

Is nedocromil effective in preventing asthmatic attacks in patients with asthma?

■ EVIDENCE-BASED ANSWER

Nedocromil (Tilade) is effective for the treatment of mild persistent asthma. It has not been shown to be effective in more severe forms of asthma for both children and adults. Although no studies looked specifically at exacerbation rates, multiple clinical and biologic outcomes (symptom scores, quality of life measures, bronchodilator use, forced expiratory flow in 1 second [FEV₁], and peak expiratory flow rate [PEFR]) improved with nedocromil use compared with placebo.

The most effective dose for preventing exacerbations appears to be 4 mg (2 puffs) 4 times a day (SOR: **A**, multiple randomized controlled trials [RCTs] and meta-analyses). More severe forms of asthma respond better to inhaled steroids than to nedocromil (SOR: **A**, multiple RCTs). Nedocromil may allow some patients with severe asthma to use lower doses of inhaled steroids (SOR: **C**, conflicting RCTs). Nedocromil is also effective for the treatment of exercise-induced asthma (SOR: **A**, multiple RCTs and meta-analyses).

In general, about 50% to 70% of patients respond to nedocromil (SOR: **A**, multiple RCTs and meta-analyses). Unfortunately, which patients respond is not predictable from clinical parameters.¹ Nedocromil is worth trying in mild persistent asthma, particularly for children where the parents are worried about the growth issues associated with inhaled steroids. Side effects (sore throat, nausea, and headache) are mild and infrequent. Maximal efficacy is usually seen after 6 to 8 weeks.

■ EVIDENCE SUMMARY

A systematic review encompassing 127 trial centers and 4723 patients concluded that inhaled nedocromil was effective for a variety of patients with asthma. Significant improvements were noted in FEV₁, PEFR, use of bronchodilators,

symptom scores, and quality of life scores. The reviewers found nedocromil to be most effective for patients with moderate disease already taking bronchodilators,² corresponding to the “mild persistent asthma” category (**Table**).

A contemporaneous European RCT, not included in the review, compared 4 mg of inhaled nedocromil 4 times daily with inhaled placebo among 209 asthmatic children for 12 weeks.³ After 8 weeks, they found a statistically significant reduction in total daily asthma symptom scores (50% nedocromil vs 9% placebo; $P < .01$). The proportion of parents and children rating treatment as moderately or very effective was 78% in the treatment group and 59% in the placebo group (number needed to treat [NNT]=5.2; $P < .01$); clinicians' ratings were 73% for nedocromil and 50% for placebo (NNT=4.3; $P < .01$). The frequency of side effects—including nausea, headache, and sleepiness—did not reach statistical significance; however, the nedocromil group reported up to a 20% incidence of sore throat. Most of the studies reported no dropouts due to side effects.

When patients are already using inhaled steroids, the evidence is less clear whether nedocromil confers additional benefits, such as fewer exacerbations or lower inhaled steroid doses. Two small studies of patients either already on inhaled steroids⁴ or considered to be steroid-resistant⁵ found nonsignificant trends towards reductions in bronchodilator use, increased PEFR, increased FEV₁, and improved quality of life. Although both studies were underpowered, the study on steroid-resistant asthma did find a statistically significant 20% improvement in PEFR and decreased bronchodilator use for 50% of patients at 8 and 12 weeks.

The inherent waxing and waning nature of asthma makes demonstrating benefits difficult. Furthermore, nedocromil tends to have an all-or-nothing effect rather than a dose-response gradient. Unfortunately, none of these trials found useful predictors to help clinicians determine which patients respond.^{1,5}

In a Cochrane Review, 20 RCTs involving 280

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TABLE		
Classification of asthma		
Classification	Symptom frequency	Spirometry findings
Severe persistent	Continual symptoms	PEFR <60% Variability >30%
Moderate persistent	Daily symptoms, more than 1 night per week	PEFR >60% but <80% Variability >30%
Mild persistent	More than twice per week but less than daily; more than 2 nights per month	PEFR >80% Variability 20%–30%
Mild intermittent	Less than once per week; less than or equal to 2 nights per month	PEFR >80% Variability <20%

Source: Global Initiative for Asthma, National Heart, Lung and Blood Institute 2003.⁷

participants showed that 4 mg (2 puffs) of nedocromil inhaled 15 to 60 minutes prior to exercise significantly reduced the severity and duration of exercise-induced asthma for both adults and children. The maximum percentage fall in FEV₁ improved significantly compared with placebo, with a weighted mean difference of 15.5% (95% confidence interval, 13.2–18.1). In addition, the time to complete recovery was shortened from 30 minutes with placebo to 10 minutes with nedocromil.⁶

■ **RECOMMENDATIONS FROM OTHERS**

The Global Initiative for Asthma and the National Heart, Lung and Blood Institute Expert Panel Report list nedocromil as an option for the treatment of exercise-induced asthma and mild persistent asthma for adults and children. However, it is listed as a second choice to the use of inhaled steroids in the case of mild persistent asthma. It is not recommended for moderate or severe persistent asthma, or for mild intermittent asthma.⁷

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■ **CLINICAL COMMENTARY**

Nedocromil and cromolyn sodium are safe but many patients do not respond

Inhaled nedocromil and cromolyn sodium have long been recognized as agents with an excellent safety profile. Unfortunately, as pointed out above, many patients do not respond to these agents. In addition, 4-times-daily dosing makes compliance difficult. Clinicians and parents must weigh the theoretical risk of inhaled corticosteroid-induced growth retardation with this potential differential in effectiveness.

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