

## Is there adequate evidence for quadrupling inhaled corticosteroid doses?

In an article in the February issue of *Canadian Family Physician*, Kouri et al promote an asthma action plan (“evidence-based tool”) that encourages quadrupling doses of inhaled corticosteroids for patients with worsening asthma.<sup>1</sup> The authors and other guideline writers have suggested the quadrupling recommendation is based on strong levels of evidence. Given that *strong* is a somewhat subjective term, I thought clinicians might find it of value to look in some detail at the best available evidence for this recommendation.

To date, 2 studies in adults with asthma have specifically looked at the effect of quadrupling inhaled corticosteroids as part of an asthma action plan. The details and results are outlined in **Table 1**.<sup>2,3</sup>

In 2009, Osborne et al showed in a 12-month double-blind trial a 5% non-statistically significant absolute reduction in the need for oral corticosteroids.<sup>2</sup> However, in those patients who actually started the study inhaler, they did show a statistically significant reduction in the need for oral corticosteroids but also an increase in adverse events.

In 2018, these same investigators showed in a 12-month open-label study that quadrupling the inhaled corticosteroid dose reduced severe exacerbations by 7%, but again, more people experienced adverse events.<sup>3</sup>

Assuming these results represent what one would actually see in practice, it appears a quadrupling action plan (note that not all people will need to invoke the action plan) will lead to a number needed to treat (NNT) of 14 people for the end point of not having to receive a course of oral corticosteroids. However, to get this benefit for 1 person you need to expose a number of people (roughly 5 or so if the baseline rate of exacerbations was about 50%) to 1 to 2 weeks of a quadrupling of the dose (800 µg increased to 3200 µg for the beclomethasone equivalent) of their inhaled corticosteroid. The authors of these studies state “the quadrupled dose in these participants could have had the same systemic effects on adrenal suppression as a course of prednisolone that is used to treat severe asthma exacerbations.”<sup>3</sup> While the evidence is incomplete, this amount of daily inhaled steroid is likely roughly equivalent systemically to 10 to 20 mg of daily prednisone.<sup>4</sup>

In addition, many guidelines recommend combination inhalers (steroid–long-acting β-agonist) as baseline asthma therapy, especially for those with poor control. Therefore, this action plan would require many patients to purchase an additional corticosteroid-alone inhaler to use if their asthma worsens. The cost would be anywhere from \$50 to \$150 and unfortunately these inhalers typically expire only about 1 year after purchase. Finally, for those who quadruple the dose there is a number needed to harm of roughly 20, primarily for candidiasis or dysphonia.

**Table 1.** Details and results of 2 studies in adults with asthma that examined the effect of quadrupling inhaled corticosteroids as part of an asthma action plan: *The Osborne et al study cohort was about 54 y of age and 39% male; the McKeever et al study cohort was about 56 y of age and 33% male.*

STUDY GROUP	OBORNE ET AL, <sup>2</sup> 2009 (N 403)			MCKEEVER ET AL, <sup>3</sup> 2018 (N 1922)			
	STARTED ORAL CS	ADVERSE EVENTS IN THOSE WHO STARTED THE INHALER*	SEVERE EXACERBATION†	STARTED ORAL CS	HOSPITALIZATION FOR ASTHMA	THOSE WHO REACHED ZONE 2 OF THEIR SELF MANAGEMENT PLAN*	
						NONSERIOUS ADVERSE EVENTS	ORAL CANDIDIASIS OR DYSPHONIA
Placebo or control <sup>§</sup>	14%	8% (3 of 38)	52%	40%	1.8%	2% (10 of 552)	1.6% (9 of 552)
Quadruple dose	9% <sup>  </sup>	16% (9 of 56)	45%	33%	0.3% <sup>¶</sup>	7% (41 of 562)	6.4% (36 of 562)

CS—corticosteroids.

\*23% of the cohort.

†Treatment with oral CS or an unscheduled health care consultation for asthma.

‡58% of the cohort.

§Placebo group in the study by Osborne et al<sup>2</sup> and control group in the study by McKeever et al.<sup>3</sup>

||Not statistically different; however, in those patients who actually started the study inhaler there was a statistically significant reduction: 50% (19 of 38) versus 21% (12 of 56).

¶No statistical tests reported.

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It is important to remember that both trials were done by the same investigators and the only study that showed a statistical benefit was an open-label trial. Of interest, a double-blind trial in which the dose of inhaled corticosteroid was quintupled showed no effect on clinical outcomes in children aged 5 to 11 years with mild to moderate asthma.<sup>5</sup>

Given the above, I would disagree this would be considered an adequate evidence base to justify a *carte blanche* recommendation of quadrupling the dose of inhaled corticosteroids. In fact, the authors of the 2 studies state that “a group of local general practitioners, asthma nurses, and asthma experts suggested that a reduction of one third in the number of people initiating a course of systemic glucocorticoids is a worthwhile treatment effect,” yet in their trial they reported only a relative reduction in exacerbations of 19%.<sup>3</sup> They also state “guideline committees will need to consider whether the magnitude of the reduction achieved is clinically meaningful.”<sup>3</sup>

A true evidence-based tool would include the concept of shared decision making and so, at a minimum, patients should be told that adopting a quadrupling of inhaled corticosteroids action plan will lead to an NNT of 14 (about a 7% absolute difference) for not having to start oral corticosteroids. But to achieve that NNT, a number of people (depending on the baseline exacerbation rate) will have to receive doses of inhaled corticosteroids for 7 to 14 days that would be systemically about half (10 to 20 mg) of what would be used for an exacerbation (Osborne et al used 30 mg of oral prednisone for exacerbations<sup>2</sup>). In addition, for those who quadruple the dose there is a number needed to harm of about 20 (a 5% absolute increase) primarily for candidiasis and dysphonia, and there is an additional inhaler cost and inconvenience to this action plan. Given this information, some might choose this option while others might just want a discussion of what to look out for with regard to exacerbations and when to seek medical help.

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#### Competing interests

None declared

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## Value of monkey bars?

As an 8-year-old I fell from monkey bars that were 8 feet tall (I was half that height), with my elbow striking a rock conveniently placed beneath them. I had a complex fracture that led to external fixation and a lifelong gunstock deformity but no other sequelae. I spent 3 weeks in traction, during which time I read the *Golden Book Encyclopedia* from A to Z, much to my doctor's amazement. I am now an academic family physician, and a dual Canadian-American national, and can twist my left arm in ways that both amaze and disgust my younger relatives.

Of course, play cannot and should not be without risk. But reasonable bounds should be put in place to mitigate the risk of serious injury (ie, assuring age-appropriate heights for falls, removing rocks, and eliminating equipment that could lead to rare but catastrophic spinal injuries). The authors of the rapid systematic review on playground injuries in the March issue of *Canadian Family Physician* appear to minimize the suffering of 1500 hospitalized children per year in Canada alone, and fail to cite high-quality evidence that risky play provides greater social and intellectual benefits than less risky or safe play.<sup>1</sup>

Bad things happen rarely. But just because your child is fortunate enough to go through childhood unharmed despite a *laissez-faire* attitude, it does not mean you should broadly advocate for it without better evidence that the small potential benefits for all outweigh the rare but severe harms to the few.

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#### Competing interests

None declared

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## Link between dietary changes and tinnitus management

I congratulate Dr Wu and colleagues for their very good and practical clinical review of tinnitus management in the July 2018 issue of *Canadian Family Physician*.<sup>1</sup> As part of conservative management, the authors also recommend reducing caffeine consumption.<sup>1</sup> As a nutrition scientist, I am surprised because there is no supporting empirical scientific evidence for the commonly advocated restriction of caffeine for tinnitus patients.<sup>2</sup>

Dietary changes are also named as a management strategy in the case resolution of the article.<sup>1</sup> However, there was still no well-founded review on the nutritional modifications that are repeatedly discussed among patients as well as doctors. I would like to point out the following: In the March 2019 issue of the *Australian Journal of General Practice*, my article titled “Do dietary factors significantly influence tinnitus?” was published.<sup>2</sup> It would be desirable for family physicians and *Canadian*