Ranking of Evidence in Network Meta-Analysis Results in Misleading Conclusion: A Case Study in Opioid Therapy for Chronic Non-Cancer Pain.

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Background

Opioids are often prescribed for chronic non-cancer pain (CNCP). Thus far, systematic reviews have pooled different opioids assuming a common effect; however, the comparative effectiveness of individual opioids, and of long-acting (LA) versus short-acting (SA) opioids, on pain relief is uncertain.

Objective

We conducted a network meta-analysis (NMA) to inform whether pooling opioids is a source of heterogeneity or not.

Methods

Study Eligibility Criteria

Population: CNCP; **Design**: Randomized controlled trials

Intervention: oral or transdermal opioid

Control: Alternative opioids, placebo

Duration of follow-up: ≤4 weeks

Outcome : Pain intensity.

Data source:

MEDLINE/ PubMed; EMBASE; CINAHL; PsycInfo; and CENTRAL

Risk of bias assessment:

We assessed the following risk of bias issues in eligible trials: (1) random sequence generation, (2) allocation concealment, (3) blinding of study participants, personnel, and outcome assessors, (4) incomplete outcome data (≥ 20% missing were considered as high risk of bias).

Data synthesis:

Direct comparisons: we performed pairwise meta-analysis for direct comparisons using the DerSimonian–Laird random-effects model.

Indirect and mixed comparisons: we performed a frequentist NMA exploring effects on a 10 cm visual analogue scale for pain (1 cm is the minimally important difference).

Ranking effectiveness of competing opioids

Probability ranking

- We estimated ranking probabilities using the surface under the cumulative ranking curve (SUCRA), which assigns the probability for each opioid to be the best.

Minimally contextualized approach

- We used GRADE approach for assessing the certainty of evidence (dichotomized as “moderate-to-high” or “low-to-very-low” certainty of evidence).
- We categorized opioids first based on their effectiveness vs. placebo and then vs. other competing opioids, and finally according to GRADE quality of evidence ratings.
- Null value (RR=1.0) was used as threshold for contextualization

Results

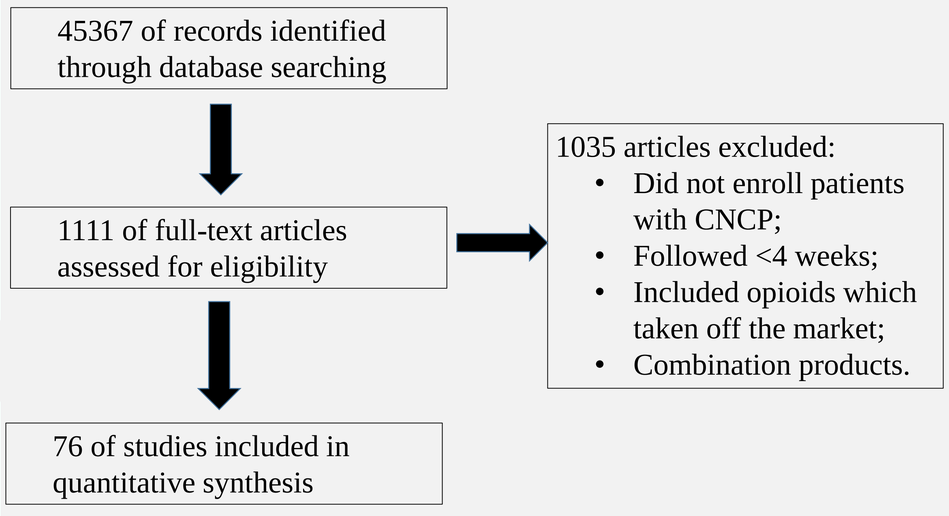

Figure 1: Study flow

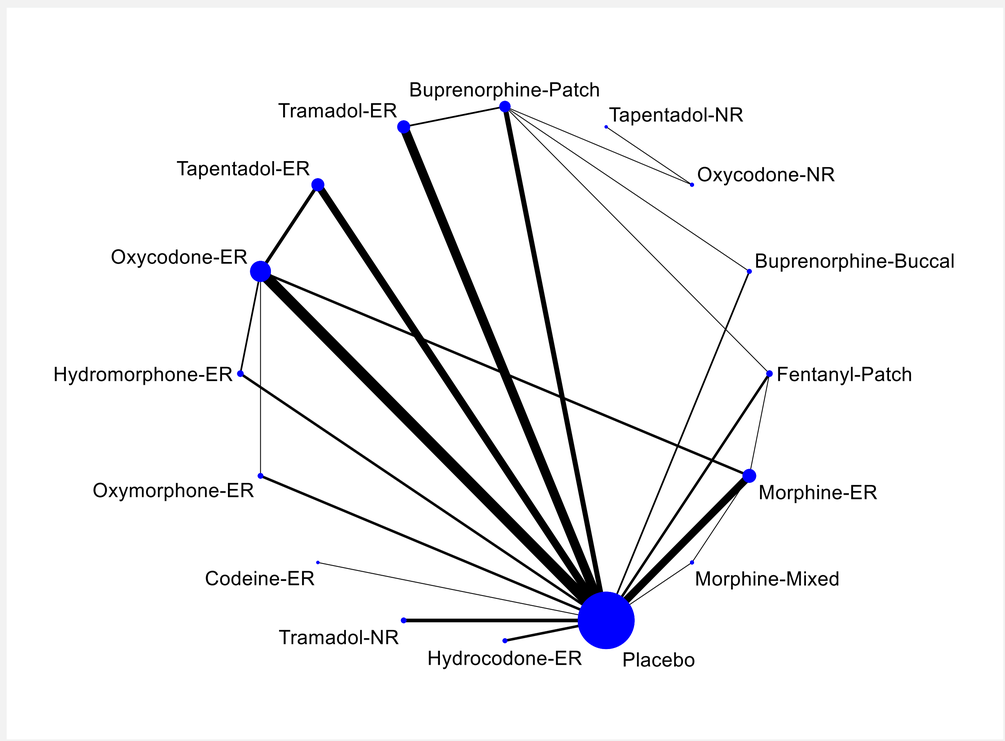

Figure 2: Network plot

Study characteristics:

- We included 76 studies with 21,752 patients that evaluated 15 individual opioids, of which 4 were SA and 11 were LA.
- Most of the included studies were 2 arms; 5 had multiple arms trials (3 4 or 5 arms).
- The median of duration of follow-up was 84 days, and only 16 (21%) of included trials have followed up their participants equal or longer than 3 months.
- An enrichment design which proceed randomization after a run-in period was conducted in 20 (26%) of included trials.

- The SUCRA values suggested codeine-extended release (ER) (94.2%) and oxymorphone-ER (88.1%) as the best opioids for pain relief. The certainty of evidence for both these drugs relative to placebo was, however, low.
- **All comparisons supported by moderate–to-high certainty evidence demonstrated that opioids were more effective than placebo, but that none were superior to others. (Table)**
- Low certainty evidence suggested a statistically significant, but clinically unimportant, advantage of SA vs. LA opioids for pain relief (weighted mean difference 0.18cm, 95% CI: 0.06, 0.29).

Table: summary of network meta-analysis results

Certainty of evidence	Classification	Intervention	Intervention vs. Placebo Mean Difference in cm (95% CI)	SUCRA (%)
Moderate to High certainty evidence	Among the most effective	Morphine-ER*	-0.87 (-1.18, -0.56)	54.8
		Buprenorphine-Buccal	-0.86 (-1.36, -0.37)	52.6
		Tapentadol-ER	-0.82 (-1.10, -0.54)	49.5
		Tramadol-ER	-0.79 (-1.05, -0.54)	46.3
		Fentanyl-PTCH	-0.78 (-1.18, -0.38)	45.1
		Buprenorphine-PTCH	-0.71 (-1.01, -0.41)	36.2
		Oxycodone-ER	-0.70 (-0.93, -0.48)	35.6
		Hydrocodone-ER	-0.53 (-0.98, -0.08)	22.7
Low to Very Low certainty evidence	May be amongst the most effective	Codeine-ER	-2.03 (-3.29, -0.77)	94.2
		Oxymorphone-ER	-1.46 (-1.95, -0.96)	88.1
	May be inferior to the most effective/superior to placebo	Tramadol-NR	-1.12 (-1.62, -0.62)	72.6
		Morphine-Mixed	-1.03 (-1.94, -0.13)	61.8
		Oxycodone-NR*	-0.99 (-1.82, -0.15)	59.2
		Hydromorphone-ER	-0.49 (-0.87, -0.10)	18.5
	Not different from placebo	Tapentadol-NR	-1.09 (-2.24, 0.06)	62.4

*Extended release=ER; Normal release=NR

Summary

- Our findings suggest that apparent differences in effectiveness between opioids, when ranked according to SUCRA values, result from the failure to consider the certainty of evidence.
- Using the minimally contextualized approach for interpreting results of the NMA highlights its advantages relative to relying solely or largely on SUCRA values.

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