Observational studies and “the eye of the beholder”

To the Editor:

NWARU *et al.* [1] report a dose-related association between short-acting β_2 -agonists (SABA) and poorer clinical outcomes (exacerbations, emergency department visits, hospital admissions and mortality) in asthma. Acknowledging that observational studies cannot establish causality, they conclude: “Regardless of whether there is a causal effect of SABA use and these adverse effects, or if they are mainly a marker for more severe asthma and/or a reflection of the frailty of the patients, increased use of SABA should alert clinicians to monitor these patients more closely.” These are important conclusions that should inform clinical care and be incorporated into international guidelines.

We would like to draw attention to a known, but rarely explicitly discussed, limitation in observational study design by comparing the hypotheses and interpretations in this study with a similarly designed study in another area of symptom treatment: the use of opioids in COPD [2]. NWARU *et al.* [1] frame their hypothesis in the context of SABA overuse as a potential marker of poorly controlled asthma. The possibility of a causal effect of SABA use on adverse effects is allowed, but the possible underpinning mechanisms were not discussed despite known adverse effects [3–5].

In an observational study of opioid use in people with COPD, VOZORIS *et al.* [2] set their paper in the context of possible opioid-related harm. The design-related limitations in inferring causality with regard to the demonstrated association between opioid prescription and respiratory adverse events (emergency room visits, COPD/pneumonia-related mortality and all-cause mortality) was acknowledged. However, the summary findings in the discussion largely dismissed the possibility that opioid prescription could be a marker of poorly controlled disease or poorly controlled symptoms when the disease was no longer amenable to modification despite the absence of clinical data for the reason for prescribing opioids: “frailer long-term care resident older adults display vulnerability for several serious adverse respiratory outcomes with use of these agents.”

The design limitations of observational studies with regard to confounders, including bias by indication or underlying disease severity, are well recognised. Many limitations can be mitigated by adherence to a well-designed protocol with predefined outcomes. However, *interpretation bias*, driven by our pre-conceived expectations and concerns, may remain unless all reasonable explanations for both directions of association are allowed in the rationale for the study and explored in understanding the findings.

Direct toxicity is a potential consequence of both therapies. Being a marker of poor disease control or poor symptom control is also an important conclusion to consider for both interventions based on the available data. We must recognise our human tendency for the “eye of the beholder” to bias our messages.

@ERSpublications

Observational studies need explanations in both directions of association to avoid interpretation bias
<https://bit.ly/3d7kLnG>

Cite this article as: Johnson MJ, Ekström M, Currow DC. Observational studies and “the eye of the beholder”. *Eur Respir J* 2020; 56: 2001637 [<https://doi.org/10.1183/13993003.01637-2020>].

Miriam J. Johnson^{1,2}, Magnus Ekström^{2,3} and David C. Currow^{1,2}

¹Wolfson Palliative Care Research Centre, University of Hull, Hull, UK. ²IMPACCT, Faculty of Health, University of Technology Sydney, Ultimo, Australia. ³Lund University, Faculty of Medicine, Dept of Clinical Sciences Lund, Respiratory Medicine and Allergology, Lund, Sweden.

Correspondence: Miriam J. Johnson, Wolfson Palliative Care Research Centre, University of Hull, Allam Medical Building, Cottingham Road, Hull, HU6 7RX, UK. E-mail: miriam.johnson@hums.ac.uk

Received: 7 May 2020 | Accepted after revision: 20 May 2020

Conflict of interest: M.J. Johnson has nothing to disclose. M. Ekström has nothing to disclose. D.C. Currow is an unpaid member of an advisory board for Helsinn Pharmaceuticals, is a consultant to Specialised Therapeutics and Mayne Pharma and has received intellectual property payments from Mayne Pharma.

References

- 1 Nwaru BI, Ekstrom M, Hasvold P, *et al.* Overuse of short-acting β_2 -agonists in asthma is associated with increased risk of exacerbation and mortality: a nationwide cohort study of the global SABINA programme. *Eur Respir J* 2020; 55: 1901872.
- 2 Vozoris NT, Wang X, Fischer HD, *et al.* Incident opioid drug use and adverse respiratory outcomes among older adults with COPD. *Eur Respir J* 2016; 48: 683–693.
- 3 Burggraaf J, Westendorp RG, Veen JC, *et al.* Cardiovascular side effects of inhaled salbutamol in hypoxic asthmatic patients. *Thorax* 2001; 56: 567–569.
- 4 Cekici L, Valipour A, Kohansal R, *et al.* Short-term effects of inhaled salbutamol on autonomic cardiovascular control in healthy subjects: a placebo-controlled study. *Br J Clin Pharmacol* 2009; 67: 394–402.
- 5 Cazzola M, Matera MG, Donner CF. Inhaled β_2 -adrenoceptor agonists: cardiovascular safety in patients with obstructive lung disease. *Drugs* 2005; 65: 1595–1610.

Copyright ©ERS 2020