 (95% CI, 0.99-1.64), and 1 case-control study, adjusted OR, 1.27 (95% CI, 1.21-1.33).
Myocardial infarction	1 cohort study (n = 426 124) 1 case-control study (n = 11 693 case patients)	No limitations	No inconsistency	No imprecision	3	None identified	Current opioid use associated with increased risk of myocardial infarction vs nonuse, adjusted OR, 1.28 (95% CI, 1.19-1.37) and IRR, 2.66 (95% CI, 2.30-3.08).
Endocrinologic harms	1 cross-sectional study (n = 11 327)	Serious limitations	Unknown (1 study)	No imprecision	3	None identified	Long-term opioid use associated with increased risk for use of medications for erectile dysfunction or testosterone replacement vs nonuse, adjusted OR, 1.5 (95% CI, 1.1-1.9).

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SNRI/opioids

- Tramadol- 3 studies demonstrating it works
- Tapentadol- 1 study demonstrating it works
- However, same long term side effects as other opioids
- Don’t use tramadol and tapentadol for chronic pain

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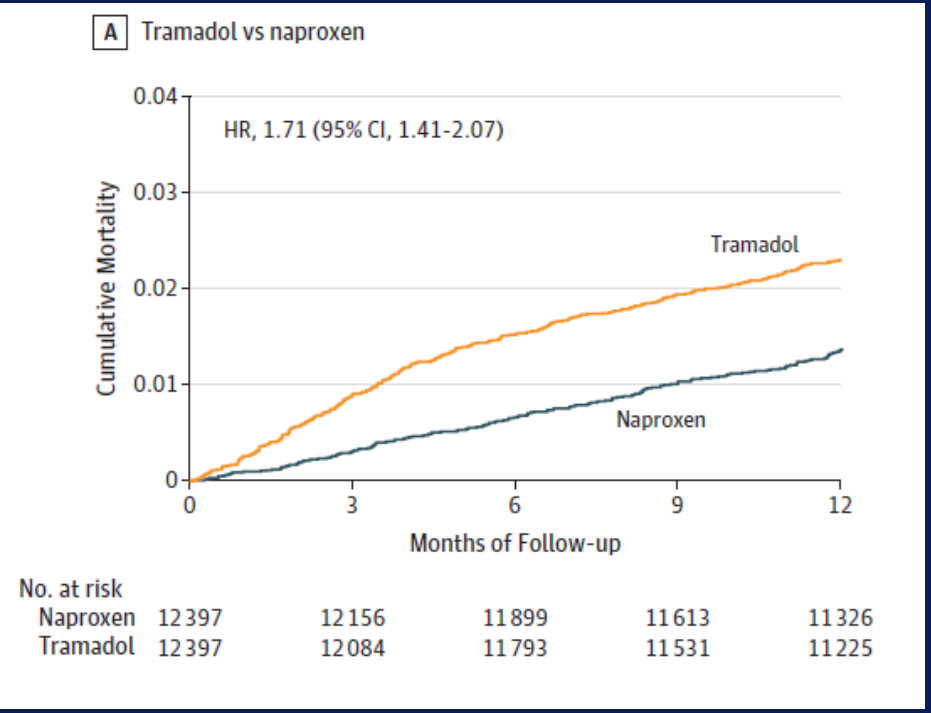
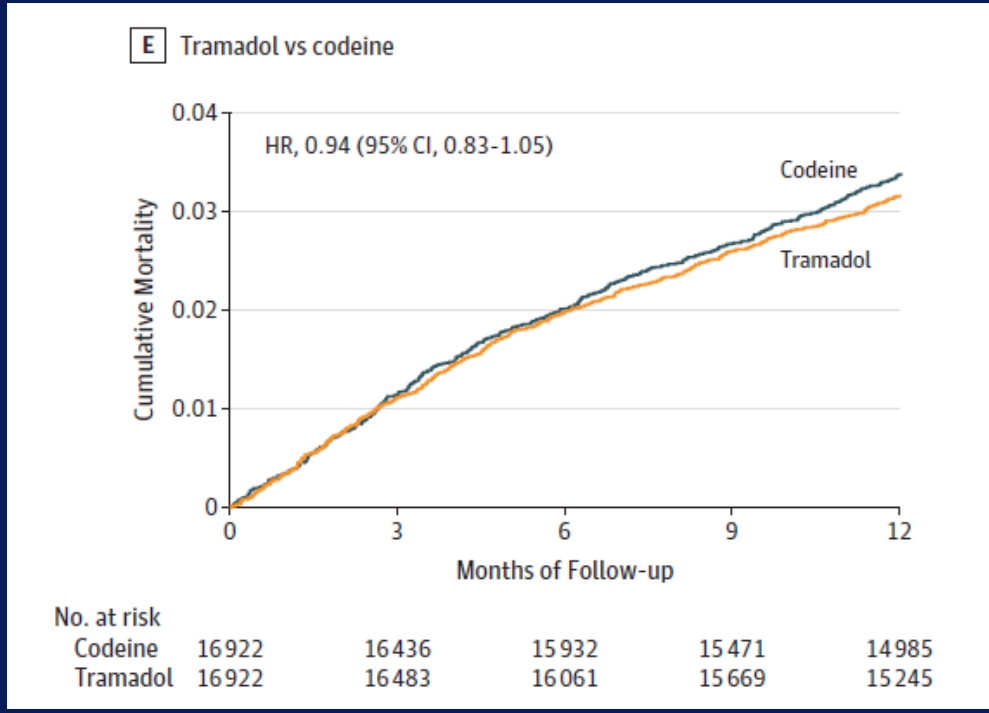
Tramadol and mortality





Zeng et al, JAMA 2019

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Opioids are common

Table 1. Data on Opioids Prescribed to Patients With Polyneuropathy and Matched Controls

Data	No. (%)	
	Patients With Polyneuropathy (n = 2892)	Matched Controls (n = 14 435)
Duration of opioid therapy, d		
<90	1464 (50.6)	5117 (35.4)
≥90	545 (18.8)	780 (5.4)

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Opioids- worse functional status

Table 3. Self-reported Markers of Functional Status Among Patients With Polyneuropathy Receiving Opioids

Surrogate Marker of Functional Status	Patients With Data, No./Total No. (%)		OR (95% CI)	Adjusted OR (95% CI)
	<90 d of Therapy	≥90 d of Therapy		
Preparing meals	167/1113 (15.0)	90/414 (21.7)	1.6 (1.2-2.1)	1.2 (0.9-1.7)
Feeding yourself	23/1113 (2.1)	16/414 (3.9)	1.9 (1.0-3.6)	1.9 (0.9-3.9)
Dressing	115/1113 (10.3)	77/414 (18.6)	2.0 (1.4-2.7)	1.7 (1.2-2.4)
Using the toilet	72/1113 (6.5)	42/414 (10.1)	1.6 (1.1-2.4)	1.4 (0.9-2.2)
Housekeeping	220/1113 (19.8)	144/414 (34.8)	2.2 (1.7-2.8)	1.6 (1.2-2.2)
Bathing	135/1113 (12.1)	90/414 (21.7)	2.0 (1.5-2.7)	1.6 (1.1-2.2)
Walking	258/1113 (23.2)	151/414 (36.5)	1.9 (1.5-2.4)	1.5 (1.1-1.9)
Using transportation	142/1113 (12.8)	75/414 (18.1)	1.5 (1.1-2.0)	1.2 (0.9-1.7)
Getting in and out of bed	88/1113 (7.9)	56/414 (13.5)	1.8 (1.3-2.6)	1.4 (1.0-2.1)
Limb weakness	207/1113 (18.6)	110/414 (26.6)	1.6 (1.2-2.1)	1.3 (0.9-1.7)
Limb numbness/shooting pain	258/1113 (23.2)	127/414 (30.7)	1.5 (1.1-1.9)	1.3 (1.0-1.7)
Fall tendency	129/1113 (11.6)	69/414 (16.7)	1.5 (1.1-2.1)	1.2 (0.9-1.2)
Any pain (yes or no)	381/901 (42.3)	241/337 (71.5)	3.4 (2.6-4.5)	2.5 (1.9-3.4)
Stair intolerance	618/980 (63.1)	291/355 (82.0)	2.7 (2.0-3.6)	1.7 (1.2-2.4)
Assistive device	399/1010 (39.5)	221/361 (61.2)	2.4 (1.9-3.1)	1.9 (1.4-2.6)
Unable to work	71/1053 (6.7)	44/374 (11.8)	1.8 (1.2-2.7)	1.3 (0.8-2.0)
Assisted living or nursing home	80/1036 (7.7)	41/362 (11.3)	1.5 (1.0-2.3)	1.3 (0.8-2.1)

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Opioids- adverse outcomes

Table 4. Adverse Outcomes and Mortality Among Patients With Polyneuropathy Receiving Opioids

Adverse Outcome	Opioid Treatment, No. (%) <90 d (n = 1452)	Opioid Treatment, No. (%) ≥90 d (n = 541)	HR (95% CI)	Adjusted HR (95% CI)
Depression	633 (43.6)	341 (63.0)	1.97 (1.68-2.30)	1.53 (1.29-1.82)
Abuse				
Alcohol	109 (7.5)	54 (10.0)	1.63 (1.10-2.39)	1.38 (0.90-2.11)
Opioid	2 (0.1)	9 (1.7)	10.66 (2.71-70.27)	3.97 (0.87-28.9)
Other substance	27 (1.9)	25 (4.6)	2.37 (1.29-4.36)	1.81 (0.92-3.58)
Overdose				
Opioid	4 (0.3)	14 (2.6)	8.29 (2.93-29.44)	5.12 (1.63-19.62)
Other substance	24 (1.7)	22 (4.1)	2.53 (1.37-4.65)	1.82 (0.92-3.6)
Dependence				
Opioid	20 (1.4)	39 (7.2)	5.59 (3.20-10.18)	2.85 (1.54-5.47)
Other substance	129 (8.9)	95 (17.6)	2.41 (1.73-3.34)	1.73 (1.21-2.49)
Deceased by 11/25/16	530 (36.5)	256 (47.3)	1.22 (1.05-1.41)	0.99 (0.84-1.16)

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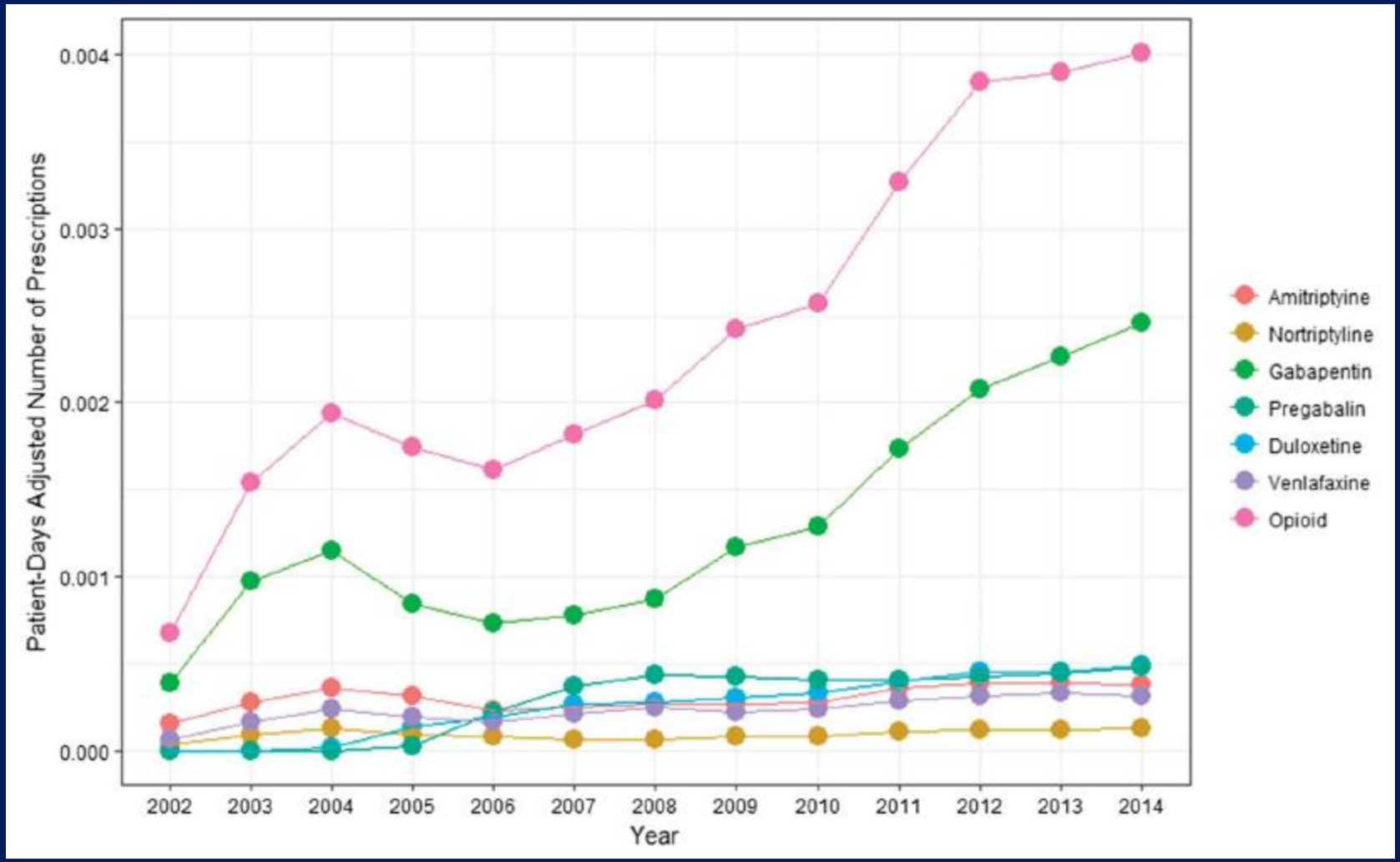
Opioids are increasing fastest



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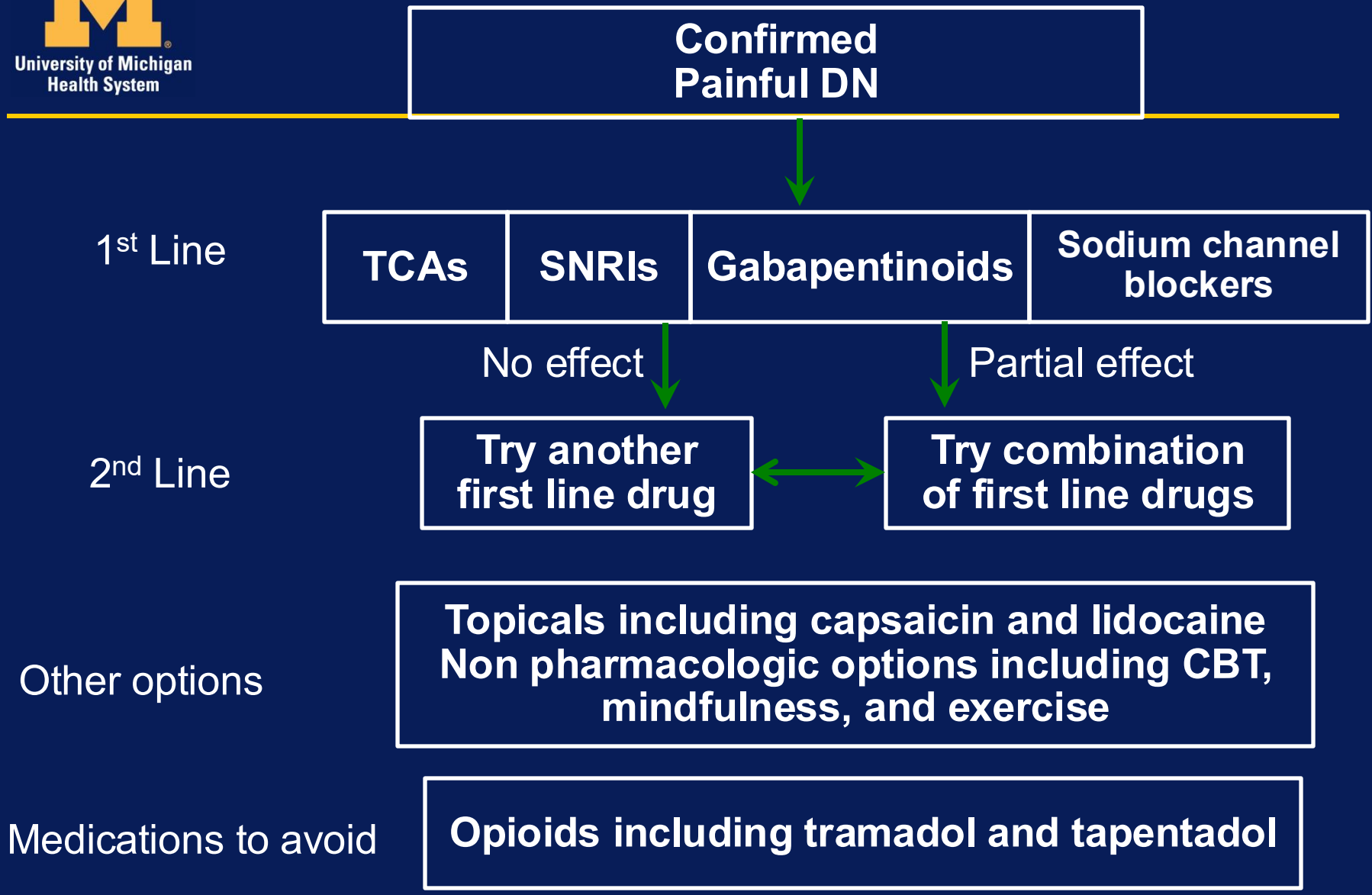

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Ask about pain and set expectations

Recommendation Statement 1

Clinicians should assess patients with diabetes for peripheral neuropathic pain and its effect on these patients' function and quality of life (Level B).

Recommendation Statement 2

When initiating pharmacologic intervention for PDN, clinicians should counsel patients that the goal of therapy is to reduce, and not necessarily to eliminate, pain (Level B).

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Sleep and mood are important

Recommendation Statement 3

Clinicians should assess patients with PDN for the presence of concurrent mood and sleep disorders and treat them as appropriate (Level B).

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4 effective oral medication classes

Recommendation Statement 4

In patients with PDN, clinicians should offer TCAs, SNRIs, gabapentinoids, and/or sodium channel blockers to reduce pain (Level B).

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Don't forget topical and non-pharm

Recommendation Statement 5a

Clinicians may assess patient preferences for effective oral, topical, nontraditional, and nonpharmacologic interventions for PDN (Level C).

Recommendation Statement 5b

In patients preferring topical, nontraditional, or nonpharmacologic interventions, providers may offer topical (capsaicin, glyceryl trinitrate spray, *Citrullus colocynthis*), nontraditional (*Ginkgo biloba*), or nonpharmacologic interventions (CBT, exercise, Tai Chi, mindfulness) (Level C).

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Given they work the same, other factors important

Recommendation Statement 6a

Given similar efficacy, clinicians should consider factors other than efficacy, including potential adverse effects, patient comorbidities, cost, and patient preferences, when recommending treatment for PDN (Level B).

Recommendation Statement 7a

Clinicians should counsel patients that a series of medications may need to be tried to identify the treatment that most benefits patients with PDN (Level B).

Recommendation Statement 7b

Clinicians should determine that an individual intervention to reduce neuropathic pain is a failure either when the medication has been titrated to a demonstrated efficacious dose for approximately 12 weeks without clinically significant pain reduction or when side effects from the medication outweigh any benefit in reduced neuropathic pain (Level B).

Recommendation Statement 7c

Clinicians should offer patients a trial of a medication from a different effective class when they do not achieve meaningful improvement or if they experience significant adverse effects with the initial therapeutic class (Level B).

Recommendation Statement 7d

For patients who achieve partial improvement with an initial therapeutic class, clinicians should offer a trial of a medication from a different effective class or combination therapy by adding a medication from a different effective class (Level B).

- Often need to trial multiple options
- 12 weeks or side effects
- *Change classes*
- *Combination works*

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No opioids including tramadol!

Recommendation Statement 8a

Clinicians should not use opioids for the treatment of PDN (Level B).

Recommendation Statement 8b

If patients are currently on opioids for the treatment of PDN, clinicians may offer the option of a safe taper off these medications and discuss alternative nonopioid treatment strategies (Level C).

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Unique challenges

Medication	NNT	NNH
Pregabalin	7.7	17
SNRIs	6.4	13
Gabapentin	7.2	17
TCAs	3.6	15

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Unique challenges

- Limited therapeutics
  - Neuropathy (diabetes, idiopathic, alcohol)
  - Radiculopathy
  - Mononeuropathy
  - Stroke, multiple sclerosis, traumatic injury

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Promising future options

- Other options
  - Cognitive behavioral therapy
  - Mindfulness
  - Acupuncture
  - Be skeptical of expensive or cash only options

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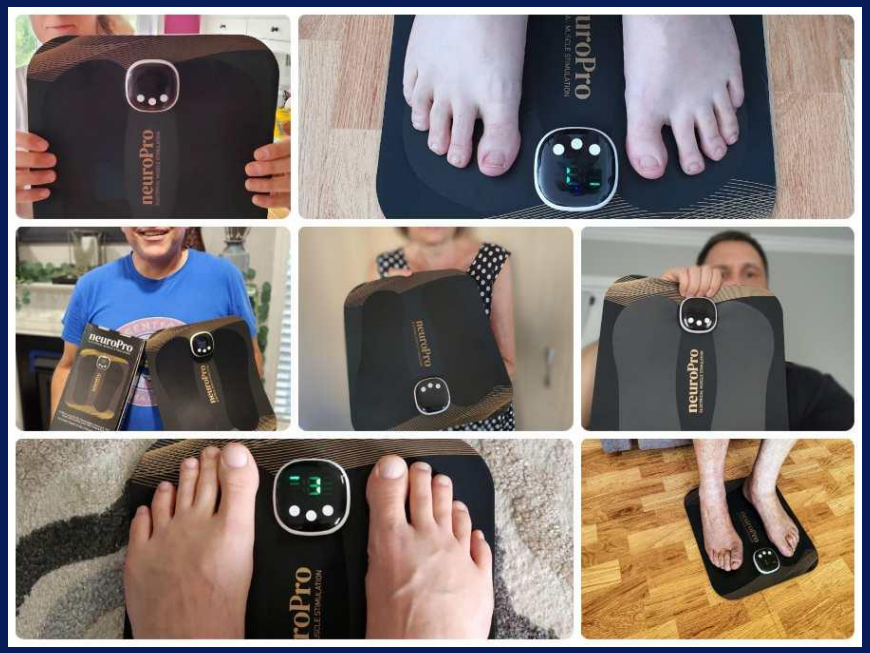
Don't get scammed



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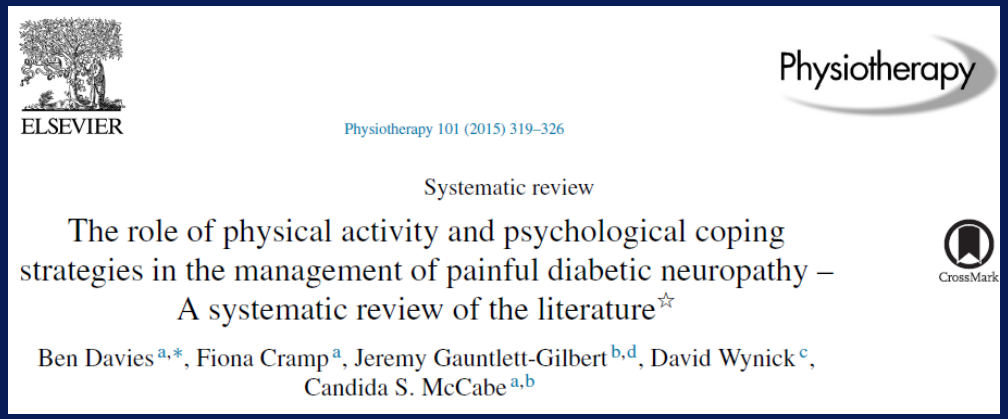
Non-pharmacologic



ELSEVIER

Physiotherapy

Physiotherapy 101 (2015) 319–326

Systematic review

The role of physical activity and psychological coping strategies in the management of painful diabetic neuropathy – A systematic review of the literature☆

Ben Davies[a,*], Fiona Cramp[a], Jeremy Gauntlett-Gilbert[b,d], David Wynick[c], Candida S. McCabe[a,b]

CrossMark

- 2015 systematic review

- Trials in Tai chi, treadmill exercise, mindfulness, and CBT
- Not the best studies
- Little downsides and can be useful as non-opioid options

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Overall takeaways

- Neuropathic pain is unique
- TCAs, SNRIs, gabpentinoids and sodium channel blockers work
- Capsaicin and lidocaine are the topicals of choice
- Exercise, CBT, and mindfulness might work
- Opioids including tramadol/tapentadol should be avoided
- NNT and NNH close and underlying treatment difficult
- Need new treatments

Thanks for joining us!

ANY QUESTIONS?!

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HOW WAS IT?

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