Evidence Analysis for the Use of Non-Opioid Analgesics

Ameet Nagpal, MD, MS, MEd
Associate Professor, Department of Anesthesiology, UT Health San Antonio
Texas Pain Society 11th Annual Meeting
October 27th, 2019

UT Health San Antonio

Twitter: @Sympathy4TheDr
https://www.facebook.com/ameet.nagpal.121

Disclosures

Consultant: Avanos Medical; Texas Medical Board

Speaker: American Society of Regional Anesthesia & Pain Medicine (ASRA), American Academy of Pain Medicine (AAPM), Spine Intervention Society (SIS), Texas Pain Society (TPS)

Committee Membership:

SIS Standards Division, Education Division, Annual Meeting Program Planning Committee, SpineNet Committee;

AAPM&R Self Assessment Committee, Pain Management & Opioid Task Force, AMA Opioid Task Force Physician Delegate

Medical Directorship: Dannemiller, Inc.

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Objectives

1. Describe the basis for which categorical data is superior to continuous data in clinical, chronic pain trials and how that impacts the data that we consume.

2. Describe the methods to correctly interpret a pain study.

3. List the evidence for the use of a given non-opioid analgesic for a given chronic pain condition.

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You design a trial to determine if a novel neuropathic pain agent can treat painful diabetic neuropathy.

You create two groups: a control (placebo) group and an interventional (drug) group, and assess them at baseline and at 3 months.

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	Drug Group Pre-Intervention	Drug Group Post-Intervenion	Difference	Placebo Group Pre-Intervention	Placebo Group Post-Intervenion	Difference
	6	6	0	6	5	1
	8	1	7	8	5	3
	10	5	5	10	5	5
	8	9	-1	8	5	3
	7	1	6	7	5	2
	9	8	1	9	5	4
Mean	**8**	**5**	**3**	**8**	**5**	**3**

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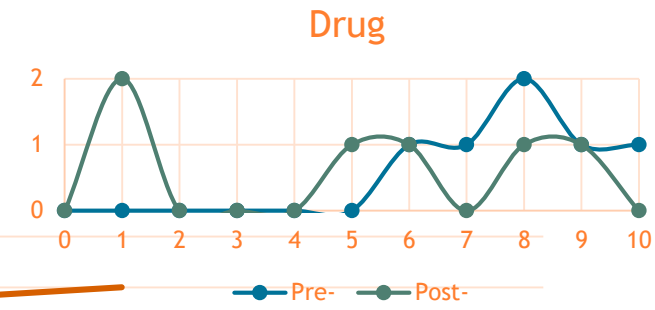
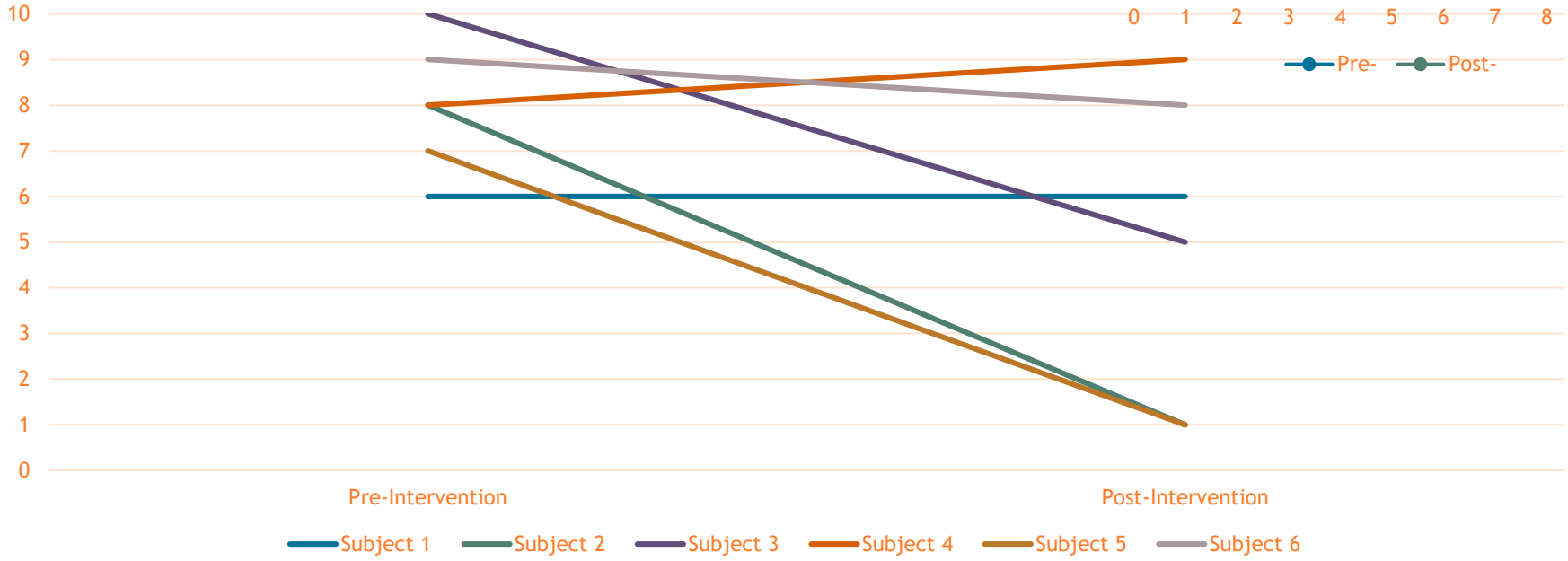


Drug Group



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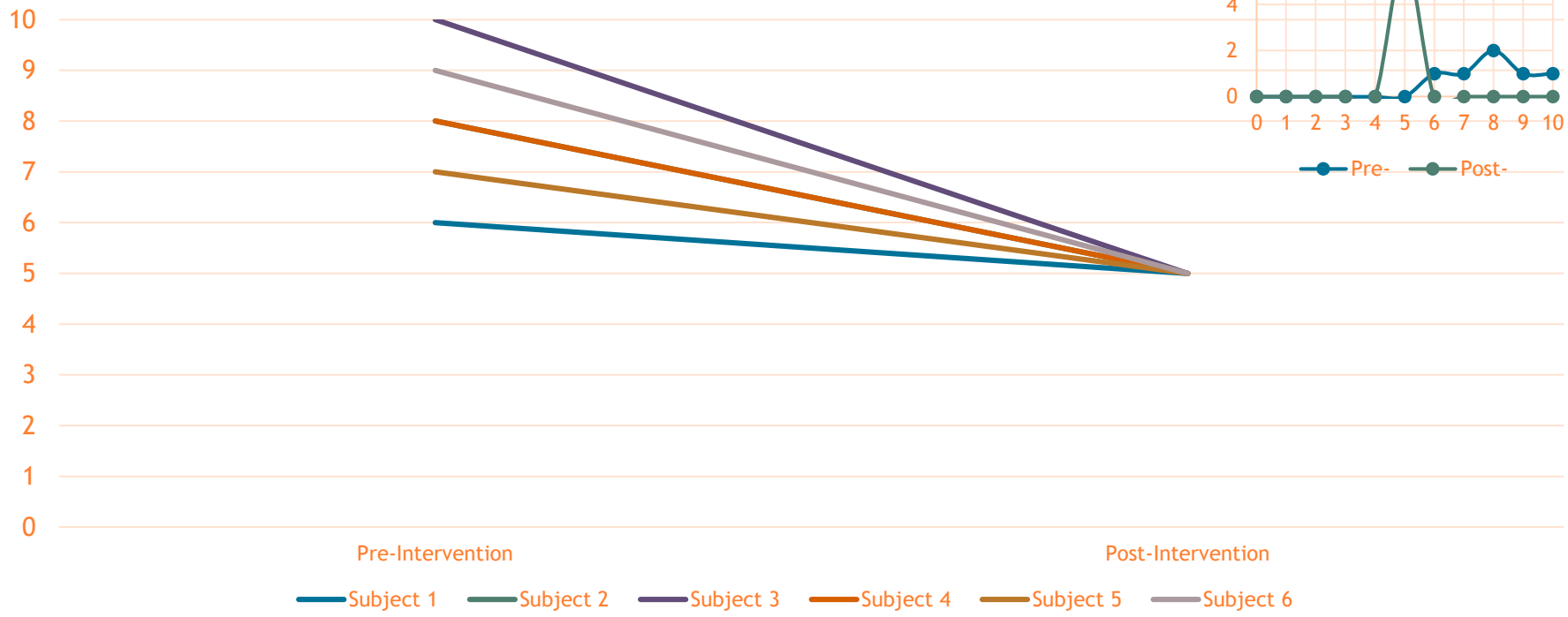
Placebo Group



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What Do You Really Want From Your Patient? Audience Response System

Improvement.

How much?

A. 10%?

B. 20%?

C. 30%?

D. 100%?

Minimal Clinically Important Difference (MCID)

The minimum change in numeric rating scale that is important/significant as a difference to the average person for a given condition

Examples: MCID low back pain = 2.5; lumbar radicular pain = 2

This is **different** than the minimal clinically detectable difference (MCDD)

Lauridsen HH, Hartvigsen J, Manniche C, Korsholm L, Grunnet-Nilsson N. Responsiveness and minimal clinically important difference for pain and disability instruments in low back pain patients. BMC Musculoskelet Disord. 2006 Oct 25;7:82.
Farrar JT, Young JP Jr, LaMoreaux L, Werth JL, Poole RM. Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. Pain. 2001 Nov;94(2):149-58.


THIS IS
UNACCEPTABLE

The Art of Medicine

Reasonable decision making must drive your research and clinical practice

Let's say a 5 point improvement on our 11 point scale is a reasonable goal

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Drug Group Pre-Intervention	Drug Group Post-Intervenion	Difference	Placebo Group Pre-Intervention	Placebo Group Post-Intervenion	Difference
6	6	0	6	5	1
8	1	7	8	5	3
10	5	5	10	5	5
8	9	-1	8	5	3
7	1	6	7	5	2
9	8	1	9	5	4
Mean	**8**	**5**	**3**	**8**	**5**	**3**

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Drug Group Pre-Intervention	Drug Group Post-Intervenion	Difference	Placebo Group Pre-Intervention	Placebo Group Post-Intervenion	Difference
[illegible]	6	0	6	5	1
8	1	7	8	5	3
10	5	5	10	5	5
8	9	[illegible]	8	[illegible]	3
7	1	6	7	[illegible]	2
9	[illegible]	1	9	5	4
Mean	8	5	3	8	5	3

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Drug Group Pre-Intervention	Drug Group Post-Intervenion	5 Points Improved: Yes or No?
6	6	NO
8	1	YES
10	5	YES
8	9	NO
7	1	YES
9	8	NO

Placebo Group Pre-Intervention	Placebo Group Post-Intervenion	5 Points Improved: Yes or No?
6	5	NO
8	5	NO
10	5	YES
8	5	NO
7	5	NO
9	5	NO

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Lay Terms…

5 Points Improved: Drug	5 Points Improved: Placebo
NO	NO
YES	NO
YES	YES
NO	NO
YES	NO
NO	NO

When treated with the experimental drug, 3 patients with painful diabetic neuropathy will experience “50% improvement” for every 1 who experiences “50% improvement” with placebo

The Number Needed To Treat (NNT) is the ratio of the experimental event rate to the control event rate – in this case, 3:1

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So What… ?

When comparing means between our two samples, there is no difference.

If this study was designed as a comparative means study, the title would be **"Experimental Drug Does Not Improve Diabetic Painful Neuropathy"**

But… the number needed to treat is 3. If the study was designed to compare categorical data, the title would be **"Experimental Drug Improves Painful Diabetic Neuropathy"**

Is one more right than the other?

The Normality Assumption

A t-test is performed under circumstances in which the data distributes normally

An ANOVA (another comparative mean statistic) also follows the normality assumption

Pain studies do not contain normally distributed data, thus violating assumptions of the t-test and ANOVA

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Bold statement

Alert

Is One More Right Than the Other?

Yes; Ameet's bold statement of the day:

Categorical data is **not only superior** to continuous data in pain studies, continuous data is **useless** in pain studies.

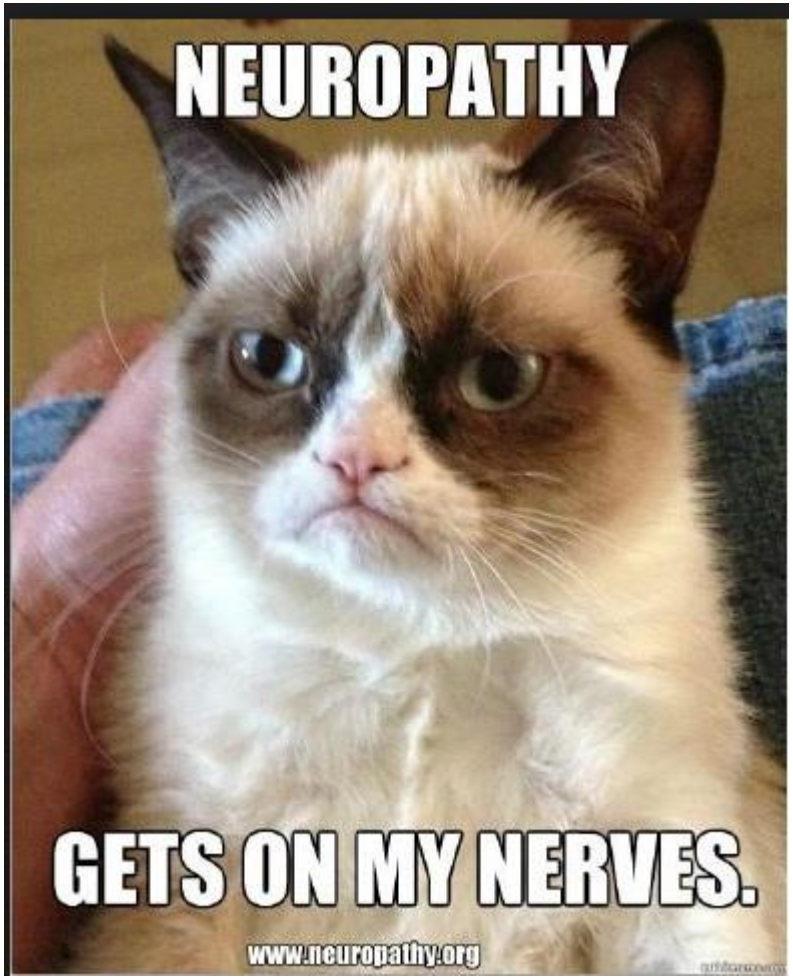
Don't take my word for it…

Categorical reductions in pain have been endorsed as a ***standard outcome measure*** for low back pain research by the United States National Institutes of Health.

Deyo RA, Dworkin SF, Amtmann D, Andersson G, Borenstein D, Carragee E, et al. Report of the NIH Task Force on research standards for chronic low back pain. Phys Ther. 2015 Feb;95(2):e1–18.


I WANT YOU TO KNOW
THAT SOMEONE OUT THERE
CARES
Not me, but someone does.

Neuropathic Pain Agents



Published in final edited form as:
Lancet Neurol. 2015 February ; 14(2): 162–173. doi:10.1016/S1474-4422(14)70251-0.

Pharmacotherapy for neuropathic pain in adults: systematic review, meta-analysis and updated NeuPSIG recommendations

Nanna B Finnerup, MD[*,a], Nadine Attal, MD[*,b,c,1], Simon Haroutounian, PhD[d], Ewan McNicol, MS[e], Ralf Baron, MD[f], Robert H Dworkin, PhD[g], Ian Gilron, MD[h], Maija Haanpaa, MD[i], Per Hansson, MD[j], Troels S Jensen, MD[a,k], Peter R Kamerman, PhD[l], Karen Lund, MD[a], Andrew Moore, DSc[m], Srinivasa N Raja, MD[n], Andrew SC Rice, MD[o], Michael Rowbotham, MD[p], Emily Sena, PhD[q], Philip Siddall, MD[r], Blair H Smith, MD[s], and Mark Wallace, MD[t]

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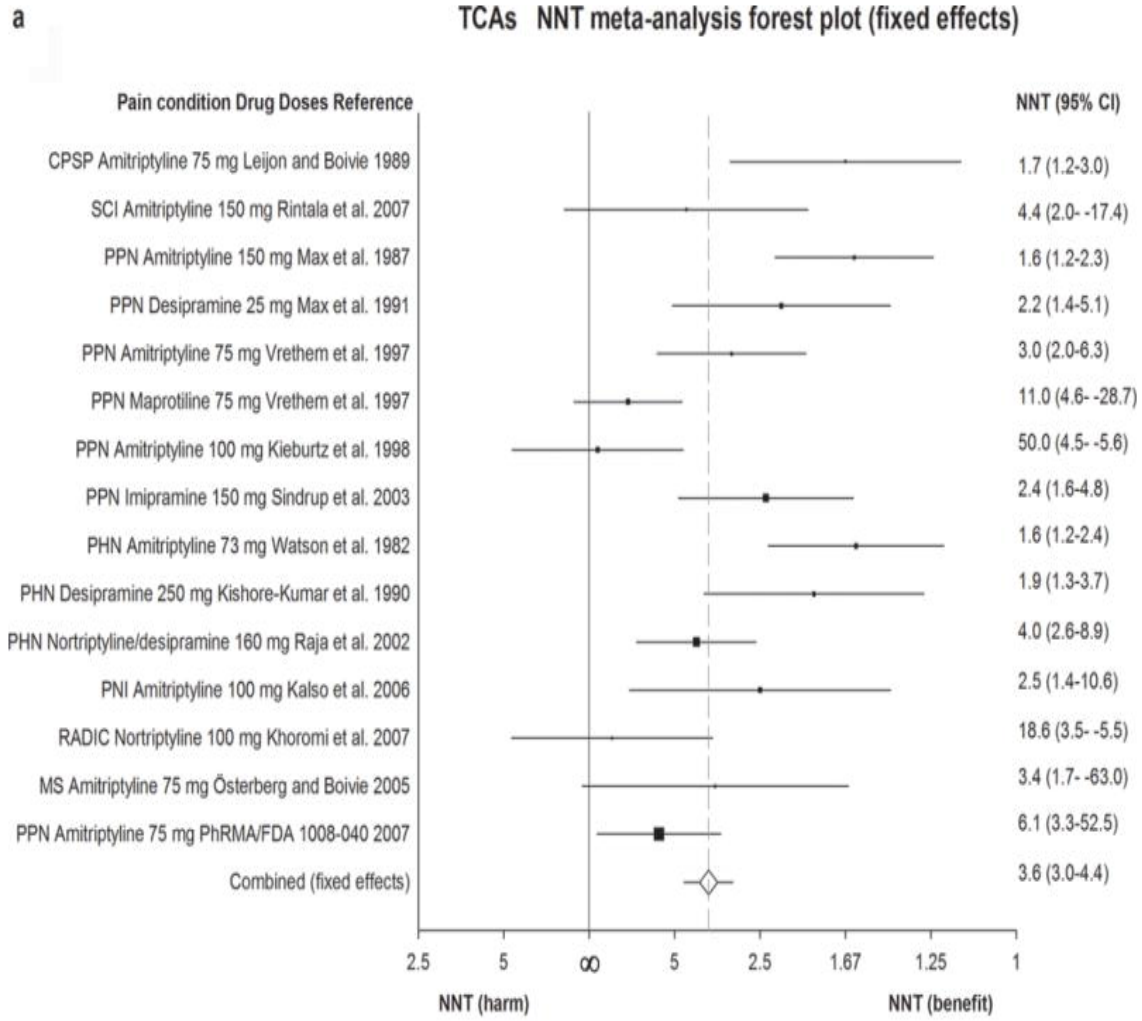
Figure 2



Risk difference:
Fixed effects (Mantel-Haenszel, Greenland-Robins)
Pooled risk difference = 0.280443 (95% CI = 0.226957 to 0.33393) Chi^2 (test risk difference differs from 0) = 105.608497 (df = 1) P < 0.0001
Random effects (DerSimonian-Laird)
Pooled risk difference = 0.330102 (95% CI = 0.222779 to 0.437425) Chi^2 (test risk difference differs from 0) = 36.341781 (df = 1) P < 0.0001
I^2 (inconsistency) = 76.1% (95% CI = 58% to 84.3%)

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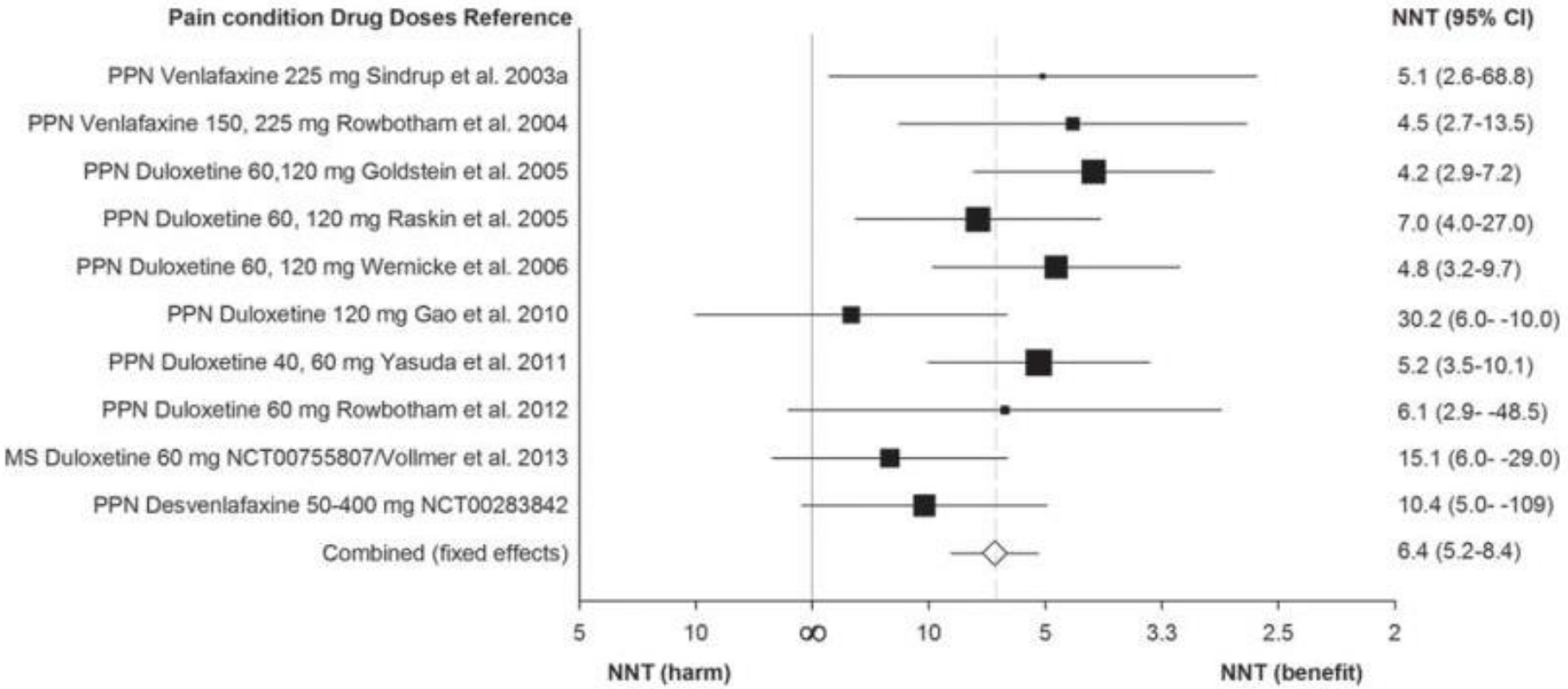
b

SNRIs NNT meta-analysis forest plot (fixed effects)



Risk difference:
Fixed effects (Mantel-Haenszel, Greenland-Robins)
Pooled risk difference = 0.156581 (95% CI = 0.119299 to 0.193863) Chi² (test risk difference differs from 0) = 67.76144 (df = 1) P < 0.0001
Random effects (DerSimonian-Laird)
Pooled risk difference = 0.155214 (95% CI = 0.110025 to 0.200403) Chi² (test risk difference differs from 0) = 45.319469 (df = 1) P < 0.0001
I^2 (inconsistency) = 30.5% (95% CI = 0% to 66%)

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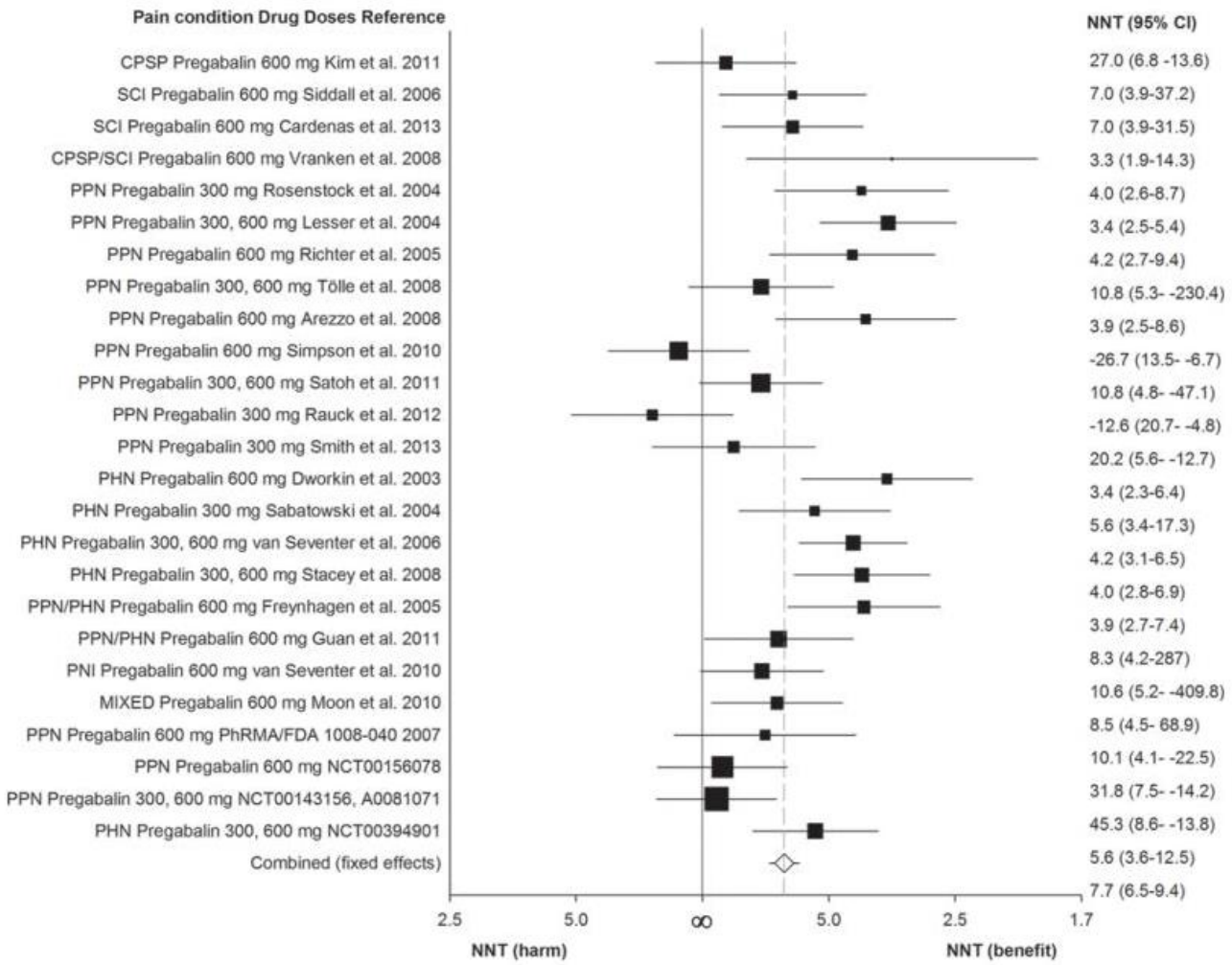
c

Pregabalin NNT meta-analysis forest plot (fixed effects)



Risk difference:
Fixed effects (Mantel-Haenszel, Greenland-Robins)
Pooled risk difference = 0.129648 (95% CI = 0.106474 to 0.152822) Chi^2 (test risk difference differs from 0) = 120.232589 (df = 1) P < 0.0001
Random effects (DerSimonian-Laird)
Pooled risk difference = 0.141856 (95% CI = 0.100874 to 0.182837) Chi^2 (test risk difference differs from 0) = 46.026479 (df = 1) P < 0.0001
I^2 (inconsistency) = 68.4% (95% CI = 49.4% to 78.2%)

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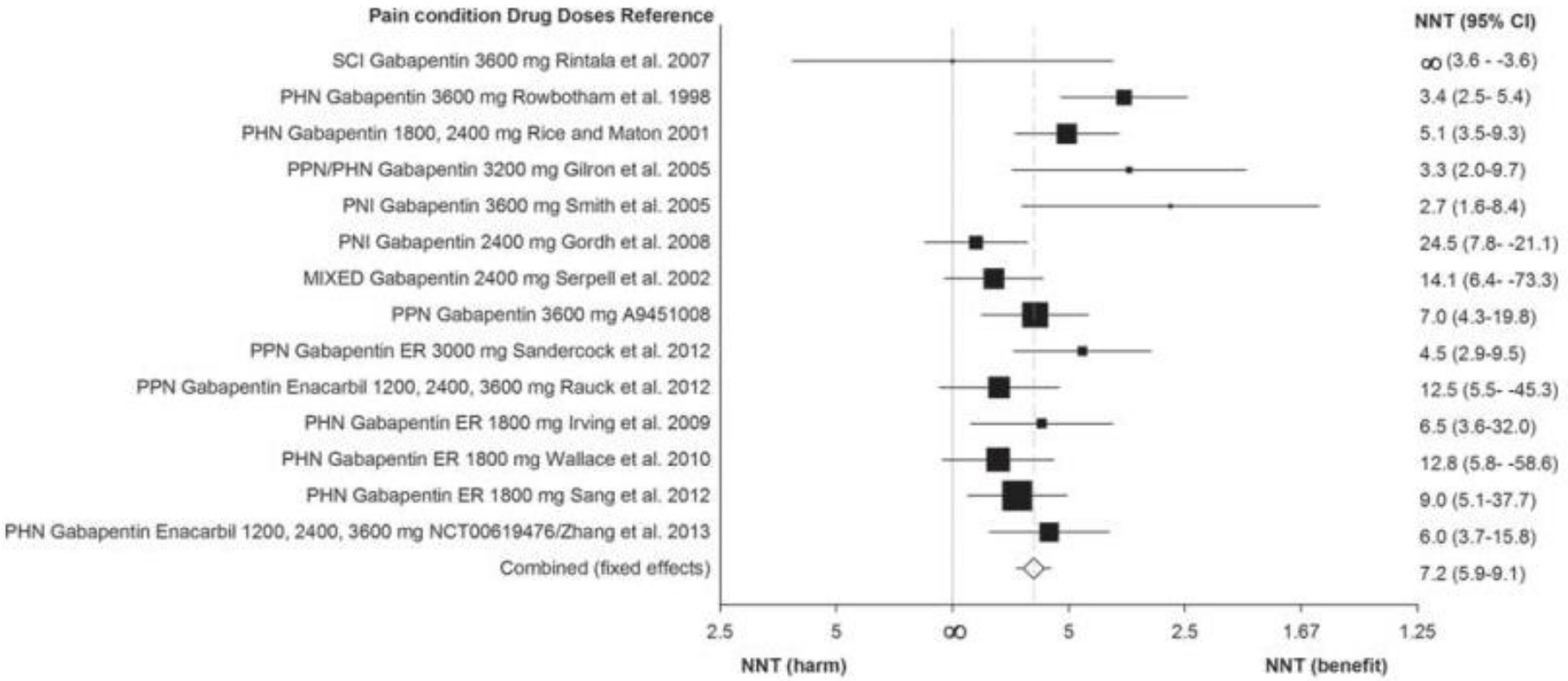
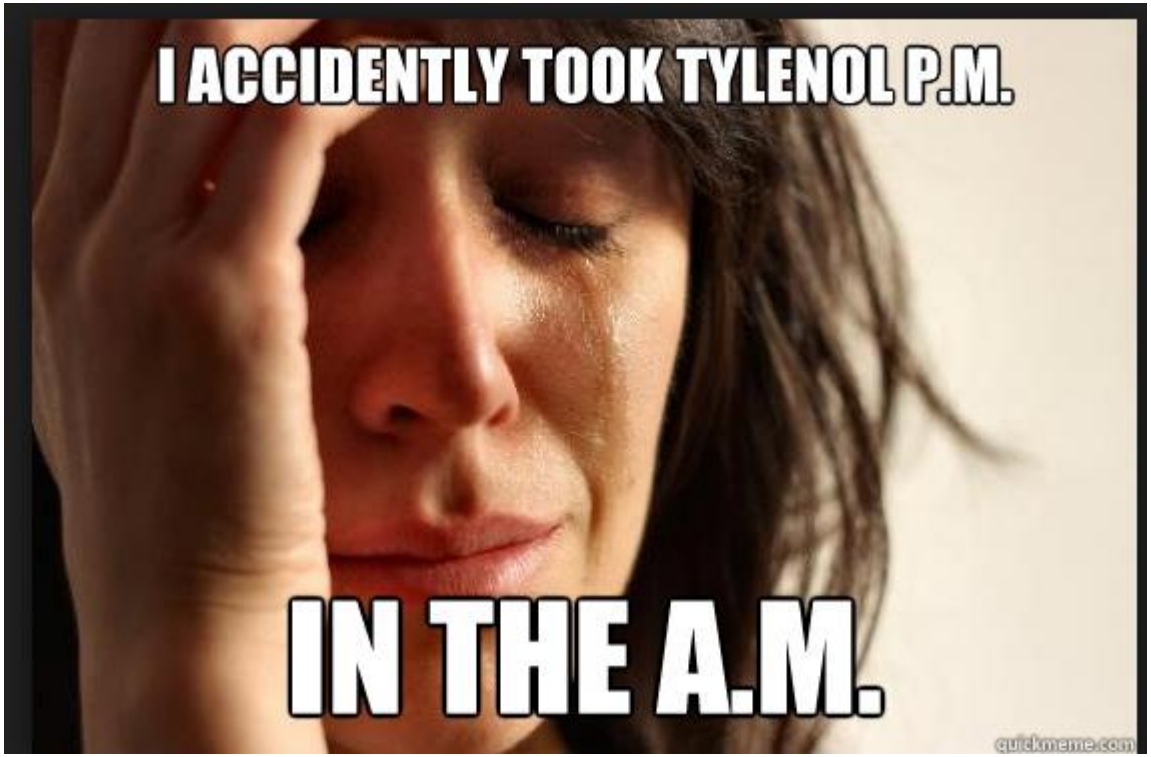
d

Gabapentin/ER/enacarbil NNT meta-analysis forest plot (fixed effects)



Risk difference:
Fixed effects (Mantel-Haenszel, Greenland-Robins)
Pooled risk difference = 0.139628 (95% CI = 0.110342 to 0.168915) Chi^2 (test risk difference differs from 0) = 87.317048 (df = 1) P < 0.0001
Random effects (DerSimonian-Laird)
Pooled risk difference = 0.146874 (95% CI = 0.102041 to 0.191707) Chi^2 (test risk difference differs from 0) = 41.228245 (df = 1) P < 0.0001
I^2 (inconsistency) = 55.5% (95% CI = 2.1% to 74.2%)

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) and Acetaminophen/Paracetamol



JAMA Clinical Evidence Synopsis

June 13, 2017

NSAIDs for Chronic Low Back Pain

Wendy T. M. Enthoven, MD, PhD[1]; Pepijn D. Roelofs, PhD[2]; Bart W. Koes, PhD[1]

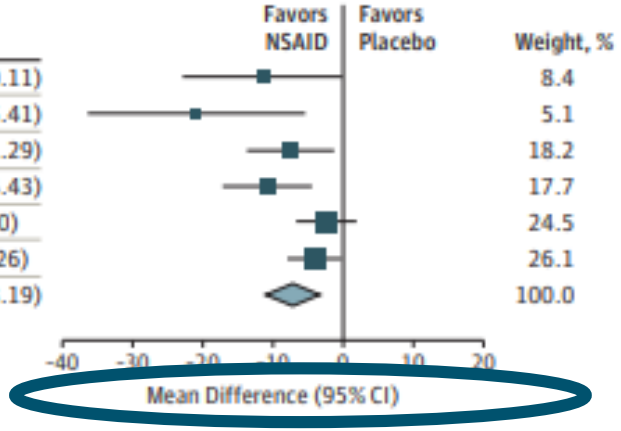
≫ Author Affiliations | Article Information

JAMA. 2017;317(22):2327-2328. doi:10.1001/jama.2017.4571

Figure. Associations of Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) With Pain and Disability for Chronic Low Back Pain vs Placebo

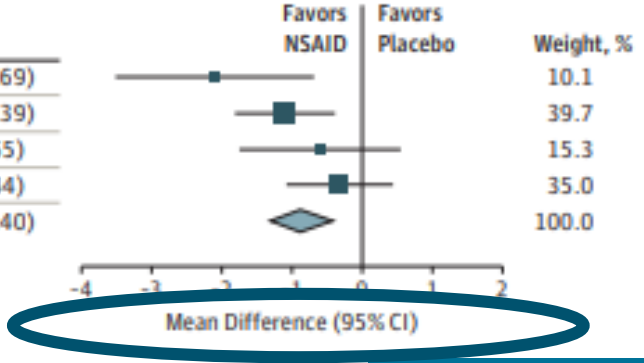
A Mean change in pain intensity from baseline on 100-mm visual analog scale[a]

Source	NSAID Total No. of Participants	NSAID Mean (SD)	Placebo Total No. of Participants	Placebo Mean (SD)	Mean Difference (95% CI)[b]	Weight, %
Allegrini, 2009	60	-28 (31.7)	59	-16.5 (31.7)	-11.50 (-22.89 to -0.11)	8.4
Berry, 1982	37	-11.5 (34)	37	9.4 (34)	-20.90 (-36.39 to -5.41)	5.1
Birbara, 2003	107	-7.5 (23.3)	109	0 (23.3)	-7.50 (-13.71 to -1.29)	18.2
Coats, 2004	148	-41.9 (27.7)	143	-31.1 (27.7)	-10.80 (-17.17 to -4.43)	17.7
Katz, 2011	88	-2.4 (11.6)	41	0 (11.6)	-2.40 (-6.70 to 1.90)	24.5
Kivitz, 2013	295	-4.1 (22.3)	230	0 (22.3)	-4.10 (-7.94 to -0.26)	26.1
Total	735		619		-6.97 (-10.74 to -3.19)	100.0



B Mean change in disability from baseline on 24-item Rowland-Morris Disability Questionnaire[c]

Source	NSAID Total No. of Participants	NSAID Mean (SD)	Placebo Total No. of Participants	Placebo Mean (SD)	Mean Difference (95% CI)[d]	Weight, %
Birbara, 2003	107	-2.1 (5.3)	109	0 (5.3)	-2.10 (-3.51 to -0.69)	10.1
Coats, 2004	148	-1.1 (3.1)	143	0 (3.1)	-1.10 (-1.81 to -0.39)	39.7
Katz, 2011	88	-0.6 (3.1)	41	0 (3.1)	-0.60 (-1.75 to 0.55)	15.3
Kivitz, 2013	295	-0.32 (4.4)	230	0 (4.4)	-0.32 (-1.08 to 0.44)	35.0
Total	638		523		-0.85 (-1.30 to -0.40)	100.0



Cochrane Database of Systematic Reviews

Acetaminophen for osteoarthritis

Review | Intervention

Tanveer Towheed, Lara Maxwell, Maria Judd, Michelle Catton, Marc C Hochberg, George A Wells

First published: 25 January 2006

Editorial Group: Cochrane Musculoskeletal Group

Table 1. Number needed to benefit (Group2) Acetaminophen vs Placebo (dichotomous; 1 study

Outcome	Plac.: % Improvement	Acet.: % Improvement	RR of Impr. w/ Acet	Abs. Risk Reduction%	NNT (95% CI) w/ Ac
Rest Pain	2/22 (4%)	16/22 (72%)	8.00 (2.08, 30.73)	64% (41, 86)	4 (2,24)
Pain on Motion	4/22 (9%)	15/22 (66%)	3.75 (1.48, 9.52)	50% (25, 75)	5 (2,24)
Physician Global Assessment	1/21 (5%)	20/21 (95%)	20.00 (2.95, 135.76)	90% (78, 103)	2 (2,11)
Patient Global	1/19 (5%)	18/19 (95%)	18 (2.66, 121.26)	89% (75, 104)	2 (2,13)

Table 2. Number Needed to Harm (Group 2) Acetaminophen (Acet.) vs Placebo (Plac.) (one st

Outcome	% w/ Plac.	% w/ Acet.	Acet: RR Outcm (95	AR Increase (95% CI)	NNH (95% CI)
Adverse Events (all clinically insignificant and did not require discontinuation of drug)	318/1239 26%	290/1146 25%	1.02 (0.89, 1.17)	1% (3,4)	Harm not estabished

Table 3. Number needed to harm - GI events Acetaminophen vs NSAIDs

Intervention	% w NSAID	% w Acetaminophen	RR (95%CI)	ARD(95%CI)	NNH (95% CI)
Traditional NSAID	91/484 (19%)	51/407(13%)	1.47 (1.08,2.00)	6%(1%, 11%)	12 (6,66)
Coxib NSAIDs	303/2320 (13%)	118/994(12%)	0.98(0.80, 1.20)	0%(-1%, 4%)	NA
Combined traditional & Coxib	394/2804(14%)	169/1401 (12%)	1.11 (0.94, 1.31)	1%(-1%,3%)	NA

Cochrane Database of Systematic Reviews

Paracetamol for low back pain

Review | Intervention

Bruno T Saragiotto ✉, Gustavo C Machado, Manuela L Ferreira, Marina B Pinheiro, Christina Abdel Shaheed, Christopher G Maher

First published: 6 June 2016

Main results

Our searches retrieved 4449 records, of which three trials were included in the review (n = 1825 participants), and two trials were included in the meta-analysis. For acute LBP, there is high-quality evidence for no difference between paracetamol (4 g per day) and placebo at 1 week (immediate term), 2 weeks, 4 weeks, and 12 weeks (short term) for the primary outcomes. There is high-quality evidence that paracetamol has no effect on quality of life, function, global impression of recovery, and sleep quality for all included time periods. There were also no significant differences between paracetamol and placebo for adverse events, patient adherence, or use of rescue medication. For chronic LBP, there is very low-quality evidence (based on a trial that has been retracted) for no effect of paracetamol (1 g single intravenous dose) on immediate pain reduction. Finally, no trials were identified evaluating patients with subacute LBP.

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JAMA | Original Investigation

Effect of Opioid vs Nonopioid Medications on Pain-Related Function in Patients With Chronic Back Pain or Hip or Knee Osteoarthritis Pain

The SPACE Randomized Clinical Trial

Erin E. Krebs, MD, MPH; Amy Gravely, MA; Sean Nugent, BA; Agnes C. Jensen, MPH; Beth DeRonne, PharmD; Elizabeth S. Goldsmith, MD, MS; Kurt Kroenke, MD; Matthew J. Bair; Siamak Noorbaloochi, PhD

JAMA March 6, 2018 Volume 319, Number 9

CONCLUSIONS AND RELEVANCE Treatment with opioids was not superior to treatment with nonopioid medications for improving pain-related function over 12 months. Results do not support initiation of opioid therapy for moderate to severe chronic back pain or hip or knee osteoarthritis pain.

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Table 2. Patient-Reported Primary and Secondary Outcomes Among Patients With Chronic Back Pain or Hip or Knee Osteoarthritis Pain Randomized to Opioid vs Nonopioid Medication

Outcome	Opioid Group, Mean (SD) (n = 119)	Nonopioid Group, Mean (SD) (n = 119)	Between-Group Difference (95% CI)[a]	Overall *P* Value[b]
Pain-Related Function (Primary Outcome)				
BPI interference scale (range, 0-10; higher score = worse)[c]				
Baseline	5.4 (1.8)	5.5 (2.0)	−0.1 (−0.6 to 0.4)	.58
3 mo	3.7 (2.1)	3.7 (2.2)	0.0 (−0.6 to 0.6)	
6 mo	3.4 (2.1)	3.6 (2.4)	−0.2 (−0.8 to 0.4)	
9 mo	3.6 (2.2)	3.3 (2.4)	0.4 (−0.2 to 1.0)	
12 mo	3.4 (2.5)	3.3 (2.6)	0.1 (−0.5 to 0.7)	
Pain Intensity (Secondary Outcome)				

Table 3. Adverse Outcomes and Measures of Potential Misuse Among Patients With Chronic Back Pain or Hip or Knee Osteoarthritis Pain Randomized to Opioid vs Nonopioid Medication

Outcome	Opioid Group	Nonopioid Group	Between-Group Difference (95% CI)[a]	*P* Value
Primary Adverse Outcome				
Medication-related symptom checklist (0-19; higher score = worse), mean (SD)[b]				
Baseline	1.2 (1.9)	1.2 (1.9)	0.0 (−0.5 to 0.5)	.03[c]
3 mo	2.3 (2.5)	1.3 (1.8)	1.0 (0.5 to 1.6)	
6 mo	2.1 (2.7)	1.3 (2.3)	0.7 (0.1 to 1.4)	
9 mo	1.9 (2.8)	0.9 (1.9)	1.0 (0.4 to 1.6)	
12 mo	1.8 (2.6)	0.9 (1.8)	0.9 (0.3 to 1.5)	

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Topical Analgesics

Cochrane Database of Systematic Reviews

Topical analgesics for acute and chronic pain in adults - an overview of Cochrane Reviews

Review | Overview

Sheena Derry, Philip J Wiffen, Eija A Kalso, Rae F Bell, Dominic Aldington, Tudor Phillips, Helen Gaskell, R Andrew Moore

First published: 12 May 2017

Summary table B: Results potentially subject to publication bias

			Percent with outcome					
Reference	Topical treatment	Studies/ partici-pants	Active	Placebo	RR 95% CI	NNT 95% CI	Susceptibil-ity to publi-cation bias	GRADE (re-view-reported)
Acute pain conditions								
Derry 2015	Ibuprofen - gel	2/241	42	16	2.7 (1.7 to 4. 2)	3.9 (2.7 to 6. 7)	377	Moderate quality
Derry 2015	Ibuprofen - cream	3/195	71	56	1.3 (1.03 to 1.6)	6.4 (3.4 to 41)	110	No spe-cific GRADE given
Pattanittum 2013	Diclofenac (unspec-ified formu-lation)	3/153	Continuous data used		Not reported	7 (3 to 21)	66	Very low quality
Derry 2015	In-domethacin	3/341	58	46	1.3 (1.03 to 1.6)	8.3 (4.4 to 65)	73	No spe-cific GRADE given
Derry 2015	Diclofenac - other gel than Emugel	1/232	94	82	1.2 (1.1 to 1. 3)	8.0 (4.8 to 24)	58	No spe-cific GRADE given
Derry 2015	Ketoprofen - plaster	2/335	73	60	1.2 (1.04 to 1.4)	8.2 (4.5 to 47)	29	No spe-cific GRADE given
Chronic pain conditions								
Derry 2014b	Salicylate rubefacient	6/455	45	28	1.6 (1.2 to 2. 0)	6.2 (4.0 to 13)	279	Very low quality

Summary table C: Results not subject to publication bias

			Percent with outcome					
Reference	Topical treatment	Studies/ partici-pants	Active	Placebo	RR 95% CI	NNT 95% CI	Susceptibil-ity to publi-cation bias	GRADE (review-reported)
Acute pain conditions								
Derry 2015	Diclofenac - Flector plas-ter	4/1030	63	41	1.5 (1.4 to 1. 7)	4.7 (3.7 to 6. 5)	5029	No spe-cific GRADE given
Derry 2015	Diclofenac - Emulgel	2/314	78	20	3.8 (2.7 to 5. 5)	1.8 (1.5 to 2. 1)	1430	High quality
Derry 2015	Ketoprofen - gel	5/348	72	33	2.2 (1.7 to 2. 8)	2.5 (2.0 to 3. 4)	1044	Moderate quality
Derry 2015	Diclofenac - other plaster	3/474	88	57	1.6 (1.4 to 1. 8)	3.2 (2.6 to 4. 2)	1007	No spe-cific GRADE given
Derry 2015	Piroxicam gel	3/522	70	47	1.5 (1.3 to 1. 7)	4.4 (3.2 to 6. 9)	664	No spe-cific GRADE given
Chronic pain conditions								
Derry 2016	Ketoprofen gel	4/2573	63	48	1.1 (1.01 to 1.2)	6.9 (5.4 to 9. 3)	1156	Moderate quality
Derry 2016	Di-clofenac (< 6 weeks' dura-tion)	5/732	43	23	1.9 (1.5 to 2. 3)	5.0 (3.7 to 7. 4)	732	Moderate quality
Derry 2016	Diclofenac - various for-mulations (> 6 weeks' du-ration)	4/2343	60	50	1.2 (1.1 to 1. 3)	9.8 (7.1 to 16)	48	Moderate quality
Derry 2017	Capsaicin (high-con-centration)	2/571	33	24	1.3 (1.0 to 1. 7)	11 (6.1 to 62)	Result above threshold of 10	Moderate quality


Normal
Lucky
Superlucky

Cannabis-based medicines for chronic neuropathic pain in adults (Review)

Mücke M, Phillips T, Radbruch L, Petzke F, Häuser W

Main results

We included 16 studies with 1750 participants. The studies were 2 to 26 weeks long and compared an oromucosal spray with a plant-derived combination of tetrahydrocannabinol (THC) and cannabidiol (CBD) (10 studies), a synthetic cannabinoid mimicking THC (nabilone) (two studies), inhaled herbal cannabis (two studies) and plant-derived THC (dronabinol) (two studies) against placebo (15 studies) and an analgesic (dihydrocodeine) (one study). We used the Cochrane 'Risk of bias' tool to assess study quality. We defined studies with zero to two unclear or high risks of bias judgements to be high-quality studies, with three to five unclear or high risks of bias to be moderate-quality studies, and with six to eight unclear or high risks of bias to be low-quality studies. Study quality was low in two studies, moderate in 12 studies and high in two studies. Nine studies were at high risk of bias for study size. We rated the quality of the evidence according to GRADE as very low to moderate.

Primary outcomes

Cannabis-based medicines may increase the number of people achieving 50% or greater pain relief compared with placebo (21% versus 17%; risk difference (RD) 0.05 (95% confidence interval (CI) 0.00 to 0.09); NNTB 20 (95% CI 11 to 100); 1001 participants, eight studies, low-quality evidence). We rated the evidence for improvement in Patient Global Impression of Change (PGIC) with cannabis to be of very low quality (26% versus 21%;RD 0.09 (95% CI 0.01 to 0.17); NNTB 11 (95% CI 6 to 100); 1092 participants, six studies). More participants withdrew from the studies due to adverse events with cannabis-based medicines (10% of participants) than with placebo (5% of participants) (RD 0.04 (95% CI 0.02 to 0.07); NNTH 25 (95% CI 16 to 50); 1848 participants, 13 studies, moderate-quality evidence). We did not have enough evidence to determine if cannabis-based medicines increase the frequency of serious adverse events compared with placebo (RD 0.01 (95% CI -0.01 to 0.03); 1876 participants, 13 studies, low-quality evidence).

Subgroup analyses

We are uncertain whether herbal cannabis reduces mean pain intensity (very low-quality evidence). Herbal cannabis and placebo did not differ in tolerability (very low-quality evidence).

Authors' conclusions

The potential benefits of cannabis-based medicine (herbal cannabis, plant-derived or synthetic THC, THC/CBD oromucosal spray) in chronic neuropathic pain might be outweighed by their potential harms. The quality of evidence for pain relief outcomes reflects the exclusion of participants with a history of substance abuse and other significant comorbidities from the studies, together with their small sample sizes.

Muscle Relaxants

ELSEVIER

Journal of Pain and Symptom Management

Volume 28, Issue 2, August 2004, Pages 140-175

Review Article

Comparative efficacy and safety of skeletal muscle relaxants for spasticity and musculoskeletal conditions: a systematic review ☆

Roger Chou MD, Kim Peterson MS, Mark Helfand MD, MPH

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pattern to suggest that one included skeletal muscle relaxant was any better than the

Meta-analysis was not possible because of marked heterogeneity in study designs, interventions used, and outcomes measured.

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EJP European Journal of Pain

EFIC

Systematic Review | Full Access

Efficacy and tolerability of muscle relaxants for low back pain: Systematic review and meta-analysis

C. Abdel Shaheed, C.G. Maher, K.A. Williams, A.J. McLachlan

First published: 22 June 2016 | https://doi.org/10.1002/ejp.907 | Cited by:3

Analysis was performed using comparison of mean data, but…

5. Conclusion

Muscle relaxant drugs do not provide clinically significant pain relief in the short term for people with acute LBP. There was a paucity of evidence around the use of benzodiazepines for LBP and effects of the three classes of medicines on disability. The present evidence does not support the recommendation for prolonged use of any of these drugs in the management of people with LBP.

What About Opioids?

Cochrane Database of Systematic Reviews

Opioids for neuropathic pain

Review | Intervention

Ewan D McNicol, Ayelet Midbari, Elon Eisenberg

First published: 29 August 2013

Editorial Group: Cochrane Pain, Palliative and Supportive Care Group

Editorial group: Cochrane Pain, Palliative and Supportive Care Group.
Publication status and date: Stable (no update expected for reasons given in 'What's new'), published in Issue 4, 2017.

Fourteen studies (845 participants, average 60 participants per study) were of intermediate duration lasting 12 weeks or less; most studies lasted less than six weeks. Most studies used imputation methods for participant withdrawal known to be associated with considerable bias; none used a method known not to be associated with bias. The evidence, therefore, derives from studies predominantly with features likely to overestimate treatment effects, i.e. small size, short duration, and potentially inadequate handling of dropouts. All demonstrated opioid efficacy for spontaneous neuropathic pain. Meta-analysis demonstrated at least 33% pain relief in 57% of participants receiving an opioid versus 34% of those receiving placebo. The overall point estimate of risk difference was 0.25 (95% confidence interval (CI) 0.13 to 0.37, P < 0.0001), translating to a number needed to treat for an additional beneficial outcome (NNTB) of 4.0 (95% CI 2.7 to 7.7). When the number of participants achieving at least 50% pain relief was analyzed, the overall point estimate of risk difference between opioids (47%) and placebo (30%) was 0.17 (95% CI 0.02 to 0.33, P = 0.03), translating to an NNTB of 5.9 (3.0 to 50.0). In the updated review, opioids did not demonstrate improvement in many aspects of emotional or physical functioning, as measured by various validated questionnaires. Constipation was the most common adverse event (34% opioid versus 9% placebo: number needed to treat for an additional harmful outcome (NNTH) 4.0; 95% CI 3.0 to 5.6), followed by drowsiness (29% opioid versus 14% placebo: NNTH 7.1; 95% CI 4.0 to 33.3), nausea (27% opioid versus 9% placebo: NNTH 6.3; 95% CI 4.0 to 12.5), dizziness (22% opioid versus 8% placebo: NNTH 7.1; 95% CI 5.6 to 10.0), and vomiting (12% opioid versus 4% placebo: NNTH 12.5; 95% CI 6.7 to 100.0). More participants withdrew from opioid treatment due to adverse events (13%) than from placebo (4%) (NNTH 12.5; 95% CI 8.3 to 25.0). Conversely, more participants receiving placebo withdrew due to lack of efficacy (12%) versus (2%) receiving opioids (NNTH -11.1; 95% CI -20.0 to -8.3).

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Cochrane Database of Systematic Reviews

Opioids compared to placebo or other treatments for chronic low-back pain

Review | Intervention

Luis Enrique Chaparro, Andrea D Furlan, Amol Deshpande, Angela Mailis-Gagnon, Steven Atlas, Dennis C Turk

First published: 27 August 2013

We included 15 trials (5540 participants). Tramadol was examined in five trials (1378 participants); it was found to be better than placebo for pain (SMD -0.55, 95% CI -0.66 to -0.44; *low quality evidence*) and function (SMD -0.18, 95% CI -0.29 to -0.07; *moderate quality evidence*). Transdermal buprenorphine (two trials, 653 participants) may make little difference for pain (SMD -2.47, 95%CI -2.69 to -2.25; *very low quality evidence*), but no difference compared to placebo for function (SMD -0.14, 95%CI -0.53 to 0.25; *very low quality evidence*). Strong opioids (morphine, hydromorphone, oxycodone, oxymorphone, and tapentadol), examined in six trials (1887 participants), were better than placebo for pain (SMD -0.43, 95%CI -0.52 to -0.33; *moderate quality evidence*) and function (SMD -0.26, 95% CI -0.37 to -0.15; *moderate quality evidence*). One trial (1583 participants) demonstrated that tramadol may make little difference compared to celecoxib (RR 0.82, 95% CI 0.76 to 0.90; *very low quality evidence*) for pain relief. Two trials (272 participants) found no difference between opioids and antidepressants for either pain (SMD 0.21, 95% CI -0.03 to 0.45; *very low quality evidence*), or function (SMD -0.11, 95% -0.63 to 0.42; *very low quality evidence*). The included trials in this review had high drop-out rates, were of short duration, and had limited interpretability of functional improvement. They did not report any serious adverse effects, risks (addiction or overdose), or complications (sleep apnea, opioid-induced hyperalgesia, hypogonadism). In general, the effect sizes were medium for pain and small for function.

There is some evidence (*very low to moderate quality*) for short-term efficacy (for both pain and function) of opioids to treat CLBP compared to placebo. The very few trials that compared opioids to non-steroidal anti-inflammatory drugs (NSAIDs) or antidepressants did not show any differences regarding pain and function. The initiation of a trial of opioids for long-term management should be done with extreme caution, especially after a comprehensive assessment of potential risks. There are no placebo-RCTs supporting the effectiveness and safety of long-term opioid therapy for treatment of CLBP.

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Cochrane Database of Systematic Reviews

High-dose opioids for chronic non-cancer pain: an overview of Cochrane Reviews

Review | Overview

Charl Els, Tanya D Jackson, Reidar Hagtvedt, Diane Kunyk, Barend Sonnenberg, Vernon G Lappi, Sebastian Straube

First published: 30 October 2017

Methods

We identified Cochrane Reviews and Overviews through a search of the Cochrane Database of Systematic Reviews (The Cochrane Library). The date of the last search was 18 April 2017. Two review authors independently assessed the search results. We planned to analyse data on any opioid agent used at high dose for two weeks or more for the treatment of chronic non-cancer pain in adults.

Main results

We did not identify any reviews or overviews meeting the inclusion criteria. The excluded reviews largely reflected low doses or titrated doses where all doses were analysed as a single group; no data for high dose only could be extracted.

Authors' conclusions

There is a critical lack of high-quality evidence regarding how well high-dose opioids work for the management of chronic non-cancer pain in adults, and regarding the presence and severity of adverse events. No evidence-based argument can be made on the use of high-dose opioids, i.e. 200 mg morphine equivalent or more daily, in clinical practice. Trials typically used doses below our cut-off; we need to know the efficacy and harm of higher doses, which are often used in clinical practice.

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Cochrane Database of Systematic Reviews

Adverse events associated with medium- and long-term use of opioids for chronic non-cancer pain: an overview of Cochrane Reviews

Review | Overview

Charl Els, Tanya D Jackson, Diane Kunyk, Vernon G Lappi, Barend Sonnenberg, Reidar Hagtvedt, Sangita Sharma, Fariba Kolahdooz, Sebastian Straube

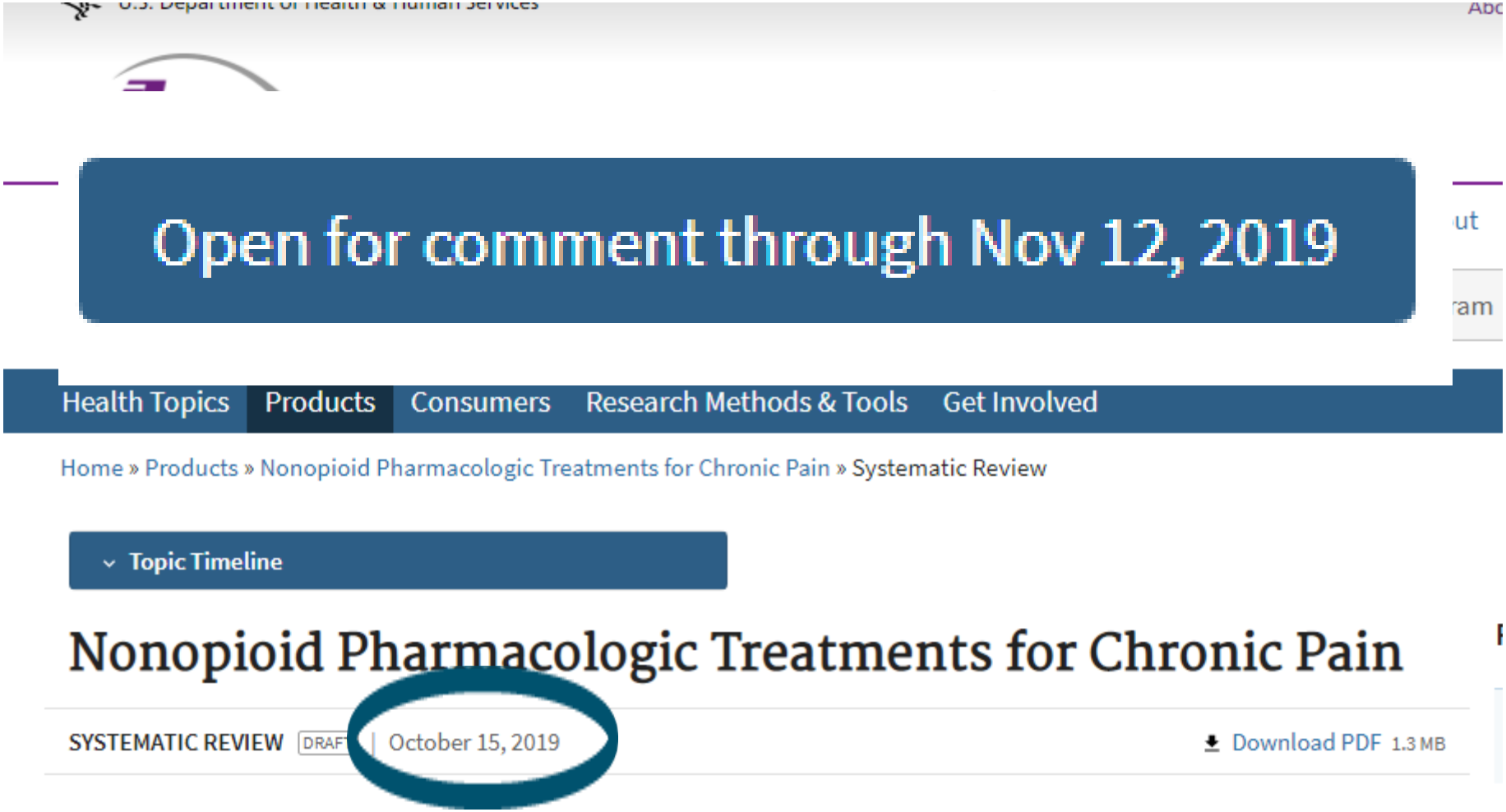
First published: 30 October 2017

We calculated the equivalent milligrams of morphine per 24 hours for each opioid studied (buprenorphine, codeine, dextropropoxyphene, dihydrocodeine, fentanyl, hydromorphone, levorphanol, methadone, morphine, oxycodone, oxymorphone, tapentadol, tilidine, and tramadol). In the 14 Cochrane Reviews providing unique quantitative data, there were 61 studies with a total of 18,679 randomised participants; 12 of these studies had a cross-over design with two to four arms and a total of 796 participants. Based on the 14 selected Cochrane Reviews, there was a significantly increased risk of experiencing any adverse event with opioids compared to placebo (risk ratio (RR) 1.42, 95% confidence interval (CI) 1.22 to 1.66) as well as with opioids compared to a non-opioid active pharmacological comparator, with a similar risk ratio (RR 1.21, 95% CI 1.10 to 1.33). There was also a significantly increased risk of experiencing a serious adverse event with opioids compared to placebo (RR 2.75, 95% CI 2.06 to 3.67). Furthermore, we found significantly increased risk ratios with opioids compared to placebo for a number of specific adverse events: constipation, dizziness, drowsiness, fatigue, hot flushes, increased sweating, nausea, pruritus, and vomiting.

There was no data on any of the following prespecified adverse events of interest in any of the included reviews in this overview of Cochrane Reviews: addiction, cognitive dysfunction, depressive symptoms or mood disturbances, hypogonadism or other endocrine dysfunction, respiratory depression, sexual dysfunction, and sleep apnoea or sleep-disordered breathing. We found no data for adverse events analysed by sex or ethnicity.

Authors' conclusions

A number of adverse events, including serious adverse events, are associated with the medium- and long-term use of opioids for CNCP. The absolute event rate for any adverse event with opioids in trials using a placebo as comparison was 78%, with an absolute event rate of 7.5% for any serious adverse event. Based on the adverse events identified, clinically relevant benefit would need to be clearly demonstrated before long-term use could be considered in people with CNCP in clinical practice. A number of adverse events that we would have expected to occur with opioid use were not reported in the included Cochrane Reviews. Going forward, we recommend more rigorous identification and reporting of all adverse events in randomised controlled trials and systematic reviews on opioid therapy. The absence of data for many adverse events represents a serious limitation of the evidence on opioids. We also recommend extending study follow-up, as a latency of onset may exist for some adverse events.



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Key Messages

- In the short-term,
  - Anticonvulsants pregabalin, gabapentin, and oxcarbazepine show small improvements in pain and function in patients with diabetic peripheral neuropathy/post-herpetic neuralgia and fibromyalgia.
  - SNRI antidepressants duloxetine and/or milnacipran show small to moderate improvements in pain, function and quality of life in patients with diabetic peripheral neuropathy/post-herpetic neuralgia and fibromyalgia. Patients with low back pain had small improvements in pain and no improvement in function.
  - NSAIDs show small improvements in pain and function in patients with osteoarthritis and inflammatory arthritis. Acetaminophen did not result in improvements in pain and function in patients with osteoarthritis.
- In the short- and intermediate-term, limited evidence found memantine to moderately improve pain, function and quality of life in patients with fibromyalgia.
- For all conditions, evidence on long-term treatment effectiveness, comparative effectiveness, and quality of life is limited
- Small to moderate, dose-dependent, increases in withdrawal due to adverse events was found with TCAs, SNRIs duloxetine and milnacipran, pregabalin and gabapentin, and NSAIDs. Large increases seen with oxcarbazepine. NSAIDs have increased risk of serious GI and CV adverse events.

Summary

Twitter: @Sympathy4TheDr
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Continuous data analysis violates statistical assumptions in almost all pain research and so categorical data should be used to analyze and interpret pain research studies

The most valuable statistical information in an investigational trial for pain studies is the ‘number needed to treat’

Summary

Many non-opioid pharmacologic treatments have acceptable NNTs that make them a good tool to use in clinic, but most are not studied past a 6 week endpoint to establish long-term efficacy or **number needed to harm**

Last thought: you can calculate the number needed to treat yourself, even if the authors of the manuscript didn't… if you have the raw data.