Use of the Edmonton Classification System for Cancer Pain and the Management of Refractory Cancer-induced Bone Pain

Merlina Sulistio[1,2], Patrick Tee[1,2], Alexandra Gorelik[4,5], David Kissane[1,2,3], Robert Wojnar[1], Natasha Michael[3]

[1]Palliative and Supportive Care Department, Cabrini Health; [2]School of Translational Medicine, Monash University; [3]School of Medicine, University of Notre Dame Australia; [4]School of Public Health and Preventive Medicine, Monash University; [5]Department of Medicine, RMH

Background

Cancer-induced bone pain (CIBP) is recognised as a complex pain syndrome and is associated with significant morbidity. The lack of standardised routine screening and the limited availability of appropriate therapies both contribute to inadequately managed pain. This poster consolidates the findings of two published studies. ***Study 1*** explores the standardised use of the Edmonton Classification System for Cancer Pain (ECS-CP) in identifying patients with CIBP requiring more intensive pain management. ***Study 2*** compares the outcomes of methadone rotation against other opioid rotation for the management of refractory CIBP.

Study 1

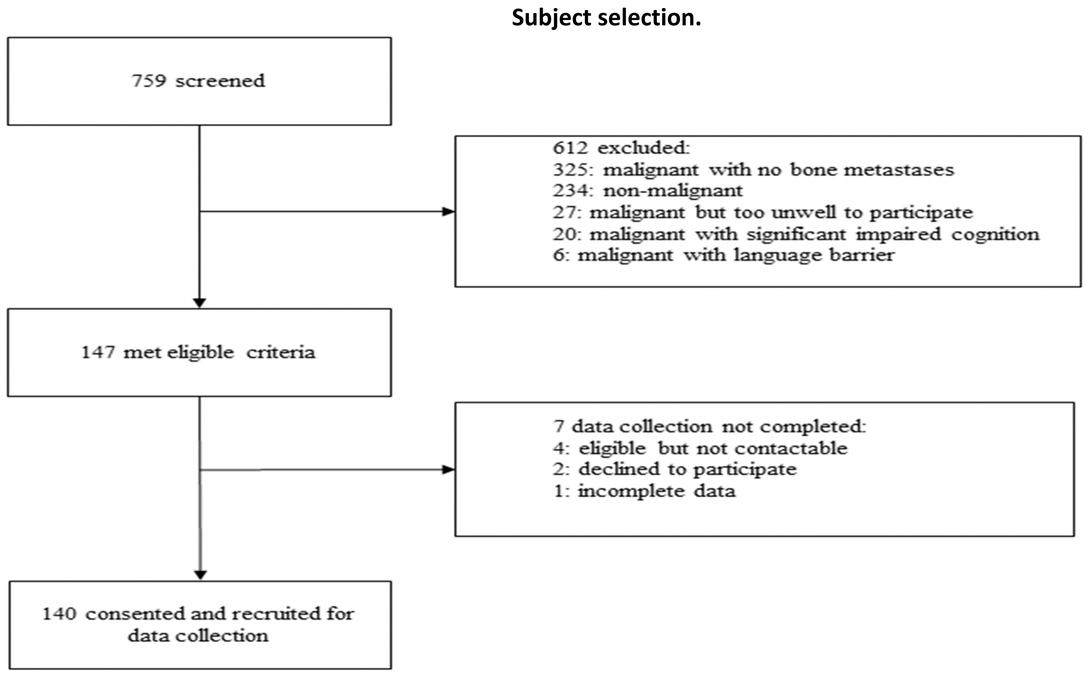
Aim: explore the standardised use of the Edmonton Classification System for Cancer Pain (ECS-CP) in identifying patients with CIBP requiring more intensive pain management

Method: A cross-sectional survey of cancer patients with bone metastasis was conducted in Cabrini Health. The study utilised the ECS-CP tool to assign a pain classification profile, the 11-point numerating rating scale (NRS-11) for pain intensity, and medication chart review in assessing the use of background and breakthrough opioid.

Statistical Analysis: The Mann-Whitney U test was used to examine the association between pain intensity, breakthrough pain characteristics, opioid requirements and the various ECS-CP features. Multivariable gamma regression analysis was used to analyse the relationship between ECS-CP composite score and pain intensity while controlling for patients' age and sex. A two-tailed p-value <0.05 indicated statistical significance.

Results:

Subject selection.



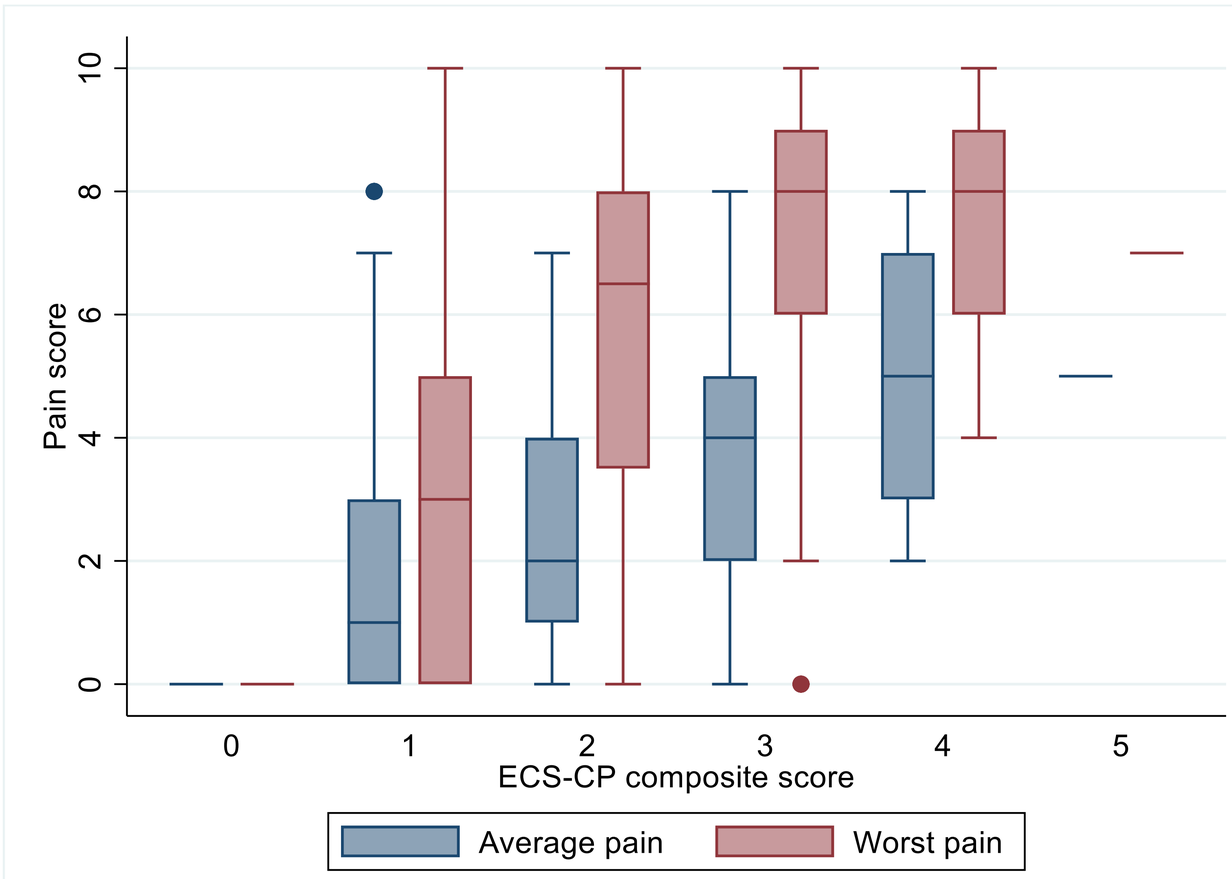
Association between the ECS-CP features, pain intensity and opioid requirements*

ECSCP features		Average pain	Worst pain	Background OMEDD#, mg	Breakthrough opioid frequency#
Pain mechanism	Nociceptive	3 (2–5)	6.5 (3–8)	25 (6.7–47)	1.5 (1–3)
	Neuropathic	4 (2–5)	7 (5–9)	26.7 (4.8–60)	1.3 (0.3–2.8)
		P=0.510	*P* =0.105	*P* =0.539	*P* =0.746
Incident pain	Present	3.5 (2–5)	7 (5–8)	26.7 (6.7–60.0)	1.7 (0.7–3.0)
	Absent	0 (0–2)	0 (0–4)	11.7 (6.7–18.0)	0.7 (0.3–1.3)
		P <0.001	*P* <0.001	*P* =0.005	*P* =0.007
Psychological distress	Present	4 (0.5–5)	7 (2–8)	26.7 (6.7–60.0)	1.2 (0.3–2.8)
	Absent	2 (1–3)	5 (2–7)	23.5 (1.2–30.0)	1.3 (0.7–2.8)
		P =0.009	*P* =0.054	*P* =0.238	*P* =0.988
Addictive behaviour	Present	4 (2–5)	6.5 (5–8)	33.8 (7.0–60)	2.0 (0.3–3.3)
	Absent	2 (0–4)	6 (2–8)	21.8 (6.7–40.0)	1.0 (0.3–2.3)
		P =0.099	*P* =0.497	*P* =0.268	*P* =0.217
Cognitive dysfunction	Present	4 (0–6)	7 (0–8)	30 (18–60)	1.0 (0.7–1.7)
	Absent	3 (0.75–4)	6 (2–8)	24 (3.2–47)	1.3 (0.3–3)
		P =0.298	*P* =0.825	*P* =0.221	*P* =0.409

OMEDD, Oral Morphine Equivalent Daily Dose

*Mann-Whitney U-test; #values are based on those who had opioids

Association of ECS-CP composite score and pain intensity.



Studies Conclusion

A standardised approach to the assessment and classification of pain syndromes allows us to consider CIBP more systemically and develop a personalized pain interventions according to the pain profile identified. Opioid rotation to methadone or other opioids in patients with refractory CIBP is feasible and acceptable with comparable efficacy. Methadone rotation may have the added benefit of further reducing overall opioid requirement, providing earlier and more sustained pain reduction over fourteen days with no significant worsening of opioid toxicity compared to baseline.

Study 2

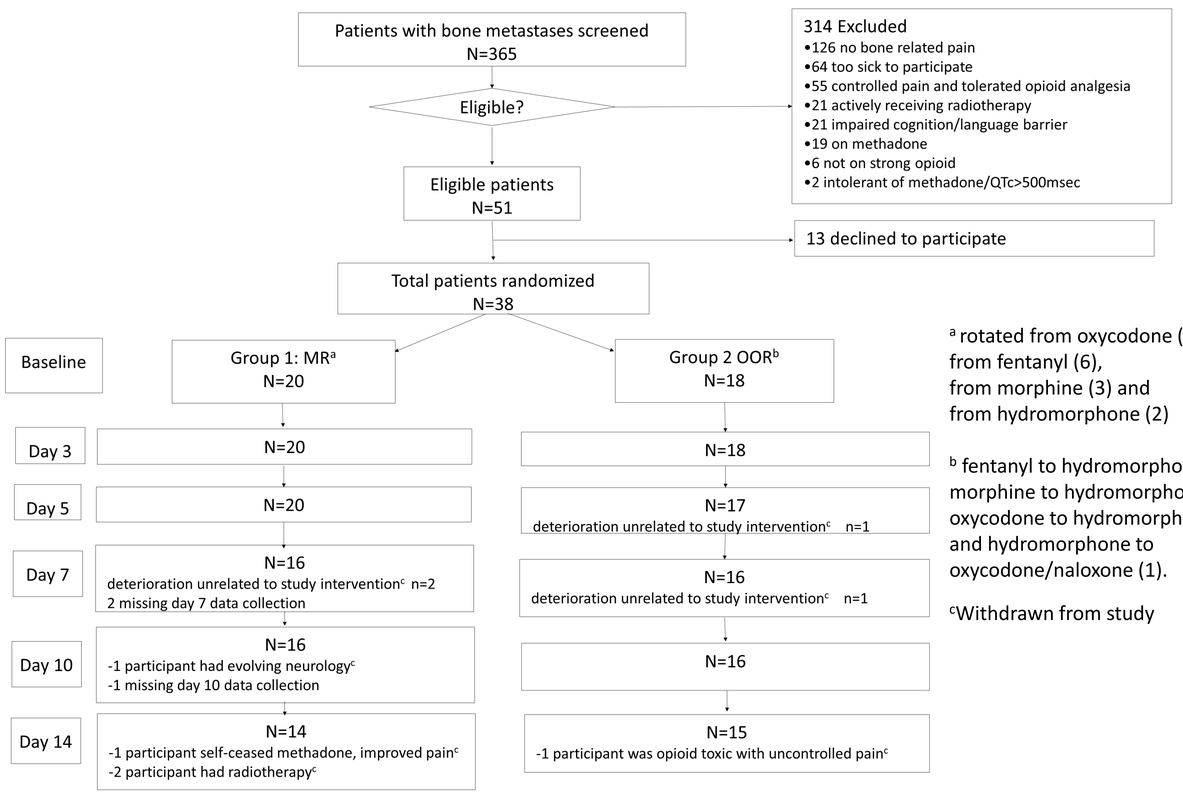
Aim: compares the outcomes of methadone rotation (MR) against other opioid rotation (OOR) in refractory CIBP.

Method: A pilot, open-labelled, randomized controlled trial of patients with refractory CIBP was conducted between March 2021-23 in Cabrini Health. Opioid rotation to methadone or another strong opioid was conducted in the inpatient setting. Methadone rotation was conducted using the rapid conversion stop-and-go method. Unlimited dosing of breakthrough opioids was permitted, whilst titration of co-analgesic medications was restricted during the 14 days study. Pain intensity, opioid adverse effects, brief pain inventory, quality of life score, anxiety and depression screen and opioid usage were documented.

Statistical Analysis: Summary statistics were used to describe study cohort. The changes in all outcomes were calculated as a difference between the baseline and the end of the study results. One-sample t-test was used to assess within-group change, while between-group differences were assessed using either the Student T-test or Wilcoxon rank-sum test for continuous data or Chi-square or Fisher's exact test for categorical variables subject to data distribution and frequencies. Effect sizes were calculated using Cohen's *d* to provide guidance about the strength of effect given the exploratory nature of this pilot work. The oral methadone-to-oral morphine conversion ratio used to calculate oral morphine equivalent daily dose at day 14 was 1:4.7. The data analysis was performed using Stata17 with $p<0.05$ considered statistically significant for all tests.

Results:

Consolidated Standards of Reporting Trials participant flow diagram.



[a] rotated from oxycodone (9), from fentanyl (6), from morphine (3) and from hydromorphone (2)

[b] fentanyl to hydromorphone (8), morphine to hydromorphone (6), oxycodone to hydromorphone (3) and hydromorphone to oxycodone/naloxone (1).

[c]Withdrawn from study

Total number of grade ≥2 adverse events as reported by participants at five pre-defined time points

CTCAE variables	Grade[a]	MR (N=14)	OOR (N=15)
Constipation	2	8 events, 6 participants (3^{b}, 2^{c})	10 events, 6 participants (2^{bc})
	3	0	1
Somnolence	2	7 events, 6 participants (1^{b}, 2^{c})	9 events, 7 participants (3^{b}, 1^{c})
	3	0	1
Xerostomia	2	5 events, 4 participants (2^{bc})	7 events, 6 participants (2^{b})
nausea	2	3 events, 2 participants (1^{bc})	3 events, 1 participant[c]
Pruritus	2	3 events, 1 participant[b]	0
Vomiting	2	0	1
Confusion	2	1	0
Hallucinations	2	1	0

CTCAE, Common Terminology Criteria for Adverse Events. [a]Grade2 – moderate severity requiring local or non-invasive intervention, limiting the age-appropriate instrumental activity of daily living. Grade 3 – severe or medically significant events requiring hospitalisation or prolongation of hospitalisation, impacting self-care but not life-threatening [b]Number of participants with event present from screening / baseline [c]Number of participants with event present at the end of study (day 14)

At the end of the study, 10 participants (6 MR, 4 OOR participants) had grade 2 adverse events (constipation, somnolence, dry mouth and nausea) and there were no reported grade 3 adverse events.

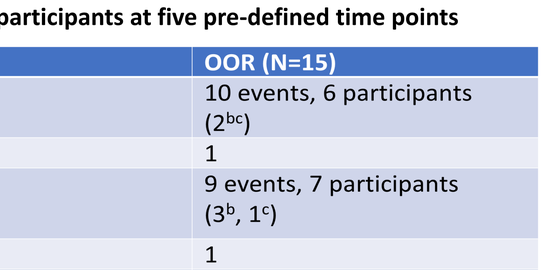
Changes in pain intensity over 14 days.

There was a significant within groups reduction in average [MR: d=-1.2 (95% CI -1.9 to -0.4), p=0.003 vs OOR: d= -0.8 (95% CI -1.5 to -0.1), p=0.015] and worst [MR: d=-0.9 (95% CI -1.6 to -0.2), p=0.042 vs OOR: d=-0.6 (95% CI -1.3 to 0.1), p=0.048] pain intensities, with no statistical significance between groups [d = -0.3 (95% CI -1.0 to 0.5), p=0.458 for average pain intensity and d= -0.1 (95% CI -0.8 to 0.6), p=0.761 for worst pain intensity].

At least 30% reduction in average pain intensity was observed in 10 participants on methadone (71.4%; 95% CI 47.7-95.1) vs 8 participants in the OOR group (53.3%; 95% CI 28.1-78.5%), a mean group difference of 18.1 (95% CI -16.5 to 52.7, p=0.32). Similarly, at least 50% reduction in average pain intensity was observed in 8 participants on methadone (57.1%; 95% CI 31.2-83.0%) and 4 participants in the OOR group (26.7%; 95% CI 4.3-64.7%), a mean group difference of 30.4 (95% CI -3.9 to 64.7, p=0.097). The proportions of responders were less when the worst pain intensity was assessed [MR: 35.7% with at least 30% pain reduction and 28.6% with at least 50% pain reduction vs OOR: 26.7% and 6.7%, p=0.7 and p=0.169, respectively).

Changes in pain interference over 14 days.

Both MR and OOR participants demonstrated a significant reduction in total pain interference [MR: d=-1.1 (95% CI -1.8 to -0.3), p=0.0420; OOR: d= -0.7, (95% CI -1.4 to 0.001), p=0.007] with no significant between group differences (p=0.772).



Changes in pain intensity over time.
NRS, numerical rating score

OMEDD following MR reduced significantly compared to OOR [d= -0.8 (95% CI -1.5 to -0.001), p=0.05] but there was no difference in the opioid escalation index between groups (p=0.141).

There were no significant differences between arms in participants' **HADS-Depression** (p=0.842) or **quality of life scores** (p=0.835) at the end of the study. Participants in the OOR group demonstrated a non-significant reduction in the **HADS-Anxiety** score at the end of study, resulting in a significant between group difference (d=0.8; p=0.043).

For further information or suggestions, please email author at: msulistio@cabrini.com.au