



Response to Ekström *et al* regarding low-dose opioids in advanced chronic obstructive pulmonary disease

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Caring for individuals with advanced chronic obstructive pulmonary disease (COPD) with refractory breathlessness is undoubtedly challenging and I commend the authors for undertaking important and necessary research in this area. I did not write that opioids 'should not be used' in patients with advanced COPD.¹ Based on the authors' own data showing significantly increased all-cause mortality among individuals with advanced COPD receiving benzodiazepine and 'high-dose' opioids,² I expressed that some caution should be displayed when prescribing these medications to these older, respiratory-vulnerable patients, who often have multiple comorbidities. Cautionary prescribing can take the form of using low and intermittent drug dosing, closely monitoring for possible side effects following drug receipt, and in some instances, not prescribing these medications at all, such as possibly in the setting of hypercapnea or comorbidity.

I agree with Ekström *et al*, and mentioned in my editorial,¹ that causation cannot be inferred in observational study designs. Nonetheless, forward causality remains one possible explanation for the observed association between benzodiazepine and 'high-dose' opioid use and mortality in advanced COPD. While I agree that confounding by indication is difficult to eliminate, multiple markers of COPD severity were controlled for in their analysis, potentially making confounding by indication less likely.

While Ekström *et al*² reported no increased hospitalisation or death among 'low-dose' opioid recipients, I outlined several points for consideration when interpreting these results: respiratory, cognitive, psychomotor and gastrointestinal-specific outcomes were not examined; prevalent, and not incident, medication receipt was considered, and the potential bias that this

introduces; and, the approach to quantifying drug dose is questionable, as benzodiazepine and opioid use can often vary in response to varying symptom intensity and side effect development, making accurate dose quantification of these drugs challenging. Moreover, the threshold selected to identify 'high' opioid drug use is really not all that high (ie, >30 mg oral morphine equivalents per day). The authors' own data in table 2 supports that many individuals with COPD are likely receiving these 'higher' benzodiazepine and opioid doses (ie, at index, of 535 individuals receiving benzodiazepines, 260 (49%) were receiving 'higher dose'; of 509 individuals receiving opioids, 298 (59%) were receiving 'higher dose').² While Ekström *et al* refer to a study with 30 patient-years of follow-up showing safety of low-dose opioids, about 50% of study participants were patients without COPD, and during phase IV of the study, only 24/83 (29%) patients remained, with the others largely withdrawing because of drug side effects and death.³

Competing interests None.

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References

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