

Quadrupling inhaled corticosteroid doses

We thank Dr McCormack for his letter, published in the May issue of *Canadian Family Physician*, regarding our article “New evidence-based tool to guide the creation of asthma action plans for adults,” which was published in the Clinical Review section in February.^{1,2} He raises some important points that merit further discussion and clarification.

Dr McCormack’s letter raises thoughtful concerns about the relative paucity of literature that supports quadrupling the inhaled corticosteroid (ICS) dose in the face of asthma worsening as part of an asthma action plan.¹ Although we did recommend this approach in the “yellow zone” (acute loss of control) of the asthma action plan, at no point did we claim that this approach is supported by a strong level of evidence.² The crucial distinction here, and the main purpose of our article, was to support clinicians in providing their patients with asthma action plans—a practice that, when combined with education and regular clinical review, is unquestionably supported by strong evidence.

Use of asthma action plans improves quality of life, reduces symptoms, and reduces hospitalizations, emergency department visits, and unscheduled health care use in adults with asthma. This is a recommendation that has been found across international asthma guidelines for almost 30 years³ and is supported by multiple systematic reviews of well conducted randomized controlled trials (RCTs), including a more recent meta-review of 27 systematic reviews (244 RCTs) by Pinnock and colleagues.⁴⁻⁶ Despite this, our own audit of 3 large family practices in Ontario found that not a single one of 884 adults with asthma followed for 1 year received an asthma action plan,³ which was similar to findings of previous Canadian and US chart audits.^{7,8} This is a considerable evidence-to-practice gap, and represents a lamentable lost opportunity to improve the health and lives of our patients with asthma.⁹ Studies that have sought to identify reasons for this gap suggest that primary care physicians lack the training and experience required to produce an asthma action plan for their patients, and particularly to provide yellow-zone recommendations.¹⁰ This is what motivated us to develop a

practical bedside tool for this purpose, which is the subject of our article.²

Here, as strong as the evidence is for provision of asthma action plans, we recognize Dr McCormack’s point that the evidence for how inhaled medications should actually be augmented in the yellow zone of an asthma action plan is not nearly as strong. In our original article describing the development of our evidence-based asthma action plan tool, published in the *European Respiratory Journal* in 2017, we outlined the various levels of evidence for different yellow-zone escalation strategies (including quadrupling ICS), as assigned in relevant international asthma guidelines, and found them to range from strong to consensus based.¹¹ We also reviewed primary evidence for adjusting ICS dose in the asthma action plan yellow zone and noted 3 negative trials of doubling the ICS dose and 2 positive trials of quadrupling.¹²⁻¹⁷ The latter include an RCT by Osborne and colleagues¹⁷ (mentioned by Dr McCormack in his letter¹) and another by Foresi and colleagues (which he did not mention),¹⁶ which showed statistically significant reductions in asthma exacerbations and days receiving oral corticosteroids in the quadrupling group versus standard therapy, with similar rates of adverse events.¹⁶ Since the publication of our original article,¹¹ a third positive trial, the largest to date, by McKeever and colleagues was published.¹⁸ These authors found a number needed to treat (NNT) of 14 people with quadrupling ICS doses to avoid a course of oral corticosteroids and an NNT of 17 to avoid unscheduled health care use (including a reduction in hospitalizations). In contrast with Dr McCormack, we contend that each of these represents a clinically significant reduction in an important health care event. For comparison, the widely accepted standard of care to provide patients experiencing acute exacerbations of chronic obstructive pulmonary disease with oral corticosteroids has an NNT of 10 to avoid treatment failure (hospital readmission or return to the emergency department), and a number needed to harm of 7.¹⁹ Although we agree with his argument that the systemic effects of high ICS doses are not negligible, and that local side effects such as oral candidiasis and dysphonia can occur, we believe these compare favourably with the demonstrated morbidity and mortality associated with severe asthma exacerbations, including the

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costs of urgent health care use and the known risks of systemic glucocorticoids.²⁰ Unlike high ICS doses, even short courses of systemic glucocorticoids carry a risk of avascular necrosis, viral infections, ocular hypertension and open-angle glaucoma in susceptible patients, severe mood changes and psychotic reactions, gastrointestinal upset, insomnia, weight gain, increased blood pressure, and perturbations in blood sugar in patients with diabetes.²¹⁻²³ It is also of note that the higher-than-expected exacerbation rate in the McKeever et al trial might have been a function of late activation of the asthma action plan—an issue that might also have affected the magnitude of the benefit and reinforces the importance of providing education alongside the asthma action plan.²⁴

This is not the first, nor will it be the last, scientific forum in which the observed magnitude of benefit of quadrupling ICS in the yellow zone of the asthma action plan will be debated. Accordingly, we strongly agree with Dr McCormack that the best approach is to present patients with the benefits and harms and to reach a conclusion based on shared decision making. However, we also strongly disagree with his conclusion that a reasonable alternative to an asthma action plan with quadrupling would be to just have “a discussion of what to look out for with regard to exacerbations and when to seek medical help” (suggesting that a written action plan is not needed).¹ With this statement, Dr McCormack appears to conflate the debate around dosing in the asthma action plan yellow zone with the benefits of asthma action plans themselves. It is critical to note that patients in the control arms of all the mentioned studies of yellow-zone ICS dosing received an asthma action plan.^{12,18} Accordingly, their results do not offer any insight into the benefits of asthma action plans themselves, and should not be misappropriated to challenge the well established literature supporting the use of asthma action plans. Aside from the dose intensification recommendation in the yellow zone, action plans likely affect outcomes through multiple other mechanisms, including by reinforcing adherence to green-zone (daily preventive) medications; by providing warning signs meriting urgent attention (averting deterioration into life-threatening asthma); and through general educational information (eg, trigger avoidance).²⁵

In conclusion, although we agree with Dr McCormack that more research is required, to date we believe that the balance of the evidence favours a recommendation to quadruple the ICS dose as part of the asthma action plan. Most important, asthma action plans remain a cornerstone of asthma management, and our focus must be to redouble efforts to help primary care physicians to deliver this complex intervention.

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Competing interests

None declared

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Breast cancer screening

In the Prevention in Practice article in the May issue of *Canadian Family Physician*, Dickinson and colleagues describe the quality of common screening tests to help family physicians “understand the issues they need to