The Use of Tramadol for Cancer-Associated Pain – A Systematic Review

[1]Shivani Garlapati MBBS, [2]Rachel Alexander DO, [3]Candice Kaminski MD, [3]Pavan Challa MBBS, [3]Zsuzsanna Nemeth MLIS, [4]Eduardo Bruera MD FAAHPM, [5,6]Ronald Chow MD MS PStat FACE FRSPH, [3]Elizabeth Prsic MD

[1]Vydehi Institute of Medical Sciences and Research Centre, Bengaluru, Karnataka, India;
[2]Medstar Georgetown University Hospital, Washington DC, USA;
[3]Yale Cancer Center, Yale School of Medicine, Yale University, New Haven, CT, USA;
[4]University of Texas MD Anderson Cancer Center, Houston, TX, USA;
[5]Temerty Faculty of Medicine, University of Toronto, Toronto, ON, Canada;
[6]Centre for Evidence-Based Medicine, University of Oxford, Oxford, UK.

Introduction

- Tramadol has been used for cancer pain and reported in the literature with varying relative effect compared to other analgesics
- To our knowledge, there is no comprehensive systematic review documenting the efficacy/effectiveness and safety of tramadol for cancer-associated pain
- The aim of this review is to report on the efficacy/effectiveness and safety of tramadol for cancer-associated pain.

Methods

- Ovid MEDLINE, Embase, and Cochrane CENTRAL were searched through to September 29, 2023
- Articles were included if they reported on tramadol in a multi-arm comparative trial, employing either a randomized controlled trial design or an observational study design with a multivariable or propensity-score matched analysis, and reported on efficacy or safety data pertaining to tramadol
- Narrative synthesis was conducted to identify common themes across trials of efficacy and safety endpoints.

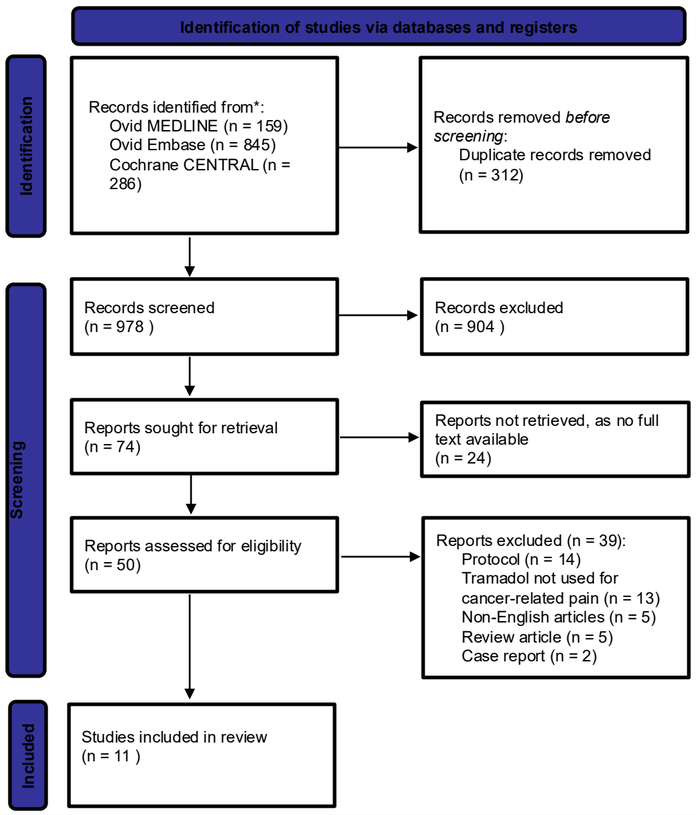
Results

- Eleven studies with 2,582 patients were included[1]. The majority had some to moderate concerns for bias[2]
- Two were cohort studies and nine were randomized controlled trials
- There were 20 efficacy endpoints; tramadol was superior in 3, inferior in 4, and neither in 13[3]
- There were 80 safety endpoints; tramadol was superior in 9, inferior in 12, and neither in 59[3]

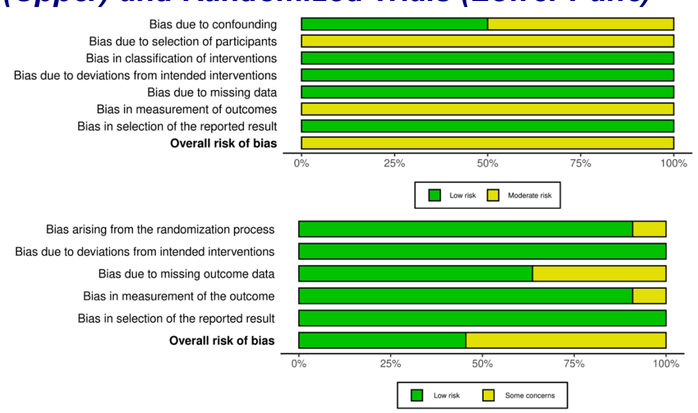
Conclusion

- Relative to other analgesics, tramadol is neither superior nor inferior This work provides encouragement for utilization of palliative
- There may exist a different safety profile, and therefore an opportunity to provide individualized patient-centered treatment strategies focused on safety and quality of life.

[1]PRISMA Flow Diagram



[2]Quality Assessment of Non-Randomized Trials (Upper) and Randomized Trials (Lower Pane)



[3]Study Characteristics

Study	Study Design	n	Age	% Female	Cancer Diagnosis	Comparison Arms	Treatment Target	Efficacy	Safety
Ahmad et al, 2023	Cohort Study	80	Mean: 51 +/- 10	100	Breast	1.Tramadol + Virtual Reality 2. Morphine	Moderate to severe cancer pain	No difference: 2/2 endpoints	Not reported
Arbaiza et al, 2007	Randomized controlled trial	36	Mean: 50	61	Breast, lung, prostate, cervical cancer, lymphoma, leukemia	1. Tramadol 2. Placebo	Cancer pain or cancer related neuropathic pain- tumor related plexuspathy, pain syndrome following surgery, chemotherapy induced neuropathy, tumor related epidural compression, entrapment of peripheral nerve by tumor mass, pain following herpes zoster	Tramadol superior: 3/4 endpoints No difference: 1/4 endpoints	Tramadol inferior: 3/3 endpoints
Grond et al, 1999	Cohort study	1658	Mean: 59 +/- 13	46	Head and neck region, gastrointestinal tract, respiratory system, breast, genitourinary system, lymphatic- hematopoietic system, skin, bones, connective tissue	1. Tramadol 2. Morphine	Somatic (bone), somatic (soft tissue), visceral, neuropathic	No difference: 1/1 endpoint	Tramadol superior: 3/14 endpoints No difference: 11/14 endpoints
Joshi et al, 2021	Randomized controlled trial	128	Not reported	22	Head and neck cancer	1. Tramadol 2. Diclofenac	Mucositis related	No difference: 1/1 endpoint	No difference: 15/15 endpoints
Leppert, 2001	Randomized controlled trial	40	Not reported	Not reported	Alimentary system, lung, urinary system, other sites	1. Tramadol 2. Morphine	Visceral, bone, neuropathic, somatic	No difference: 4/4 endpoints	Tramadol superior: 4/4 endpoints
Leppert, 2010	Randomized controlled trial	30	Mean: 70 +/- 9	63	Lung, colon, stomach, pallatinal tonsil, pharynx, oesophagus, gall bladder, pancreas, thyroid and suprarenal glands, kidney, prostate, breast, skin, skin melanoma, myelodysplastic syndrome, Hodgkin disease, ovary, abdominal and pelvic tumours and bone metastases from unknown primary site	1.Tramadol 2. DHC	Nociceptive cancer pain: visceral, somatic, bone	Tramadol inferior: 1/1 endpoint	No difference: 14/14 endpoints
Marinangeli et al, 2007	Randomized controlled trial	67	Mean: 66 +/- 13	42	Respiratory, genitourinary, gastrointestinal/biliary, musculoskeletal	1. Increasing transdermal fentanyl dosage 2. Oral tramadol added to their transdermal fentanyl before each increment of transdermal opioid dosage	Somatic, visceral	No difference: 1/1 endpoint	No difference: 7/7 endpoints
Rodriguez et al, 2007	Randomized controlled trial	177	Mean: 60 +/- 13	50	Stomach, breast, prostate, lung	1. Tramadol 2. Codeine 3. Hydrocodone	Somatic, visceral, mixed, neuropathic	No difference: 1/1 endpoint	Tramadol inferior: 4/4 endpoints
Rodriguez et al, 2008	Randomized controlled trial	118	Mean: 60 +/- 14	48	Gastric, breast, prostate, lung	1. Hydrocodone/ acetaminophen 2. Tramadol	Somatic, visceral, both somatic and visceral, neuropathic	No difference: 1/1 endpoint	No difference: 2/7 endpoints Tramadol inferior: 5/7 endpoints
Wilder Smith et al, 1994	Randomized controlled trial	20	Mean: 55	45	Lung, breast, prostate, stomach, non-Hodgkin lymphoma, colon, melanoma	1. Tramadol 2. Morphine	Neurogenic, visceral, osseous	No difference: 1/1 endpoint	Tramadol superior: 2/2 endpoints
Xu et al, 2006	Randomized controlled trial	230	Mean: 52 +/- 21	57	Breast, lung, gastrointestinal, other	1. Tramadol 2. Placebo 3. CKLQ .	Somatic, visceral, neuropathic, unknown	Tramadol inferior to CKLQ: 3/3 endpoints Tramadol inferior to placebo: 1/3 endpoints	Tramadol superior to CKLQ, inferior to placebo: 1/11 endpoints No difference: 10/11 endpoints