Nonopioid drug combinations for cancer pain:
a systematic review

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Background

- 18 million cancer cases diagnosed worldwide each year
- **80% of cancer patients bothered by pain**
  - Tumour-related
  - Treatment-related (chemo, radiation)
  - Post-surgical (nociceptive, neuropathic)
- No gold standard management: **opioids are commonly used** despite side effects.
- **Antidepressants** and **anti-epileptics** have shown promise in non-cancer settings. **Non-opioid drug combinations:**
  - Additive or synergistic analgesic effect
  - Fewer adverse events
  - Lower dosages needed[1-4]

Purpose

- What is the safety and efficacy of non-opioid drug combinations for the management of cancer pain?

Methods

- **Systematic Review** following PRISMA guidelines
- Search Strategy: PubMED, Embase, CENTRAL, Hand search
- Double-blinded RCTs comparing non-opioid drug combination to placebo or individual component drug.
- Primary outcome: pain relief
- Secondary outcomes: safety

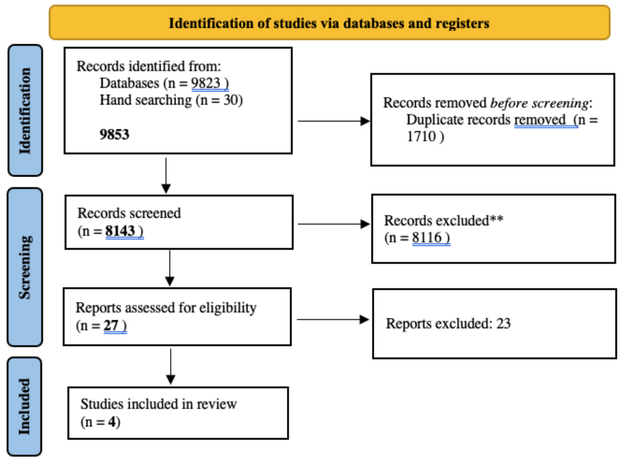

Figure 1: PRISMA diagram illustrating study flow

Nonopioid drug combinations may be effective in the management of cancer pain, although existing evidence is limited.

Author & Year	Combination	Study Population (n)	Treatment Arms	Results	Adverse Events	Proportion of patients reporting >30% pain relief or moderate pain relief
Minotti 1998	Diclofenac + Imipramine	184	1) DP - Diclofenac + placebo 2) DC - Diclofenac + codeine 3) DI - Diclofenac + imipramine	no significant differences in pain scores at Day 4 inadequate pain control was noted in all groups	GI discomfort, dry mouth, CNS disturbance - reported in all 3 groups, most commonly in **DC**	**DI** - 68.9% (42/61) **DC**- 65.6% (40/61) **DP** - 56.5% (35/62)
Ernst 2003	Mitoxantrone + Prednisone + Clodronate	227	1) D2P + clodronate 2) DP + placebo	no significant differences in pain scores were noted	**DP + clodronate** - 44% experienced severe (Grade 3 or 4) adverse events **DP + placebo** - 43% experienced severe adverse events	**DP/clodronate** - 44% **DP/placebo** - 39%
Matsuoka 2019	Pregabalin + Duloxetine	70	1) opioid + pregabalin + duloxetine (D) 2) opioid + pregabalin + placebo (P)	**D** had better pain relief (p = 0.053) more patients in **D** achieved 30 and 50% reduction in pain vs. **P**	Group D - 1 patient withdrew consent due to toxicity, 1 deteriorated; Group P - 1 patient suffered toxic events, 1 withdrew consent due to toxicity, 2 deteriorated	**D** - 44.1% (15/34) **P** - 18.2% (6/33) reported >30% pain reduction at day 10
Delanian 2019	PENTOCLO (pentoxifylline, tocopherol, clodronate)	59	1. PENTOCLO (pentoxifylline, tocopherol, clodronate) 2. triple placebo (3P)	no significant differences in SOMA score at 18 months	81% of all patients reported AEs; no significant between-group differences were reported	median pain scores at the end of the trial demonstrated no significant treatment effect

Table 2: Summary of included studies

Conclusions

- **More research is needed** to develop **safe** and **effective** analgesic combinations that will **improve patient care** in the setting of **cancer pain.**
- **Neuropathic pain** has demonstrated some response to nonopioid treatment.
- **Antidepressant** medications were associated with **fewer adverse events.**

Future Steps

- Work towards a clear classification of **the etiology of cancer pain**.
- Establish parameters for **high quality trials** to generate reasonable evidence for pain management in cancer patients.
- Educate prescribers about **opioid stewardship** and **nonopioid combination** options in managing cancer pain.

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Figure 2: QR code linking to project manuscript

Key References
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