The Palliative Care Research Cooperative and The National Palliative Care Research Center

Comparing Apples, Oranges...and Bacon Bits: Systematic Review and Meta-Analysis in Palliative Care

a webinar in the Investigator Development series

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Overview

• What is “evidence synthesis?”
  • Systematic review vs meta-analysis
  • Why is evidence synthesis important?

• Three key questions to consider in evidence synthesis
  ◦ WHAT kinds of studies were included?
  ◦ HOW did authors critically evaluate study bias/quality?
  ◦ WHO: Are the interventions and outcomes homogeneous?
Association Between Palliative Care and Patient and Caregiver Outcomes
A Systematic Review and Meta-analysis

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Janel Hanmer, MD, PhD; Zachariah P. Hoydich, BS; Dara Z. Ikejiani; Michele Klein-Fedyshin, MSLS, BSN, RN, BA;
Camilla Zimmermann, MD, PhD; Sally C. Morton, PhD; Robert M. Arnold, MD; Lucas Heller, MD; Yael Schenker, MD, MAS
What are the challenges in synthesizing the palliative care evidence base?
Types of evidence syntheses

- **Narrative review**
  - Broad summaries
  - Not replicable
  - Inclusion/exclusion unclear

- **Systematic review**
  - Focused, comprehensive, structured
  - Methods clearly specified

- **Meta-analysis**
  - Statistical method of pooling results from multiple studies
Why conduct evidence synthesis?

- Highest level of evidence
- Provides a succinct and digestible summary of evidence
- Great in disciplines with multiple sources of evidence

- "Palliative care"
- By setting
- By population
- By modality
- By specialization
- By outcome

Diagram:

- Cochrane Database of Systematic Reviews
- DARE
- TRIP Database
- Systematic Review/Meta Analysis filters in PubMed, CINAHL, PsycINFO, etc.

- UpToDate
- Dynamed
- Clinical Evidence
- ACP Journal Club
- Essential Evidence +
- Evidence Updates

- PubMed
- CINAHL
- PsycINFO
- CENTRAL
- TRIP
- Web of Science

- ClinicalKey
- AccessMedicine
- Other Clinical Textbooks

- Meta Analysis
- Systematic Reviews
- Critically Appraised Sources
- Randomized Controlled Trials
- Cohort Studies
- Case Control Studies
- Case Reports/Case Series
- Background Information & Expert Opinion
What is the evidence for palliative care?
Why conduct evidence synthesis?

• Highest level of evidence

• Provides a succinct and digestible summary of evidence
  • Great in disciplines with multiple sources of evidence
    • ”Palliative care”
      • By setting
      • By population
      • By modality
      • By specialization
      • By outcome

• Highly influential for policy and practice change; encouraged by funders

• Great tool for early career investigators
Three key questions to consider

- **WHAT kinds of studies were included?**
- **HOW** did authors critically evaluate study bias/quality?
- **WHO**: Are the interventions and outcomes homogeneous?
What is the evidence for palliative care?
What is “palliative care?”

Early Initiation of #Palliative Care Improves Overall Well-being in Patients with #Cancer
bit.ly/2mkBBrL  hpm @CClinicJournal
What is “palliative care?”

• WHO
  ◦ “Palliative care is an approach that improves the quality of life of patients and their families facing the problem associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual.”

• CAPC
  ◦ “Palliative care, and the medical sub-specialty of palliative medicine, is specialized medical care for people living with serious illness. It focuses on providing relief from the symptoms and stress of a serious illness. The goal is to improve quality of life for both the patient and the family.
  ◦ Palliative care is provided by a team of palliative care doctors, nurses, social workers and others who work together with a patient’s other doctors to provide an extra layer of support. It is appropriate at any age and at any stage in a serious illness and can be provided along with curative treatment.”

• What is the conceptual framework/model for palliative care?
No need for routine #palliativecare meetings for families of pts w chronic #criticalillness ja.ma/28Z6xnp

Re-phrased: No need for routine "fast food style" #palliativecare meetings for families of pts w chronic #criticalillness @JAMA_current hpm
WHAT kinds of studies were included?

Do the authors provide information needed to recreate review?

• A HQ review should specify explicit inclusion/exclusion criteria

• Key constructs must be defined in a tangible way
  • What is a “Palliative care intervention?”

• Search string(s) should be provided
  • Are there obvious gaps in the search terms?

PubMed/MEDLINE Search strategy


Inclusion Criteria

• Sample: Life-limiting illness (defined by classifications of disease severity, such as tumor stage or New York Heart Association class)

• Intervention: Self described as "palliative care" and/or comprises at least two domains of palliative care, as defined by the National Consensus Project for Quality Palliative Care

• Study design: randomized

• Comparators: usual care, enhanced usual care, attention control

Exclusion Criteria

• Sample: Indication for palliative care is not related to life-limiting illness (e.g., chronic non-malignant pain)

• Intervention: single focus intervention (e.g., opioid therapy only), or study does not otherwise meet our definition of "palliative care" based on National Consensus Project for Quality Palliative Care

• Intervention: patient is not the target of intervention

• Intervention: caregiver is the exclusive or primary target of intervention

Study design: non-randomized

Prognosis: advanced illness OR palliat* OR palliat*[tiab] OR hospice

Three key questions to consider

◦ WHAT kinds of studies were included?
◦ HOW did authors critically evaluate study bias/quality?
◦ WHO: Are the interventions and outcomes homogeneous?
HOW was study quality evaluated?

Strength of evidence should be based on quality, not quantity, of studies.

- Bias: Factors that +/- lead to “systematic deviations from underlying truth”
  - “Systematic” implies that bias is predictable; not random error or chance
- Cochrane Risk of Bias Tool is the gold standard for evaluating risk bias
  - Risk of bias does not confirm the presence of bias
- Palliative care trials will always have some bias, but can still be high-quality
  - What are some examples of unavoidable risk of bias in palliative care?
Interesting - answer is survival was not specified a priori as outcome of interest in Temel trial protocol. Thanks 4 email @diokavalieratos!

Systematic review on effectiveness of palliative care. Why is Temel RCT ‘high bias’ for survival but not for PROMs? jamanetwork.com/journals/jama/...
### Example Risk of Bias table

<table>
<thead>
<tr>
<th>Entry</th>
<th>Judgement</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adequate sequence generation?</td>
<td>Yes</td>
<td>Quote: &quot;patients were randomly allocated.&quot; Comment: Probably done, since earlier reports from the same investigators clearly describe use of random sequences (Cartwright 1980).</td>
</tr>
<tr>
<td>Blinding? (Patient-reported outcomes)</td>
<td>Yes</td>
<td>Quote: &quot;double blind, double dummy&quot;; ‘High and low dose tablets or capsules were indistinguishable in all aspects of their outward appearance. For each drug an identically matched placebo was available (the success of blinding was evaluated by examining the drugs before distribution).&quot; Comment: Probably done.</td>
</tr>
<tr>
<td>Blinding? (Mortality)</td>
<td>Yes</td>
<td>Obtained from medical records; review authors do not believe this will introduce bias.</td>
</tr>
<tr>
<td>Incomplete outcome data addressed? (Short-term outcomes (2-6 wks))</td>
<td>No</td>
<td>4 weeks: 17/110 missing from intervention group (9 due to 'lack of efficacy'); 7/113 missing from control group (2 due to 'lack of efficacy').</td>
</tr>
<tr>
<td>Incomplete outcome data addressed? (Longer-term outcomes (&gt;8 wks))</td>
<td>No</td>
<td>12 weeks: 31/110 missing from intervention group; 18/113 missing from control group. Reasons differ across groups.</td>
</tr>
<tr>
<td>Free of selective reporting?</td>
<td>No</td>
<td>Three rating scales for cognition listed in Methods, but only one reported.</td>
</tr>
<tr>
<td>Free of other bias?</td>
<td>No</td>
<td>Trial stopped early due to apparent benefit.</td>
</tr>
</tbody>
</table>
Box. Quality Criteria*  

Participants  
Reported  
1. Clear description of inclusion and exclusion criteria12,18  
2. Comprehensive strategy for identification of potential cases12  
3. Patient recruitment rate ≥70%12  
4. Evaluation of nonparticipants to judge generalizability12  

Adequate  
5. Specific objectives and hypotheses12,18  
6. Clearly defined primary and secondary outcome measure(s)12,18  
7. Use of validated outcome measures12  
8. Blinding to group assignment of those assessing outcome measures2,16  

Objectives and Outcome Measures  
Reported  
9. Baseline demographics and clinical characteristics of each group prior to intervention22,26  
10. Baseline outcome measures of each group prior to the intervention19  

Adequate  
11. No significant differences present across study groups2,16  

Randomization and Concealment of Allocation  
Reported  
12. Study design and method of randomization, including details of any restriction (eg, blocking, stratification, matching)12,18  

Adequate  
13. Method to generate the randomization sequence explicitly described and adequate16  
14a. Unit of allocation was by institution, team, or professional, and the number of clusters was adequate (cluster randomization only)10,12  
14b. Unit of allocation was by patient and a centralized randomization scheme was implemented by calling a central number, an on-site computer system, or sealed opaque envelopes (individual randomization only)13,14  

Sample Size and Attrition  
Reported  
15. How sample size was determined and, when applicable, explanation of interim analyses12,18  
16. Flow of participants through each stage12,18  

Adequate  
17. Intended sample size attained at baseline and based on an adequate sample size calculation12  
18. Outcome measures obtained for 90% to 100% of participants ("yes") or 70% to 89% ("partial") randomized (stated, explicitly)12,18  

Intervention, Control, and Protection Against Contamination  
Reported  
19. Precise details of the intervention and how and when it was administered22,27,28  
20. Precise details of the control (contrast between intervention and control clearly defined)12  

Adequate  
21. It is unlikely that control patients received the study intervention or a similar intervention12,16  
22. It is documented that intervention patients actually received the intervention19  

Analyses  
Reported  
23. Statistical methods used to compare groups for primary and secondary outcomes and for subgroup analyses, if relevant12,18  
24. For each primary and secondary outcome, a summary of results for each group and estimated effect size and precision (eg, P value or 95% confidence interval)19  

Adequate  
25. Analysis by “intention to treat” (analysis is performed on groups initially produced by the randomization process) and, in cluster trials, accounting for between-cluster variations10,22,26  

*Each of the 25 items is scored 4 (complete marks), 2 (partial marks), or 0.
Three key questions to consider

- WHAT kinds of studies were included?
- HOW did authors critically evaluate study bias/quality?
- WHO: Are the interventions and outcomes homogeneous?
WHO: Study heterogeneity

Are the included studies and their results consistent?

<table>
<thead>
<tr>
<th>Source</th>
<th>No. of Patients</th>
<th>Intervention</th>
<th>Control</th>
<th>Setting</th>
<th>Instrument</th>
<th>Disease</th>
<th>Standardized Mean Difference (95% CI)</th>
<th>Favors</th>
<th>Weight, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bakitas et al, 2015</td>
<td>72</td>
<td>83</td>
<td>Home</td>
<td>FACT-Pal</td>
<td>Cancer</td>
<td>0.19 (-0.13 to 0.50)</td>
<td>Control</td>
<td>6.81</td>
<td></td>
</tr>
<tr>
<td>Clark et al, 2013</td>
<td>54</td>
<td>63</td>
<td>Ambulatory</td>
<td>FACT-G</td>
<td>Cancer</td>
<td>0.42 (0.06 to 0.79)</td>
<td>Control</td>
<td>6.70</td>
<td></td>
</tr>
<tr>
<td>Given et al, 2002</td>
<td>53</td>
<td>59</td>
<td>Home</td>
<td>SF-36</td>
<td>Cancer</td>
<td>0.21 (-0.16 to 0.58)</td>
<td>Control</td>
<td>6.69</td>
<td></td>
</tr>
<tr>
<td>McCorkle et al, 2015</td>
<td>36</td>
<td>56</td>
<td>Ambulatory</td>
<td>FACT-G</td>
<td>Cancer</td>
<td>-0.20 (-0.62 to 0.22)</td>
<td>Control</td>
<td>6.57</td>
<td></td>
</tr>
<tr>
<td>Northouse et al, 2005</td>
<td>69</td>
<td>65</td>
<td>Ambulatory</td>
<td>SF-36</td>
<td>Cancer</td>
<td>0.09 (-0.25 to 0.43)</td>
<td>Control</td>
<td>6.77</td>
<td></td>
</tr>
<tr>
<td>Sidebottom et al, 2015</td>
<td>79</td>
<td>88</td>
<td>Hospital</td>
<td>MLHFQ</td>
<td>Heart failure</td>
<td>5.39 (4.74 to 6.05)</td>
<td>Control</td>
<td>5.87</td>
<td></td>
</tr>
<tr>
<td>Wong et al, 2016</td>
<td>43</td>
<td>41</td>
<td>Home</td>
<td>MQOL-HK</td>
<td>Heart failure</td>
<td>0.58 (0.15 to 1.02)</td>
<td>Control</td>
<td>6.53</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (I² = 97.4%, P = .000)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>45.94</td>
</tr>
<tr>
<td>Bakitas et al, 2009</td>
<td>108</td>
<td>97</td>
<td>Home</td>
<td>FACT-Pal</td>
<td>Cancer</td>
<td>0.12 (-0.16 to 0.39)</td>
<td>Control</td>
<td>6.90</td>
<td></td>
</tr>
<tr>
<td>Higginson et al, 2014</td>
<td>42</td>
<td>40</td>
<td>Ambulatory</td>
<td>EQSD</td>
<td>Mixed</td>
<td>0.05 (-0.38 to 0.49)</td>
<td>Control</td>
<td>6.54</td>
<td></td>
</tr>
<tr>
<td>Rummans et al, 2006</td>
<td>47</td>
<td>49</td>
<td>Ambulatory</td>
<td>Spitzer</td>
<td>Cancer</td>
<td>0.16 (-0.24 to 0.56)</td>
<td>Control</td>
<td>6.62</td>
<td></td>
</tr>
<tr>
<td>Temel et al, 2010</td>
<td>60</td>
<td>47</td>
<td>Ambulatory</td>
<td>FACT-L TOI</td>
<td>Cancer</td>
<td>0.52 (0.13 to 0.90)</td>
<td>Control</td>
<td>6.65</td>
<td></td>
</tr>
<tr>
<td>Zimmermann et al, 2014</td>
<td>140</td>
<td>141</td>
<td>Ambulatory</td>
<td>FACT-Sp</td>
<td>Cancer</td>
<td>0.21 (-0.03 to 0.44)</td>
<td>Control</td>
<td>6.96</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (I² = 0.0%, P = .500)</strong></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>33.67</td>
</tr>
<tr>
<td>Bekelman et al, 2015</td>
<td>172</td>
<td>180</td>
<td>Home</td>
<td>KCCQ</td>
<td>Heart failure</td>
<td>0.01 (-0.20 to 0.22)</td>
<td>Control</td>
<td>7.00</td>
<td></td>
</tr>
<tr>
<td>Grudzen et al, 2016</td>
<td>39</td>
<td>30</td>
<td>Hospital</td>
<td>FACT-G</td>
<td>Cancer</td>
<td>-0.01 (-0.48 to 0.47)</td>
<td>Control</td>
<td>6.42</td>
<td></td>
</tr>
<tr>
<td>Northouse et al, 2013</td>
<td>198</td>
<td>104</td>
<td>Ambulatory</td>
<td>FACT-G</td>
<td>Cancer</td>
<td>-0.26 (-0.50 to -0.02)</td>
<td>Control</td>
<td>6.96</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (I² = 33.3%, P = .223)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>20.39</td>
</tr>
<tr>
<td><strong>Overall (I² = 94.8%, P &lt; .001)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>100.00</td>
</tr>
</tbody>
</table>
Assessment of Publication Bias Regarding Quality of Life at 1–3 Month Follow-up in Randomized Clinical Trials of Palliative Care Interventions

Funnel plot with pseudo 95% confidence limits

Note: Egger's test bias estimate (SE): 8.25 (3.39), P=0.03.
Legend: Dotted lines indicate pseudo 95% confidence intervals around the overall summary estimate.
Abbreviation: SMD, standardized mean difference.
Limitations in the PC evidence base

- Of 43 trials, 12% (n=5) deemed at low risk of bias
- Heterogeneity of outcome assessment
- Inadequately defined interventions
Three key questions to consider

◦ WHAT kinds of studies were included?
◦ HOW did authors critically evaluate study bias/quality?
◦ WHO: Are the interventions and outcomes homogeneous?
Summary

- The scope of a review should be defined by its intent
  - Palliative care: philosophy or sub-specialty?
  - What is a “palliative care” intervention?

- Clinical practice should be guided by quality, not quantity, of evidence
  - What are mutable vs. immutable sources of bias in palliative care research?
  - How conservative should we be when discussing the impact of palliative care?

- Consistency of evidence lends confidence to our conclusions
  - Is it surprising that we see disparate findings across some palliative outcomes?
Questions?

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