The most fundamental change in asthma management in 30 years?

To the Editor:

We would like to raise our considerable concern regarding a potential major change in the management of exacerbations of asthma which is soon to be discussed in the European Union (EU). The Global Initiative for Asthma (GINA) has recently changed their recommendation regarding management of patients with mild asthma. Instead of using only short-acting β_2-agonist (SABA) as needed, GINA suggests that all patients should also be using inhaled corticosteroids (ICS) simultaneously. This was based on a few studies that have used "as needed" ICS/long-acting β_2-agonist (LABA) for acute asthma. A group of authors has hailed this change as "the most fundamental change in asthma management in 30 years" and explained, in detail, the reasons for the change in an article recently published in the *European Respiratory Journal* [1].

Almost all data on as-needed ICS/LABA for asthma exacerbations were obtained using a dry-powder inhaler (DPI) formulation of budesonide/formoterol that is not available in the USA [2] and has never received US Food and Drug Administration/European Medicines Agency approval for use in acute asthma.

The change in recommendations by GINA leave few, if any, alternatives to this specific drug formulation and device, neither does it take account age groups that may not be able to use these devices, such as children, the aged or cognitively impaired. Currently there is only one European company that manufactures and markets this specific formulation/device combination. It should be of considerable concern that out of the 18 authors of this recently published manuscript, 12 (including all leading authors) have reported financial ties with that company.

Before the EU embraces the suggested GINA guideline change, the rather extensive ramifications should be discussed and the changes confirmed by an independent body of experts in asthma management including pharmacologists, adult and paediatric pulmonologists, internists and family practitioners with no potential conflicts of interest.

Finally, particularly in the USA, where off-label therapies may not be covered, this could cause considerable hardship for patients whose insurance would not reimburse the extremely high cost of albuterol pressurised metered-dose inhaler and formoterol DPI units.

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Conflict of interest: I. Amirav has nothing to disclose. M.T. Newhouse is employed by InspiRx Pharmaceuticals Inc. as the Chief Medical Officer and has patents through InspiRx Pharmaceuticals Inc. (6,470.882; 8,119,016; D 689,602; D 685,085; and D 686725; pending: US 2012/0318261 and 2012/0318265).

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References

1 Reddel HK, FitzGerald JM, Bateman ED, *et al.* GINA 2019: a fundamental change in asthma management: treatment of asthma with short-acting bronchodilators alone is no longer recommended for adults and adolescents. *Eur Respir J* 2019; 53: 1901046.

2 Sobieraj DM, Weeda ER, Nguyen E, *et al.* Association of inhaled corticosteroids and long-acting β-agonists as controller and quick relief therapy with exacerbations and symptom control in persistent asthma: a systematic review and meta-analysis. *JAMA* 2018; 319: 1485–1496.

From the author:

I. Amirav and M.T. Newhouse have commented on the April 2019 recommendations by the Global Initiative for Asthma (GINA) that, for safety, adults and adolescents with asthma should not be treated with short-acting bronchodilators alone, and that instead, to reduce the risk of serious exacerbations, they should receive either symptom-driven (in mild asthma) or daily ICS-containing treatment (www.ginasthma.org/reports). The background evidence and rationale for the GINA recommendations were further explained in an editorial published in the *European Respiratory Journal* [1].

While discussion about the GINA recommendations is welcomed, an error in the authors' opening sentence must be corrected. The key changes in GINA 2019 are not about the "management of exacerbations of asthma" or "acute asthma" as stated, but about treatment of day-to-day asthma symptoms to prevent exacerbations. These recommendations were also integrated by GINA into home-based management of worsening asthma, but there is inadequate evidence to date about treatment of acute asthma with ICS–formoterol, with only two studies in emergency departments [2, 3]. In such settings, short-acting β_2-agonists (SABAs) are still recommended [4].

The evidence supporting the new GINA recommendations for adults and adolescents was not, as claimed by I. Amirav and M.T. Newhouse, limited to "a few studies that have used 'as needed' ICS/LABA for acute asthma". Instead, as described in the *European Respiratory Journal* editorial [1], it included decades of evidence about the risks of treating asthma only with SABA, the substantial reduction in this risk with low dose ICS in population studies and randomised controlled trials even when symptoms were infrequent [5], and two large studies in over 8000 patients with mild asthma showing that the benefits of as-needed low dose ICS–formoterol were obtained without the need for daily treatment, and with <25% of an already low comparator ICS dose [6, 7]. GINA also took into account poor adherence with ICS in mild asthma, and the confusion (from the patient's perspective) in promoting SABA for symptom relief in Step 1 but then in Step 2 recommending regular ICS treatment in order to reduce use of SABA. Two additional randomised controlled trials of as-needed low dose ICS–formoterol in mild asthma have been published subsequently [8, 9].

The authors stated their concerns that most of the data about as-needed ICS–LABA were obtained with a specific dry powder device. However, in patients with moderate to severe asthma, a similar reduction in risk of severe exacerbations was found [10] in studies that instead used a pressurised metered-dose inhaler to deliver budesonide–formoterol [11] or beclometasone–formoterol [12], suggesting that neither the device nor the specific ICS is crucial to this benefit. Globally, several low dose ICS–formoterol formulations and devices are available that may be suitable for an as-needed regimen in mild asthma.

With regard to patients' ability to use inhalers, there was no evidence in the recent studies [8, 9] of differential outcomes between younger and older adults. There is an obvious evidence gap for children with mild or intermittent asthma, for whom, to reduce the risks of SABA-only treatment, GINA suggests considering a strategy used in several studies of taking a low dose ICS inhaler whenever they use their SABA inhaler [13, 14].

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The authors raised concerns about potential conflicts of interest by GINA members, but in the context of their criticism of a dry powder device, one author notably failed to declare, until requested by the Editors, that he is employed by a manufacturer of aerosol delivery devices. All members of the GINA Science Committee and Board are active asthma researchers and, as described in the *European Respiratory Journal* editorial [1], the studies of as-needed low dose ICS–formoterol were initiated by GINA members rather than by a manufacturer. Before the 2019 recommendations were developed, the GINA Board undertook a careful review of processes for handling potential conflicts of interest; information about methodology is available on the GINA website (https://ginasthma.org/about-us/methodology/). The randomised controlled trials contributing to the GINA recommendations have already been reviewed by independent experts, including by national guideline bodies and regulatory authorities in several countries.

Finally, to the issue of medication access, the authors rather puzzlingly claim that, due to "the extremely high cost of albuterol pressurised metered-dose inhaler and formoterol DPI units", the GINA recommendations would cause potential hardship for patients in the USA if off-label therapies were not covered. The GINA report is a global strategy and GINA strongly supports efforts to improve global medication access, including for patients in low- and middle-income regions. However, GINA's recommendations, particularly about safety, as in the present case, cannot wait for access to be achieved in every country. It is for each country and jurisdiction to determine at a local level the options best suited to their resources and needs in order to reduce the burden of asthma exacerbations and mortality, including in mild asthma.

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References

1 Reddel HK, FitzGerald JM, Bateman ED, *et al.* GINA 2019: a fundamental change in asthma management: treatment of asthma with short-acting bronchodilators alone is no longer recommended for adults and adolescents. *Eur Respir J* 2019; 53: 1901046.
2 Balanag VM, Yunus F, Yang PC, *et al.* Efficacy and safety of budesonide/formoterol compared with salbutamol in the treatment of acute asthma. *Pulm Pharmacol Ther* 2006; 19: 139–147.
3 Bateman ED, Fairall L, Lombardi DM, *et al.* Budesonide/formoterol and formoterol provide similar rapid relief in patients with acute asthma showing refractoriness to salbutamol. *Respir Res* 2006; 7: 13.
4 Global Initiative for Asthma (GINA). Global Strategy for Asthma Management and Prevention. 2019. Available from: http://ginasthma.org/
5 Reddel HK, Busse WW, Pedersen S, *et al.* Should recommendations about starting inhaled corticosteroid treatment for mild asthma be based on symptom frequency: a post-hoc efficacy analysis of the START study. *Lancet* 2017; 389: 157–166.
6 O'Byrne PM, FitzGerald JM, Bateman ED, *et al.* Inhaled combined budesonide-formoterol as needed in mild asthma. *N Engl J Med* 2018; 378: 1865–1876.
7 Bateman ED, Reddel HK, O'Byrne PM, *et al.* As-needed budesonide-formoterol *versus* maintenance budesonide in mild asthma. *N Engl J Med* 2018; 378: 1877–1887.
8 Beasley R, Holliday M, Reddel HK, *et al.* Controlled trial of budesonide-formoterol as needed for mild asthma. *N Engl J Med* 2019; 380: 2020–2030.
9 Hardy J, Baggott C, Fingleton J, *et al.* Budesonide-formoterol reliever therapy *versus* maintenance budesonide plus terbutaline reliever therapy in adults with mild to moderate asthma (PRACTICAL): a 52-week, open-label, multicentre, superiority, randomised controlled trial. *Lancet* 2019; 394: 919–928.
10 Sobieraj DM, Weeda ER, Nguyen E, *et al.* Association of inhaled corticosteroids and long-acting β-agonists as controller and quick relief therapy with exacerbations and symptom control in persistent asthma: a systematic review and meta-analysis. *JAMA* 2018; 319: 1485–1496.
11 Patel M, Pilcher J, Pritchard A, *et al.* Efficacy and safety of maintenance and reliever combination budesonide–formoterol inhaler in patients with asthma at risk of severe exacerbations: a randomised controlled trial. *Lancet Respir Med* 2013; 1: 32–42.
12 Papi A, Corradi M, Pigeon-Francisco C, *et al.* Beclometasone–formoterol as maintenance and reliever treatment in patients with asthma: a double-blind, randomised controlled trial. *Lancet Respir Med* 2013; 1: 23–31.

13 Martinez FD, Chinchilli VM, Morgan WJ, *et al.* Use of beclomethasone dipropionate as rescue treatment for children with mild persistent asthma (TREXA): a randomised, double-blind, placebo-controlled trial. *Lancet* 2011; 377: 650–657.
14 Sumino K, Bacharier LB, Taylor J, *et al.* A pragmatic trial of symptom-based inhaled corticosteroid use in African-American children with mild asthma. *J Allergy Clin Immunol Pract* 2019; in press [https://doi.org/10.1016/j.jaip.2019.06.030].