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## Reading past the $p < 0.05$ 's: The secondary messages of systematic reviews and meta-analyses in palliative care

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Palliative care firmly and finally has a seat at the table. Truly pioneering clinical trials, along with fierce advocacy and messaging, have thrust palliative care to the forefront of clinical practice and international policy. All of this effort has underscored the notion, based at least in part on intuition and a moral imperative, that a palliative approach is in its essence, synonymous with high-quality care for those suffering from the burdens of life-threatening and life-limiting illness. Given the attention that it has received over the past several decades, one might assume that the evidence base undergirding palliative care is strong, consistent, and nuanced. Yet, is that the case?

As advocates for our field, we (understandably) often celebrate and perhaps even cling to positive findings from studies of palliative care interventions, even if those results are sometimes weak or inconsistent (e.g. positive for some outcomes and null for others). Evidence syntheses (i.e. systematic reviews and meta-analyses) afford the opportunity to reflect upon a comprehensive body of knowledge regarding a phenomenon or intervention. Perhaps more importantly, they offer us a lens through which to critically appraise that body itself for at least two important factors: the quality and consistency of the constituent studies. In the presence of a methodologically rigorous and critical systematic review or meta-analysis, priority and credence generally shifts from an individual trial's findings to those of the cumulative review. Through evidence synthesis, our vantage point is elevated such that we can holistically appraise and critique the history, the strengths, and the opportunities for growth within our field.

In 2008, Zimmermann and colleagues published a seminal systematic review comprising 22 trials in which they found scant and patchy evidence of palliative care's benefit.<sup>1</sup> For example, of 13 trials assessing patient quality of life, 4 reported a significant intervention benefit, whereas only 1 of 14 trials evaluating symptom burden showed a benefit. Furthermore, Zimmermann and colleagues noted critical methodological shortcomings in nearly all 22 trials, such as contamination, and failures to account for clustering. Nearly 7 years later, Kavalieratos et al.<sup>2</sup> added to the literature, performing an updated systematic review as well as the first comprehensive meta-analysis of palliative care interventions,

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comprising 43 trials. Indeed that review had two messages, one of which gained much more traction than the other. Overall, we found that palliative care was associated with improvements in patient quality of life and symptom burden, and observed no association with survival. Yet, when meta-analyses were restricted to trials of the highest quality (defined as low risk of bias per Cochrane Collaboration criteria),<sup>3</sup> the previously clinically significant association with quality of life attenuated, while the association with symptom burden lost statistical significance. Our secondary message—a signal that perhaps the evidence base for palliative care wasn't as robust as a first glance would suggest—received hardly any attention.

In this issue of *Palliative Medicine*, Fulton and colleagues offer a focused systematic review and meta-analysis, zeroing in on oncology palliative care interventions in the outpatient setting.<sup>4</sup> In addition to updating the literature, the authors undertook the noteworthy task of attempting to elucidate the mechanisms of palliative care interventions— that is, what “dose” of palliative care yields greater impact, and to what degree does integration of palliative care within the usual oncology care context relate to impact?

Once again, the pattern of evidentiary inconsistency in palliative care persists. Overall, Fulton and colleagues found improvements in short-term (but not long-term) quality of life associated with palliative care. Regarding symptoms, no association was found with receipt of palliative care, whereas a sensitivity analysis excluding a prominent trial of early versus late palliative care intervention<sup>5</sup> did yield a reduction in symptom burden. Similar to the analysis by Kavalieratos et al.,<sup>2</sup> Fulton et al. found no association between palliative care and overall survival; again, only in a secondary sensitivity analysis that removed a study<sup>6</sup> was all-cause mortality found to be lower among recipients of palliative care. The notion that positive findings for two noteworthy outcomes (symptom burden and survival) were achievable only upon the exclusion of certain studies, is perhaps a finding in and of itself.

Perhaps the most important contributions of Fulton and colleagues to the literature are their analyses attempting to explain the processes underlying their observed positive associations. Using a theory-driven approach, the authors classified each study by the degree to which the palliative care intervention was integrated within usual care, arguably hypothesizing that greater integration might yield stronger, more positive results. Yet, no association was found between degree of integration and intervention impact. Regarding intervention elements (defined by the National Consensus Project's<sup>7</sup> domains of palliative care), there was no pattern seen between the number of palliative care domains included in interventions and their overall impact, a finding similarly reported by others previously.<sup>2</sup> Perhaps this is the secondary message that we take away from Fulton and colleagues' analysis—that despite some benefits of palliative care in outpatient oncology, we still are woefully unclear on how and why these benefits come to bear.

As research in palliative care continues to develop, the sophistication of the questions we attempt to answer will similarly need to mature. Numerous trials have shown that *something* in palliative care “moves the needle,” yet we as a discipline continue to be mystified by what precisely that is. Inarguably, additional high-quality clinical trials are needed to advance our understanding of the complex mechanisms by which palliative care confers the benefits that

we all instinctively believe it does. In order to disentangle these operant mechanisms, future interventions should root themselves in theoretical models whose pathways can be isolated and tested, allowing for iterative intervention refinement. While common practice in behavioral treatment development,<sup>8</sup> palliative care interventions, to date, have often lacked clear a priori explications of their theoretical underpinnings, as well as the hypothesized mediating and moderating variables that may be relevant along the way to affecting the intervention's target outcomes. And perhaps most critically, trials must provide clear, precise, and specific reporting of an intervention's components (as well as the comparator condition's components), dosing, and fidelity; inadequate reporting of these elements has been noted as a key limitation in many palliative care reviews to date.<sup>1,2,9</sup>

The future of palliative care research is both promising and challenging. Although we have data to support that something about a palliative approach to serious illness care “works,” our evidence base is far from perfect and requires further scrutiny. As scientists, the healthy skepticism that interventions (or components of interventions) may not yield the benefits we hypothesize (and hope for) is vital to our ability to learn from our history and lay the groundwork for our innovation. Evidence syntheses, such as that of Fulton and colleagues, are essential to communicating a message of where we are as a field, and where the path ahead must lead us. Yet, with all communication in life, invariably more than one message exists, and often, the subtext is just as meaningful than the headline, if not more so. As we advance our field, it behooves us to recognize and harness the power in both the headline and the subtext within the evidence for palliative care.

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