# On demand use of $\beta_2$ agonists led to better asthma control than regular use in moderate to severe asthma

*Richter B, Bender R, Berger M.* ***Effects of on-demand $\beta_2$-agonist inhalation in moderate-to-severe asthma. A randomized controlled trial.*** *J Intern Med 2000 Jun;**247**:657–66.*

**QUESTION:** In patients with moderate to severe asthma, is on demand use of $\beta_2$ agonists as effective and safe as regular use?

## Design
Randomised {allocation concealed*}†, blinded (outcome assessors and statistician),* crossover trial with 24 weeks follow up for each treatment condition.

## Setting
Outpatient clinic at Düsseldorf University Medical Centre in Germany.

## Patients
80 patients (mean age 48 y, 74% women) with moderate to severe asthma on regularly scheduled $\beta_2$ agonist (minimum daily intake of 6 puffs) and inhaled corticosteroids (ICS) for ≥2 years. Exclusion criteria were non-respiratory illnesses or pregnancy. 73 patients (91%) completed the study.

## Intervention
Two 24 week periods in which patients were allocated to on demand inhalation (salbutamol or fenoterol) or regular use of $\beta_2$ agonist (2 inhalations 4 times daily plus salbutamol or fenoterol on demand) and crossed over to the other regimen after completion of the first period. All patients used constant doses of inhaled corticosteroids.

## Main outcome measures
The primary outcome measure was asthmatic episodes defined as an asthma attack that could only be treated by $\beta_2$ agonist inhalation. Secondary outcome measures were safety and consequences of reducing $\beta_2$ agonist.

## Main results
The treatment groups did not differ for asthmatic episodes and exacerbations (66% of symptom free days in on demand treated patients *v* 62% in regularly treated patients). However, daytime use of $\beta_2$ agonist was lower in on demand treated patients than in regularly treated patients (3.3 *v* 7.9 puffs/d, $p < 0.001$). Patients in the on demand group also had fewer days of prednisone use for asthma exacerbations than did those in the regular use group (mean of 44 *v* 52 d, $p = 0.001$). $FEV_1$, FVC, and midexpiratory flow rate at 25% to 75% of FVC were all higher in patients in the on demand group than in those in the regular use group (2.53 *v* 2.42 l, $p = 0.008$; 3.66 *v* 3.54 l, $p = 0.003$; 1.85 *v* 1.74 $ls^{-1}$, $p = 0.02$, respectively). The groups did not differ for immunoglobulin E, peripheral blood eosinophils, or other blood chemistry values or for changes in unwanted effects in concomitant medications.

## Conclusion
In patients with moderate to severe asthma, on demand $\beta_2$ agonist inhalation led to better asthma control than regular $\beta_2$ agonist inhalation.

*See glossary.
†Information provided by author.

## COMMENTARY

The β agonist controversy revolves around the question of whether sustained and regular use of inhaled β adrenergic agents results in decreased bronchodilator responsiveness over time and has been addressed in epidemiological and controlled prospective trials.[1,2] Most recently, the Asthma Clinical Research Network study found no difference between patients with mild asthma who were randomly allocated to regularly scheduled or as needed albuterol over a 16 week period.[3] Richter *et al* compared the effects of short acting inhaled bronchodilators over 24 weeks in a more symptomatic patient population.

Several design and methodological issues deserve comment. Firstly, although patients were required to have used ICS for a minimum of 2 years before enrolment, no protocol was provided for titrating to a minimum effective dose of ICS before randomisation. This would have increased the potential for patients to destabilise during the study and thereby show a difference between treatment groups. Secondly, medication compliance was not directly assessed but was extrapolated from adherence to scheduled clinic visits and completeness of diary cards. Thirdly, the crossover design did not include a washout period between treatments, which is inappropriate if the hypothesis being tested is that extended exposure to β agonists results in down regulation of the receptor. Finally, patients in this study were not blinded. For such a disease as asthma with subjective and effort dependent end points, this is clearly suboptimal.

What should the practitioner take from this study? At the least, this study and others show that regular use of short acting inhaled β agonists do not confer added benefit over those used on an as needed basis. The addition or optimisation of ICS treatment with subsequent addition of other treatments as required is a preferable management strategy.[4]

Peter K Honig, MD
*Food and Drug Administration*
*Rockville, Maryland, USA*

1 Sears MR, Taylor DR. The beta 2-agonist controversy. Observations, explanations and relationship to asthma epidemiology. *Drug Saf* 1994;**11**:259–83.
2 Lipworth B, Tan S, Devlin M, *et al.* Effects of treatment with formoterol on bronchoprotection against methacholine. *Am J Med* 1998;**104**:431–8.
3 Drazen JM, Israel E, Boushey HA, *et al.* Comparison of regularly scheduled with as-needed use of albuterol in mild asthma. Asthma clinical research network. *N Engl J Med* 1996;**19**:841–7.
4 National Heart, Lung, and Blood Institute. *National asthma education and prevention program expert panel report 2: guidelines for the diagnosis and management of asthma.* US Department of Health and Human Services. Bethesda, MD: National Institutes of Health; 1997; DHHS publication no. 97-4051.

*Source of funding: no external funding.*

*For correspondence: Dr B Richter, Heinrich-Heine-Universität Düsseldorf, Klinik für Stoffwech-selkrankheiten und Ernährung, Moorenstrasse 5, Postfach 101007, D-40001 Düsseldorf, Germany. richterb@uni-duesseldorf.de.*

*A modified version of this abstract also appears in Evidence-Based Nursing.*