Asthma: quadrupling the dose of inhaled corticosteroids reduces the number of severe asthma exacerbations

An open-label randomised controlled trial (RCT), in adults and young people with asthma aged 16 and over, compared a self-management programme that gave people the option to increase the dose of their inhaled corticosteroid (ICS) for a limited time if their asthma deteriorated. Quadrupling the ICS dose in the single steroid inhaler significantly reduced the number of people who had a severe asthma exacerbation compared with those who did not have the option to quadruple the dose (45% versus 52%). These findings are consistent with the current NICE guidance on asthma: diagnosis, monitoring and chronic asthma management, advising that quadrupling the dose of ICS can be considered in the context of a self-management programme.

Overview and current advice

Asthma is characterised by exacerbations of breathlessness and wheezing. The severity and frequency of these exacerbations can vary from person to person but, if left untreated, can be life-threatening.

Inhaled corticosteroids (ICS) are the first-choice regular preventer therapy for adults, young people and children with asthma. The NICE guideline on asthma: diagnosis, monitoring and chronic asthma management, recommends increasing the dose of ICS in a self-management programme for people who are using an ICS in a single inhaler. Adults, young people and children aged 5 and over with a diagnosis of asthma should be offered a self-management programme, comprising a written personalised action plan and education. An action plan should include a clear outline of how and when to increase their dose of ICS for 7 days if their asthma control deteriorates and what to do if their symptoms do not improve. If the plan gives the option to quadruple the ICS dose the maximum licensed daily dose should not be exceeded.

The NICE key therapeutic topic on asthma: medicines safety priorities brings together the evidence base, resources and safety alerts for managing asthma. The NICE pathway on asthma brings together all related NICE guidelines and associated products on asthma in a set of interactive topic based diagrams.

New evidence

An open-label RCT (McKeever et al. 2018) of 1,922 UK adults and young people aged 16 and over with a diagnosis of asthma who were currently being treated with ICS was conducted. It investigated the effect of adding the option of quadrupling the ICS dose to the self-management programme.
(n=957) compared with the self-management programme without this option (n=965), on the number of people who had severe exacerbations. Study participants needed to be currently treated with ICS in a single inhaler and needed to have had at least 1 exacerbation within the previous year requiring treatment with systemic corticosteroids. The mean (SD) age of participants was 57±15 years, 68% were female and 78% of participants were receiving a dose of beclomethasone, or an equivalent corticosteroid, of 1,000 micrograms per day or less. The majority of participants (81%) were identified in primary care and the rest were identified in secondary care. Participants were followed up at 6 and 12 months.

All participants were given an asthma self-management programme containing advice on identifying deterioration in asthma control. A deterioration was defined as the person having 1 or more of:

1. needing to use their reliever inhaler more than usual
2. having more difficulty sleeping because of their asthma
3. a peak flow below 80% of their normal reading.

The action to take if the participant’s asthma control deteriorated was the same in both groups with the exception of the following:

1. Quadrupling group:
   a. “Use your reliever inhaler to relieve your symptoms and quadruple your inhaled glucocorticoid dose as described."
   b. “Once your symptoms or peak flow have returned to normal or after a maximum of 14 days, return to your normal treatment.”
2. Non-quadrupling group:
   a. “Use your reliever inhaler to relieve your symptoms and continue your inhaled glucocorticoid medication at your normal dose.”

The trial was designed to be pragmatic and it was the participant’s decision whether they increased the dose of the ICS or not. A similar number of participants experienced a deterioration in asthma control in the quadrupling (57.2%, 522/965) and non-quadrupling groups (58.7%, 562/957). Approximately half of participants in the quadrupling group who experienced a deterioration in their asthma control reported quadrupling their ICS dose (50.2%, 282/562). This compared with 18.5% (102/552) of participants in the non-quadrupling group.

The primary efficacy outcome reported was the time to first severe asthma exacerbation. The authors defined this as an exacerbation requiring treatment with systemic corticosteroids or an unscheduled health care consultation for asthma. The number of participants who had a severe asthma exacerbation was significantly reduced in the quadrupling group (45%, 420/933) compared with the non-quadrupling group (52%, 484/938). The authors reported an adjusted hazard ratio for the time to first severe exacerbation of 0.80 (95% confidence interval [CI], 0.71 to 0.92, p=0.001).

Use of systemic corticosteroids was additionally reduced in the quadrupling group when compared with the non-quadrupling group, 33% (311/933) versus 40% (377/938), incidence rate ratio 0.82 (95% CI, 0.70 to 0.96). The authors also calculated the estimated mean total dose of ICS and systemic corticosteroids during the course of the trial. There was lower steroid intake in the non-quadrupling group compared with the quadrupling group overall; the mean dose of ICS was 385 mg in the quadrupling group and 328 mg in the non-quadrupling group and the mean dose of systemic corticosteroids was 121 mg and 151 mg, respectively. Unscheduled health care consultations were less frequent in the quadrupling group (41%, 379/933) compared with the non-quadrupling group (47%, 442/938), incidence rate ratio 0.86 (95% CI, 0.75 to 0.99).

There were 3 incidences of hospitalisation for asthma in the quadrupling group and 18 incidences in the non-quadrupling group. In the 14 days following the deterioration of asthma control, as defined by
the action plan, 7% (41/562) reported a total of 56 non-serious adverse events in the quadrupling group compared with the 2% (10/552) reporting a total of 13 non-serious adverse events in the non-quadrupling group. The most frequently reported adverse events were oral thrush and dysphonia (hoarseness). Statistical significance was not reported for these safety outcomes.

The authors state that the trial had many strengths including its pragmatic design, 80% recruitment in primary care and broad inclusion criteria leading to its external validity and generalisability to practice. Limitations include the open-label design with the lack of a placebo control, where the intervention could have influenced the behaviour of participants and clinicians, introducing bias. There was poor reporting of corticosteroid use across both groups of participants who experienced a deterioration in asthma control, with 28.5% (160/562) in the quadrupling group and 39.3% (217/552) in the non-quadrupling group not providing a report. There was also a high dropout rate at 12 months with only 71% (679/957) in the quadrupling group and 73% (700/965) in the non-quadrupling group attending their final visit. Most participants were taking less than 1000 micrograms of ICS per day and these findings may not be generalisable to people who need higher doses or those who have more severe asthma.

**Commentary**

*Commentary provided by NICE*

The findings of this study support the current NICE recommendation to consider quadrupling the ICS dose in the context of a self-management programme in people with a deterioration in their asthma control. This recommendation is based on a smaller RCT (n=94) where the number of severe exacerbations requiring oral corticosteroids were reduced in the quadrupling group compared with the fixed dose group, risk ratio 0.43 (95% CI, 0.24 to 0.78, Oborne et al. 2009). The committee considered the benefits and harms of quadrupling the baseline ICS dose in times of a mild exacerbation and concluded that a short-term increase in ICS was unlikely to result in significant adverse events, and the benefits of reducing exacerbations and subsequent oral steroid use outweigh the risks (NICE guideline *asthma: diagnosis, monitoring and chronic asthma management*).

The study by McKeever et al. differs to that by Oborne et al. in that it had a pragmatic study design and larger sample size. The effect size seen in this study is smaller than that seen in Oborne et al. with the authors reporting a 19% reduction in exacerbation rates. The authors stated that a 30% reduction in exacerbations was considered clinically meaningful at the point of study design, however it is not clear where the clinically meaningful reduction in exacerbations was derived. The pragmatic study design may have contributed to the difference seen between studies, as participants in McKeever et al. were able to increase or decrease their ICS dose regardless of their randomisation to either group. It would be useful to understand the reasons for participants opting not to quadruple their dose in the quadrupling group but no commentary was provided on this by the authors.

Side effects associated with ICS use are well established and the common side effects were seen in this study, including the local effects of oral thrush and hoarseness. People who are prescribed ICSs should be advised about the common side effects and how to prevent them, including: not exceeding the maximum daily dose, using the shortest duration possible, oral hygiene practices such as rinsing the mouth with water after use and using correct inhaler technique. The NICE key therapeutic topic on *asthma: medicines safety priorities*, states that people who are prescribed ICS should be observed for inhaler technique and given advice when there is deterioration in asthma control.

It is important to note that the findings of this study and the NICE recommendation on quadrupling the regular ICS dose only apply to people who are using ICS in a single inhaler. Many ICSs are taken in a combination inhaler with long-acting beta agonists (LABAs). Care is needed when considering the approach in people taking combination inhalers.
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References


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