Buprenorphine for Cancer Pain
A Systematic Review of the Literature

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Goals

Review the extent & quality of the latest literature comparing buprenorphine to full mu opioid receptor (MOR) agonists for cancer-related pain

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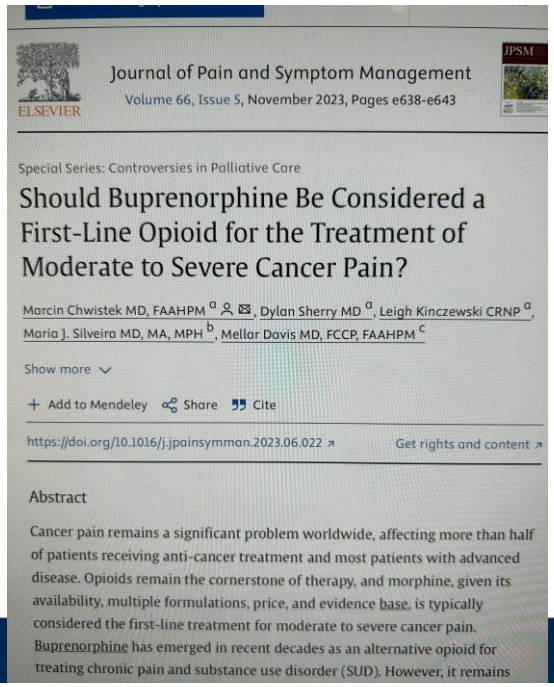
Background

- Pain affects 75% of people with advanced cancer
- Cancer pain guidelines continue to recommend WHO pain ladder and full MOR agonists as Step 3
- However, some experts in palliative care now recommend buprenorphine as first line in mod-sev cancer pain
  - Safety profile
  - Duration of action



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Special Series: Controversies in Palliative Care

Should Buprenorphine Be Considered a First-Line Opioid for the Treatment of Moderate to Severe Cancer Pain?

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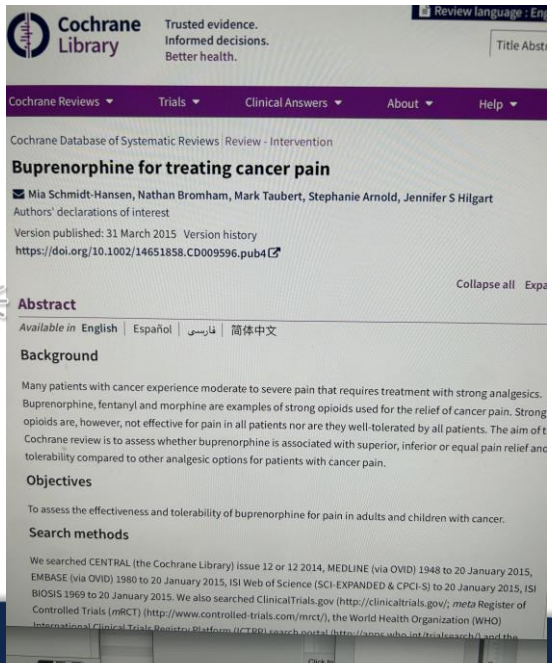
Abstract

Cancer pain remains a significant problem worldwide, affecting more than half of patients receiving anti-cancer treatment and most patients with advanced disease. Opioids remain the cornerstone of therapy, and morphine, given its availability, multiple formulations, price, and evidence base, is typically considered the first-line treatment for moderate to severe cancer pain. Buprenorphine has emerged in recent decades as an alternative opioid for treating chronic pain and substance use disorder (SUD). However, it remains

Last Review 2015

The last systematic review on buprenorphine for cancer pain was conducted by Cochrane in 2015, and included:

- 19 Studies
- 11 RCT
  - 5 RCT found Bup was better than comparison
  - 3 RCT found no difference
  - 3 RCT found Bup was *worse* than comparison



Cochrane Library
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Review language : En

Title Abst

Cochrane Reviews Trials Clinical Answers About Help

Cochrane Database of Systematic Reviews | Review - Intervention

Buprenorphine for treating cancer pain

Mia Schmidt-Hansen, Nathan Bromham, Mark Taubert, Stephanie Arnold, Jennifer S Hilgart

Authors' declarations of interest

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Abstract

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Background

Many patients with cancer experience moderate to severe pain that requires treatment with strong analgesics. Buprenorphine, fentanyl and morphine are examples of strong opioids used for the relief of cancer pain. Strong opioids are, however, not effective for pain in all patients nor are they well-tolerated by all patients. The aim of t Cochrane review is to assess whether buprenorphine is associated with superior, inferior or equal pain relief and tolerability compared to other analgesic options for patients with cancer pain.

Objectives

To assess the effectiveness and tolerability of buprenorphine for pain in adults and children with cancer.

Search methods

We searched CENTRAL (the Cochrane Library) issue 12 or 12 2014, MEDLINE (via OVID) 1948 to 20 January 2015, EMBASE (via OVID) 1980 to 20 January 2015, ISI Web of Science (SCI-EXPANDED & CPCI-S) to 20 January 2015, ISI BIOSIS 1969 to 20 January 2015. We also searched ClinicalTrials.gov (http://clinicaltrials.gov/; *meta* Register of Controlled Trials (*m*RCT) (http://www.controlled-trials.com/mrct/), the World Health Organization (WHO)

Updated Review 2024: PICOTS

POPULATION: Adult and pediatric patients with a diagnosis of cancer

INTERVENTION: Buprenorphine in any form, at any dose.

COMPARATOR: Any or none.

OUTCOMES:

1. Pain severity
2. Side effects
3. Use of breakthrough medication

TIMING: Variable, but study needs to assess pain at least once pre-treatment and once post-treatment using a validated scale.

SETTING: Any

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Databases Searched

- Cochrane
- OVID Medline
- EMBASE
- EBSCO
- Web of Science

Searches completed by April 29, 2024

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Search Terms

1. **Buprenorphine** as MeSH or title word
2. **Pain** terms as MeSH or title word
3. **Cancer** terms as MeSH or title word

1+2+3

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Review Process

Level 1: Title & Abstract Screening (2 reviewers)

- Buprenorphine as intervention
- Cancer patients as population
- Pain severity as outcome, measured twice

Level 2: Full Text Review (2 reviewers)

- Confirmed study eligibility (PICOTS)
- Excluded
  - ineligible study designs
  - no English translation

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Review Process

Level 3: Abstracted Data (2 reviewers)

- Classified type of study
- Abstracted study details, including population type/size, bup protocol, outcomes, results

Level 4: Assessed Study Risk of Bias (1 reviewer)

- Cochrane Risk of Bias Assessment for RCT
- Newcastle Ottawa Scale for Cohort & Case Control Studies
- All other study designs considered inherently high ROB

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Review Process

Data were synthesized using GRADE Criteria for each outcome (team effort)

- For each outcome of interest, the strength of the evidence was based on the quality of the body of literature that measured that outcome
- Baseline scores given based upon type of literature:
  - RCT 4 points, Observational studies 2 points, Other studies 1 point
- Final scores were adjusted for limitations and strengths

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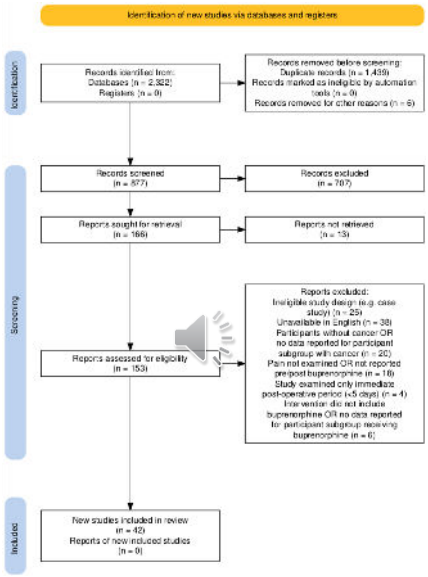
Results



Haddaway, N. R., et al (2022)., 18, e1230. *Campbell Systematic Reviews* https://doi.org/10.1002/cl2.1230

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Results

42 Studies met inclusion criteria:

- 14 RCT representing 13 unique studies
  - [Nosek 2017 & Leppert 2019] used the same population
- 5 Cohort studies
- 1 Case Control
- 22 Other (mostly pre/post uncontrolled)

The results we present today are based upon the RCTs only.

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Conclusion #1

Buprenorphine produces good pain relief for many people with moderate to severe cancer pain. (GRADE: high confidence)

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Evidence for #1

Intervention	Comparator	No. RCTs	No. patients	Timing	Result	RoB
Bup TD, SL, IM, Epi	Active	13	1149	18 h – 6 mo	Bup reduced ave pain over time by moderate to large amount (12) Bup had mixed results on average pain (1) [Ventafridda 1983]	Some concerns – High High
Bup SL	Placebo	1 [Poulain 2008]	289	4w	Bup was superior to placebo (1)	Some concerns

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Scoring for #1

Initial GRADE Score	Limitations	Strengths	Final GRADE Score	Confidence
4	-2 Serious RoB -1 Inconsistency	+2 Large effect +1 Dose response	4	High

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Conclusion #2

DESPITE CONCLUSION #1…

Up to one third of cancer patients may not respond to buprenorphine sublingual or transdermal, at rates not unlike full MOR agonists. [GRADE: Very low confidence]

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Evidence for #2

Intervention	No. of RCTs	Non-response rates for bup	Time period	RoB
Bup SL	3 [Brema 1996; Ventafridda 1983; Yajnik 1992]	0-38%	1 week to 6 mo.	Some concerns to High
Bup TD	4 [Choudry 2018; Corli 2016; Pace 2007; Pasqualucci 1987]	0-34%	4 -8 weeks	Some concerns

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Scoring for #2

Initial GRADE Score	Limitations	Strengths	Final GRADE Score	Confidence
4	-2 Serious RoB -1 Inconsistency -1 Indirectness		1	Very Low

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Conclusion #3

Buprenorphine is not inferior to full MOR agonists for cancer-related pain, and in some cases may be slightly better (GRADE: Low confidence)

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Evidence for #3

Intervention	Comparator	No. RCTs	No. patients	Result	RoB
Bup TD or SL	Morphine PO	4 [Choudry 2018; Corli 2016; Nosek 2017; Pace 2007]	697	Equivalent (3) Bup superior (1)	Some concerns - High
Bup SL	Morphine IV	2 [Jamalian 2019; Kjaer 1982]	67	Equivalent (1) Bup superior (1)	High

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Evidence for #3, continued

Intervention	Comparator	No. RCTs	No. patients	Results	RoB
Bup Epidural	Morphine epidural	1 [Pascualucci 1987]	12	Equivalent (1)	Some concerns
Bup SL	Morphine IV	2 [Jamalian 2019; Kjaer 1982]	67	Equivalent (2)	High

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Evidence for #3, continued

Intervention	Comparator	No. RCTs	No. patients	Results	RoB
Bup TD	Oxycodone PO	2 [Corli 2016; Nosek 2017]	92	Equivalent (2)	Some concerns-High
Bup TD	Fentanyl TD	3 [Corli 2016; Nosek 2017; Melilli 2014]	111	Equivalent (3)	Some concerns-High

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Evidence for #3, continued

Intervention	Comparator	Number of RCTs	Number of patients	Result	RoB
Bup PO	Tramadol PO	1 [Brema 1996]	131	Equivalence (1)	High

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Scoring for #3

Initial GRADE Score	Limitations	Strengths	Final GRADE Score	Confidence
4	-2 Serious RoB -1 Inconsistency	+1 Dose response	2	Low

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Conclusion #4

Buprenorphine may have *fewer* side effects than Morphine in cancer patients. (GRADE: Very low confidence)

Buprenorphine may have *similar* side effects to Oxycodone and Fentanyl in cancer patients. (GRADE: Very low confidence)

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Evidence for #4

Intervention	Comparator	No. RCTs	No. patients	Results		RoB
Bup	Morphine	7 [Choudry 2018; Corli 2016; Jamalian 2019; Kjaer 1982; Nosek 2017; Pace 2007; Pascualucci 1987]	776	AMS Morphine worse (1) GI Equivalence (1) Morphine worse (3) Bup worse (2) Dyspnea Morphine worse (1) Bup worse (1)	Pruritus Morphine worse (1) U retention Morphine worse (1) Lethargy Bup worse (1) Dizziness Bup worse (1)	Some concerns-High

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Evidence for #4

Intervention	Comparator	No. RCTs	No. patients	Results		RoB
Bup	Oxycodone	2 [Corli 2016; Nosek 2017]	582	Drowsiness Equivalent (2) Confusion/AMS Equivalent (2) Nausea/ Vomiting Equivalent (2)	Constipation Equivalent (2) Dyspnea Equivalent (1) Buprenorphine worse (1) Fatigue Equivalent (1)	Some concerns- High

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Evidence for #4

Intervention	Comparator	No. RCTs	No. patients	Result		RoB
Bup	Fentanyl	3 [Corli 2016;Melili 2014 Nosek 2017]	624	Drowsiness Equivalent (2) Confusion/AMS Equivalent (3) Nausea/ Vomiting Equivalent (3)	Constipation Equivalent (3) Dyspnea Equivalent (1) Buprenorphine worse (1) Fatigue Equivalent (1)	Some concerns - High

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Conclusion #5

More research is needed regarding how buprenorphine compares to full MOR agonists wrt need for rescue medications.

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Evidence for #5

Intervention	Comparator	No. RCTs	No. patients	Result	RoB
Bup TD	Morphine PO Oxy PO Fent TD	4 [Corli 2016; Nosek2017; Melilli 2014; Pace 2007]	678	Equivalence 2 Oxy and Morphine superior 1 Bup superior 1	Some concerns – High

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Scoring for #5

Initial GRADE Score	Limitations	Strengths	Final GRADE Score	Confidence
4	-2 Serious RoB -2 Serious inconsistency		1	Very low

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Summary

Buprenorphine can effectively reduce pain in patients with cancer and moderate to severe pain; however, up to 1/3 of patients may not respond.

Though there is a growing body of literature, there is insufficient evidence to conclude that buprenorphine is more effective than full MOR agonists for everyone with cancer and moderate to severe pain.

However, buprenorphine may be prioritized in subgroups who are at risk for side effects.

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Future Directions

Better quality research is needed comparing buprenorphine with full MOR agonists, that validly measure side effects and reliably assess use of breakthrough medication.

New research is needed to compare buprenorphine SL vs. TD, as well as examine a broader spectrum of buprenorphine doses than has been examined before.

Research using the Bup/Naloxone formulation in cancer is 'sorely' needed!

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