High quality phase 3 studies do not support the use of somatostatin analogues to reduce vomiting in malignant bowel obstruction.

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We read with interest this systematic review on the MASCC multidisciplinary recommendations for the management of malignant bowel obstruction in people with advanced cancer (MBO) [1]. Malignant bowel obstruction is difficult to manage and clear guidance is welcome. This article covers important aspects of MBO such as advance care planning and goals of care conversations [1].

This review had a detailed search and included nearly 400 articles. These were used to make recommendations for MBO management, with associated level and grade of evidence. The majority, understandably, have a low level and/or grade of evidence [1].

One recommendation is that somatostatin analogues, such as octreotide, may reduce vomiting in MBO. This is reported to be Level 1 evidence and grade A. Level 1 is "Evidence obtained from meta-analysis of multiple, well-designed, controlled studies; randomized trials with low false-positive and false-negative errors (high power)". Grade A is "Evidence of type I or consistent findings from multiple studies of type II, III, or IV." [1]. None of the other recommendations for MBO management comes close to this pinnacle of evidence [1].

The recommendation for somatostatin analogues come almost exclusively from our systematic review, from which we drew exactly the opposite conclusion [2]. The authors themselves infer the same interpretation of these data as we did [1]. They correctly state from our systematic review that the five phase 2 studies with *high risk of bias* reported that somatostatin analogues were more effective than hyoscine butylbromide and placebo for reducing vomiting. By contrast, the two high quality, appropriately powered, phase 3 studies with *low risk of bias* found no significant difference in vomiting between somatostatin analogues and placebo in their primary end points, and potentially worsened some symptoms (eg. colicky abdominal pain) in participants. One of the main reasons to assess quality in a systematic review is so appropriate weight can be given to the better quality studies. In our systematic review, the evidence from the two adequately powered, high-quality studies outweigh the evidence from five unpowered low-quality studies. We thus concluded that high-quality trials show somatostatin analogues are ineffective in their primary vomiting endpoints [2].

Uncontrolled studies do not account for the natural history of symptoms and potentially overestimate benefits [3]. There is need to understand the natural history of symptoms, including in MBO in order to understand the potential benefits and harms by adding a new therapy [3]. Without a control arm the natural history of MBO symptoms is not evaluated and the subjective symptom reporting might give the impression that the active treatment is working. Equally, when assessing harms, a symptom such as colicky abdominal pain caused by the condition (MBO) and if exacerbated by the intervention (octreotide) would be attributed to the disease, and not the intervention without a control arm identifying the excess rate in the intervention arm. In controlled studies, causality can be ascribed. We acknowledge that somatostatin analogues do have a biologically plausible mechanism of action, and that the underpowered phase 2 studies were promising. As clinicians, we are potentially susceptible to recall bias where we recall this class of medication helping patients. However, powered phase 3 studies accounting for the natural history of symptoms did not show benefit of somatostatin analogues over placebo in MBO [2, 3].

We acknowledged that there is debate regarding the clinically relevant study end point for symptom control in MBO and when it should be measured. We suggest that more powered, well-designed trials with agreed clinically important end points and measures are needed to determine the role of somatostatin analogues for MBO. To this end, we have continued to progress work in this area to develop a core outcome set of patient and clinician relevant outcomes to help inform relevant measures [4-6].

Until we have the result of these, based on the lack of high-quality trials supporting the use of octreotide in the management of MBO, we have suggested that if octreotide is used for treating this condition it should be done on an individual case-by-case basis, with patient informed consent, regular assessment/reassessment of efficacy and side effects [7, 8].

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