

Nedocromil sodium in the treatment of exercise-induced asthma: a meta-analysis

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Nedocromil sodium in the treatment of exercise-induced asthma: a meta-analysis. C. Spooner, B.H. Rowe, L.D. Saunders. ©ERS Journals Ltd 2000.

ABSTRACT: Exercise-induced asthma (or bronchoconstriction) afflicts millions of people worldwide. While generally self-limiting, it can hinder performance and reduce activity levels, thus it is an important condition to diagnose and treat. The objective of this review was to assess the prophylactic effect of a single dose of nedocromil sodium on exercise-induced asthma.

The Cochrane Airways Group trials register, the Cochrane Controlled Trials Register, Current Contents, reference lists of relevant articles, review articles and textbooks were searched for randomized trials comparing a single dose of nedocromil to placebo to prevent exercise-induced asthma in people >6 yrs of age. Authors and the drug manufacturer were contacted for additional trials. Trial quality assessments and data extraction were conducted independently by two reviewers. Authors were contacted when possible.

Twenty trials were included. All were rated as having good methodological quality. Nedocromil inhibited bronchoconstriction in all age groups. The pooled weighted mean difference for the maximum percentage fall in forced expiratory volume in one second was 15.6%, (95% confidence interval (95% CI): 13.2–18.1) and for the peak expiratory flow was 15.0% (95% CI: 8.3–21.6). These differences are both statistically and clinically significant. After nedocromil the time to recover normal lung function was <10 min compared to >30 min with placebo. Nedocromil had a greater effect on people with a fall in lung function of >30% from baseline. There were no significant adverse effects reported with this short-term use.

In conclusion, Nedocromil taken before exercise appears to reduce the severity and duration of exercise-induced bronchoconstriction. This effect appears to be more pronounced as severity increases.

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Exercise-induced asthma (EIA) is a transient increase in airway resistance resulting from bronchoconstriction that occurs following 6–8 min of strenuous exercise [1]. A postexercise fall of $\geq 10\%$ in either the forced expiratory volume in one second (FEV₁), or the peak expiratory flow rate (PEFR) compared with pre-exercise baselines, is considered diagnostic [2, 3]. An episode of EIA is associated with various symptoms *e.g.* cough, wheeze, shortness of breath, chest tightness, even stomach pain and nausea. It can result in limited endurance during, and prolonged recovery time following, the exercise. Generally, the bronchoconstriction peaks within 3–15 min post-exercise, then spontaneously returns to pre-exercise levels within 20–60 min [4].

The true prevalence of EIA is difficult to estimate. While it may exist as a single entity, 60–90% of people with asthma experience EIA and consider exercise a major trigger of their asthma symptoms [1, 5]. Furthermore, it is not uncommon for asthmatics to be adequately managed and enjoy normal lung function at rest, yet still suffer significant EIA on vigorous exercise [6]. Besides asthmatics, 35–40% of those with allergic rhinitis [7] and 12–15% of the general population also suffer from the disorder [8]. EIA is the most common respiratory problem seen in recreational and competitive sports (3–14%) but unfortunately, is regularly under-diagnosed and untreated and

thereby has the potential to severely limit the performance of athletes [9, 10].

The severity of an EIA episode is related to the degree of underlying bronchial reactivity [11]. Ambient air conditions, antigens, air pollutants, or respiratory viruses can all increase bronchial reactivity and exercising while exposed to these stimuli can provoke a severe reaction and even anaphylaxis [5, 12, 13]. Short-acting β_2 -agonists, effective in reversing the bronchoconstriction, may be required when the FEV₁ or PEFR decreases by 25–30% [14]. A small subset of asthmatics experience a second, less severe, late-phase reaction several hours after the original activity [5, 12].

One goal of treatment is to prevent or at least attenuate the EIA response so respiratory limitations do not restrict activity choices and achievement levels. Traditionally, short-acting β_2 -agonist bronchodilating agents have been the treatment of choice. However, with better understanding of the primary role of inflammatory mediators and inflammation in the pathophysiology of asthma, several other drugs have been investigated for their potential to protect against bronchoconstriction. Nedocromil sodium (NCS) is a mast cell stabilizing agent introduced in the 1980s, reportedly effective on a single-use basis for inhibiting bronchoconstriction due to antigens, fog, cold air, sulphur dioxide, and exercise [15, 16]. If effective and safe in

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EIA, these properties would make it an attractive therapeutic option for active people and one that may have the added benefit of diminishing/attenuating the late-phase reaction.

This meta-analysis examined the available randomized controlled clinical trial evidence on the use of NCS to prevent or attenuate EIA. To the authors' knowledge, no previous systematic reviews on this topic area have been published.

Methods

The protocol for this study was prepared prior to searching for trials, and it was reviewed and approved by the Editorial team of the Cochrane Airways Review Group (ARG).

Inclusion criteria

Only randomized controlled trials were included in this systematic review. Those trials comparing a single prophylactic dose of NCS to a placebo in asthmatic individuals (child ≥ 6 yrs or adult ≥ 18 yrs) with objective, reproducible evidence of EIA, were considered for inclusion. EIA was defined as a fall in either the FEV₁ or the PEF_R of at least 10%. If studies had more than one drug arm, only the comparison of NCS to placebo was included. Studies using nasal sprays were excluded.

Outcome measures

All patient outcomes were considered, however, the two main outcomes of interest were the effect of treatment on the maximum percentage decrease in pulmonary function and on function over the first 30 min of recovery postexercise.

The conventional method of quantifying the severity of EIA is to calculate the per cent fall index, which is the maximum reduction in lung function postexercise expressed as a per cent of the pre-exercise value. In addition, it is useful to establish the effect of drug therapy by determining the degree of protection from airway obstruction offered by the active drug compared to placebo (or other drug) [6].

The following formulae are used to determine these indices:

$$\text{Maximum \% fall index (FEV}_1 \text{ or PEF}_R \text{)} = \frac{\text{imm pre value} - \text{min post value}}{\text{pre value}} \times 100, \quad (1)$$

where imm=immediate; pre=pre-exercise; and post=post-exercise.

$$\text{Per cent protection index} = \frac{\text{max fall placebo (\%)} - \text{max fall NCS (\%)}}{\text{max fall placebo (\%)}} \times 100 \quad (2)$$

A 12% change in FEV₁ or PEF_R is considered clinically significant [17, 18]. If a drug provides a protection index of ≥ 40 –50% it is considered to be a clinically significant improvement [6].

The primary outcome measures reported in this review are: 1) the mean maximum per cent fall in FEV₁ or PEF_R; 2) the mean per cent fall in FEV₁ at varying time points postexercise; and 3) the mean per cent protection afforded by NCS compared to placebo.

Search strategy

Several search strategies were used to identify relevant trials. The Cochrane Collaboration's ARG, has developed an "Asthma and Wheez* randomized controlled trial (RCT) Register" from comprehensive searches of EM-BASE, MEDLINE, and CINAHL from 1966–1999 for controlled clinical trials [19]. The register is regularly updated using a systematic strategy for identifying RCTs employing the following terms: placebo* OR trial* OR random* OR double-blind OR double blind OR single-blind OR single blind OR controlled study OR comparative study. This register has been supplemented with hand searches for additional RCTs from 20 journals in which respiratory care articles are commonly found. There are no language restrictions in this register nor were any placed on the search for the present review.

An electronic search of the ARG register was performed using the following terms: asthma OR Wheez* AND exercise* OR exertion* AND NCS* OR Tilade. Searches of the Cochrane Controlled Trials Register and Current Contents, plus hand searches of the bibliography lists of included studies, pertinent review articles and textbooks were performed. The manufacturer of NCS (Rhône-Poulenc Rorer, St-Laurent, Quebec, Canada) and the authors of included studies were asked to identify additional published, unpublished or "in-progress" studies that might have potential relevance.

Study selection. One reviewer, who excluded citations that were clearly irrelevant, screened the initial searches. The second screening, conducted by two independent reviewers using abstracts, titles and keywords, identified potentially relevant trial reports requiring full text review. Foreign articles were translated when necessary. Two reviewers then independently selected trials for inclusion using defined eligibility criteria. *A priori*, this review was designed to include unpublished data that met the inclusion criteria, but to exclude data available only in abstract form. Reviewers were not blinded to authors, journal, results, or conclusions of the individual papers. Agreement was measured at each level of screening using kappa statistics and any disagreements were resolved by discussion.

Methodological quality assessment and data extraction

Independent reviewers subjected the included trials to two quality assessments. Firstly, to a scale that assesses allocation concealment (Grade A: adequate concealment, Grade B: uncertain, Grade C: clearly inadequate) [20] and second, to a five point scale described by JADAD *et al.* [21] that evaluates the quality of randomization, blinding and reasons for withdrawal (0 = worst, 5 = best).

Using standardized forms, two reviewers independently extracted data. Numeric calculations and graphic extrapolations were also confirmed by a second independent reviewer. The reviewers attempted to contact at least one author from each included trial (*via* Internet "people

searches", searches of library databases for the most recent address of that author, contact with other reviewers in the ARG) to confirm data extraction or to supply additional information about the primary research.

Statistical considerations. All included studies were small crossover trials (sample size (n) 8–24) that reported aggregate end of trial results using paired data. In this meta-analysis, the treatment and placebo group data were analysed as though from parallel group studies. This approach would be expected to yield a more conservative pooled estimate of treatment effect [22, 23].

The data were analysed using Review Manager 3.0.1 (RevMan; Update Software, Oxford, UK). Pulmonary function measures (FEV₁ and PEFr) are continuous outcomes, consequently the individual study and pooled statistics are reported as a weighted mean difference (WMD) between the treatment effect of drug and placebo with 95% confidence intervals (95% CI). The weights given to each study are based on the inverse of the variance [20, 24]. Heterogeneity among pooled estimates was tested with Chi-squared statistics using an alpha of 0.10. Sensitivity and subgroup analyses were performed to identify sources of heterogeneity when indicated. A random effects model was used throughout.

When the SD for the mean change in lung function for each treatment group was not reported, an estimate was imputed. The estimate was based on the weighted average (using sample size) of the SDs from other included studies for that category (*i.e.* adults, children, FEV₁, PEFr) using the formula [25]:

$$\text{Pooled SD} = \frac{\sqrt{(n_1 - 1)\text{var}_1 + (n_2 - 1)\text{var}_2 + \dots + (n^k - 1)\text{var}^k}}{\sum n - k} \quad (3)$$

where n=sample size, var=the variance of the study group in study i, k=the number of studies with the variance provided.

A sensitivity analysis was performed to check the effect of imputation. Since no difference was identified, the imputation was maintained throughout the analysis.

A priori subgroup analyses were planned based on six factors that could potentially influence the magnitude of treatment response: 1) age (6–17 yrs were considered children, ≥18 yrs adults); 2) sex; 3) severity of EIA (a mean maximum per cent fall in pulmonary function after placebo of <30% was considered mild EIA, of ≥30% was considered moderate/severe EIA) [14]; 4) dose of NCS given (≤2 mg, 4 mg, ≥6 mg); 5) delivery system (nebulized, metered dose inhaler (MDI), MDI with spacer); and 6) timing of pretreatment (<30 min, ≥30 min).

Time course analysis

Thirteen publications [26–38] included graphs that compared lung function post-treatment at various times up to 120 min postexercise. Unfortunately, the absolute values and SDs to accompany the graphs were not reported. To extract this valuable data, the graphs were enlarged and two reviewers visually estimated the mean per cent fall FEV₁ values for the two groups at each time point. Where estimates between reviewers differed, the

average of the two was used. The mean and SD for each time point was then calculated. The Mann-Whitney U-test was used to assess the significance of the differences at each time point using an alpha of 0.05.

Results

Search

Fifty-one trials, including two German, one Spanish and one Italian, were screened for potential inclusion. A total of 20 published [26–45] and one unpublished study [46] met the inclusion criteria however, none were foreign language trials. SINCLAIR and WINFIELD [37] did not report mean maximum per cent fall indices but did report data that were included in the time course results. Reasons for exclusion included "participants had mixed or uncertain diagnoses" (n=1), "selection of known responders" (n=2), "nonrandom allocation" (n=2) "abstract publication only" (n=1), "active drug comparisons" (n=2), "not selected outcomes" (n=2), "not primary research" (n=19).

In total, 20 studies are included in the meta-analysis and 13 studies in the time-course analysis. Nine of the 15 (60%) primary authors were successfully contacted. Where appropriate, authors confirmed that subjects participated in only one trial. Any duplicate data were included only once in the analyses.

Methodological quality

All trials included were rated as being of good to high quality using either the COCHRANE [20] or JADAD *et al.* [21] criteria. (table 1). All studies were randomized double-blind, and either described drop-outs or had none. Three studies were rated as having "adequate" concealment of allocation [28, 40, 45] all others rated an "unclear" status. (kappa = 0.88). Using the five-point validity scale of JADAD *et al.* [21], two studies were rated five (strong), nine were rated four (very good), and 10 were rated three (good) (table 1). Agreement on quality scoring was good (kappa = 0.67).

Description of studies

The analysis includes data on 280 participants: (64%/36% male/female); 58% were children aged 6–17 yrs, 42% were adults aged 18–59 yrs. No females who were either pregnant or possibly pregnant were included in any studies. Two studies selected only nonsmokers, otherwise smoking history was not clear. All subjects were described as being "stable asthmatics" at the time of challenge testing. TODARO [38] studied Olympic level athletes, none of the remaining trialists addressed level of physical conditioning.

The studies compared NCS to placebo and in some cases to one other agent (sodium cromoglycate (SCG) n=8 [29, 31, 32, 37, 41–44], furosemide n=1 [33], minocromil n=1 [35]). Concurrent therapy included a variety of common anti-asthma agents but most medications were discontinued for periods of 6 h to 1 week prior to each challenge to effect a washout and to limit confounding influences.

Table 1. – Characteristics of included studies

Author [Ref.]	Jadad Quality score	Country	Time between challenges	Index for diagnosis % fall	Drug dose compared to placebo	Delivery system	Pre-exercise therapy min	Sample size	Age yrs	Sex M/F	PFT reported
BONER [26]	4	Italy	4 days	15%	4 mg NCS	MDI, MDI +AA spacer	15	13	10 (7.5–13)	9/4	FEV ₁
BONER [27]	4	Italy	2 days	15%	4 mg NCS	MDI	30	20	11.3 (7.5–15)	15/5	FEV ₁ , PEFR, FVC, FEF _{25–75}
BUNDEGAARD [39] ⁺	3	Denmark	2 wks	20%	2 mg NCS 4 mg NCS	MDI	30	14	31 (21–49)	6/8	PEFR
CHUDRY [40] [#]	5	UK	2 days in 1 wk	20%	4 mg NCS	MDI MDI & MDI+spacer	30, 150, 270	12	13.9 (8–15)	9/3	FEV ₁
COMIS [41] ⁺	3	Italy	daily	15%	4 mg NCS, 10 mg SCG	MDI+spacer	30	12	11 (6.5–13.5)	7/5	FEV ₁
DEBENEDICTUS [29] ⁺	3	Italy	separate days	15%	4 mg NCS, 10 mg SCG	MDI	20	17	10.2 (7–15)	11/6	FEV ₁
DEBENEDICTUS [42] ⁺	3	Italy	separate days	15%	4 mg NCS, 10 mg SCG	MDI+spacer	20	8	8.7 (7–11)	5/3	FEV ₁
DEBENEDICTUS [43] ⁺	3	Italy	separate days	15%	4 mg NCS, 10 mg SCG	MDI	20 & 140	13	10 (7–15)	9/4	FEV ₁
DEBELIC [28]	3	Germany	separate days	20%	4 mg NCS	MDI	30	12	16.9 (14–19)	7/5	FEV ₁
HENRIKSEN [30]	4	Denmark	1 wk	20%	4 mg NCS	MDI	30	12	10.8 (7–14)	10/2	FEV ₁ PEFR
KONIG [44] ^{#,+}	3	USA	separate days	20%	4 mg NCS, 20 mg SCG	MDI	20, 120, 240	12	27.3 (21–38)	12/0	FEV ₁
MIHALYKA [46]	3	Australia	separate days	20%	4 mg NCS	MDI	15	14	NR(15–45)	NR/NR	PEFR
MORTON [31] ⁺	4	Australia	separate days	15%	8 mg NCS 4 mg SCG	MDI	15	16	20 (13–30)	10/6	FEV ₁
NOVEMBRE [32]	3	Italy	separate days	15%	4 mg NCS 10 mg SCG	MDI+spacer	20 min	19	NR (6–15)	13/6	FEV ₁ , PEFR, FEF _{25–75} %
NOVEMBRE [33] ⁺	3	Italy	separate days	15%	4 mg NCS 30 mg furosemide <i>via</i> nebulizer	MDI+spacer	20 min	24	NR (6–16)	16/6	FEV ₁ , PEFR, FEF _{25–75} %
OSEID [34]	4	Norway	separate days	20%	4 mg NCS	MDI	30 min	9	31.1 (16–50)	6	FEV ₁ , FVC, FEF _{25–75} %
ROBERTS [35] [§]	4	UK	separate days	20%	2 & 4 mg NCS 4 mg minocromil	MDI	30 min	9	31.1 (16–50)	6	FEV ₁
SHAW [36]	4	UK	1 wk	20%	2 mg NCS	MDI	20 min	8	NR (17–47)	8	FEV ₁ , FVC
SINCLAIR [37] ⁺	5	UK	separate days	15%	4 mg NCS 10 mg SCG	MDI	30 min	20	20.7 (17–28)	18	FEV ₁
TODARO [38]	3	Italy	separate days	15%	4 mg NCS	MDI	20 min	13	25 (19–31)	11	FEV ₁
VILSVIK [45] [§]	4	Norway	separate days	20%	1 mg, 4 mg, & 8 mg NCS	MDI	60 min	12	29 (20–45)	9	PEFR

*: mean (range); ⁺: 3-arm study; [#]: duration study; [§]: 4-arm study. PFT: pulmonary function test; NCS: nedocromil sodium; MDI: metered dose inhaler; AA spacer: Auty-Altounyan spacer device; FEV₁: forced expiratory volume in one second; PEFR: peak expiratory flow rate; FVC: forced vital capacity; FEF_{25–75}: forced mid-expiratory flow; SCG: sodium cromoglycate; NR: not reported.

No data on symptom scores, performance measures, patient preference, or physiological measures were reported; consequently, pooled analyses were not possible. Twelve of 20 studies (60%) commented on adverse effects. Seven of these (58%) stated that no adverse effects were noticed in the time period that participants were observed. Five studies mentioned minor side effects that included a bad taste, throat irritation, and cough. One study reported a mean increase in heart rate after NCS; however, the difference was not clinically significant (4 beats·min⁻¹). Higher doses of NCS did not appear to increase the side effect profile.

Pulmonary function results. All trials reported comparable outcome data that originated from populations and interventions that were similar in nature; consequently, the reviewers felt it was appropriate to combine the results for a quantitative pooled estimate of treatment effect.

Following NCS therapy, there was significant attenuation of the mean maximum per cent fall FEV₁ and PEF_R postexercise when compared to placebo therapy. The effect size did not differ significantly in further subgroup analysis based on age, dose, delivery system, or timing of pretreatment. Seventeen trials reporting changes in FEV₁ were pooled (fig. 1). The mean maximum per cent fall FEV₁ for placebo = 31.9% (95% CI: 28.1–35.8), for NCS = 15.6% (95% CI: 13.4–17.8). The WMD between the two = 15.6% (95% CI: 13.2–18.1). The Chi-squared test for heterogeneity was nonsignificant for this pooled result (Chi-squared = 17.57, degrees of freedom (df) = 16, p>0.25).

Seven trials reporting changes in PEF_R were also pooled (fig. 2). The positive effect on the mean maximum per cent fall PEF_R was of a similar magnitude. The mean maximum per cent fall PEF_R for placebo = 30.3% (95% CI: 21.0–39.6), for NCS = 14.5% (95% CI: 11.3–17.7). WMD = 15.0% (95% CI: 8.3–21.6). Significant hetero-

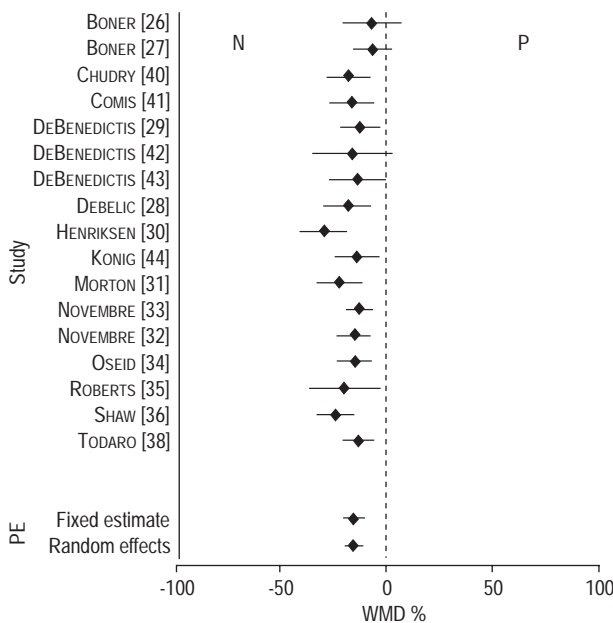


Fig. 1. – The weighted mean difference (WMD, ◆) in the maximum per cent fall in forced expiratory volume in one second (FEV₁) between treatment with nedocromil (N) and placebo (P). The horizontal bars represent the 95% confidence interval. Values either side of 0% favour either N or P, as shown. PE: pooled estimate.

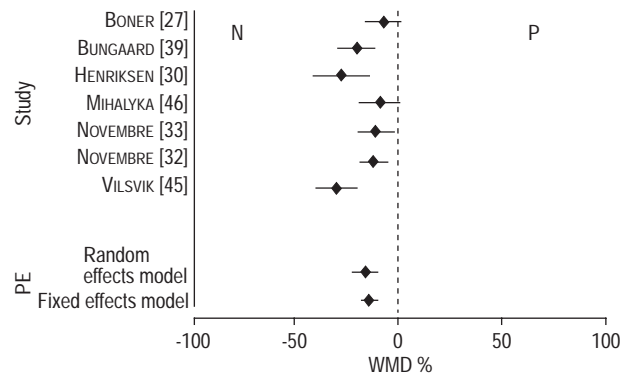


Fig. 2. – The weighted mean difference (WMD, ◆) in the maximum per cent fall in peak expiratory flow rate (PEFR) between treatment with nedocromil (N) and placebo (P). The horizontal bars represent the 95% confidence interval. Values either side of 0% favour either N or P, as shown. PE: pooled estimate.

geneity in this pooled result was demonstrated (Chi-squared = 20.28, df = 6, p<0.001). Neither subgroup comparisons based on the age, dose, delivery system, or timing explained the heterogeneity, nor sensitivity analysis based on study quality (JADAD *et al.* [21] score ≤3 *versus* scores ≥4), imputed standard deviations (n=2), random *versus* fixed effects models or publication status.

Exercise-induced asthma severity subgroup

Heterogeneity was clinically and statistically insignificant when studies were dichotomized into mild *versus* moderate/severe EIA groups (fig. 3). This analysis indicated that NCS inhibited the mean maximum per cent fall PEF_R in subjects with moderate/severe EIA, to a significantly greater degree than in subjects with mild EIA: WMD = 25.1% (95% CI: 18.7–31.1) compared to WMD = 8.3% (95% CI: 4.1–12.5) respectively. Similar results were demonstrated for mean maximum per cent fall FEV₁, WMD = 21.4% (95% CI: 17.2–25.5) for moderate/severe EIA compared to WMD = 12.8% (95% CI: 10.0–15.7) for mild EIA (fig. 4).

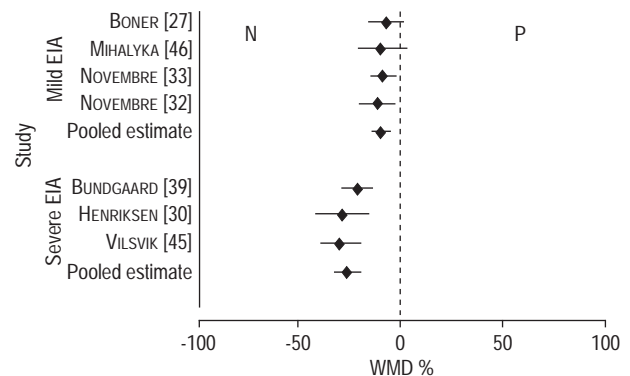


Fig. 3. – The weighted mean difference (WMD, ◆) in the maximum per cent fall peak expiratory flow rate (PEFR) between nedocromil (N) and placebo (P) by severity of exercise-induced asthma (EIA). The horizontal bars represent the 95% confidence interval. Values either side of 0% favour either N or P, as shown.

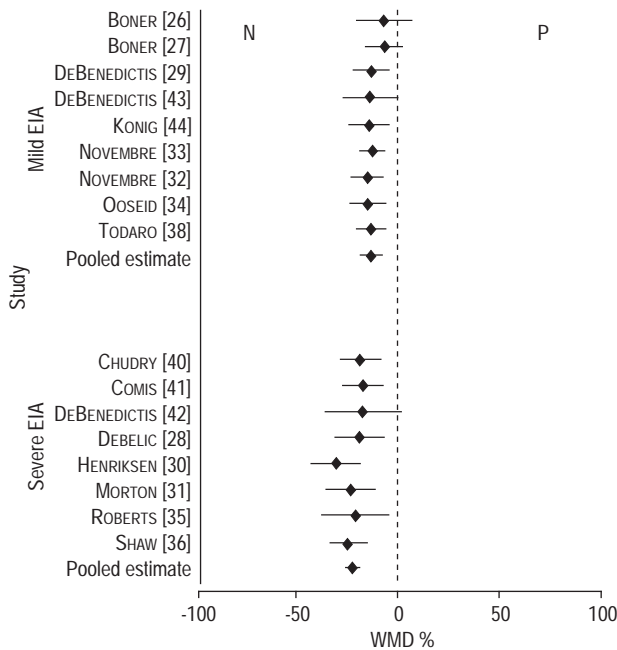


Fig. 4. – The weighted mean difference (WMD, ◆) in the maximum per cent fall in forced expiratory volume in one second (FEV₁) between nedocromil (N) and placebo (P) by severity of exercise-induced asthma (EIA). The horizontal bars represent the 95% confidence interval. Values either side of 0% favour either N or P, as shown.

The protection index

On average, NCS provided a clinically significant protection index of 51% (95% CI: 49–52) against a decrease in FEV₁ (range 30–70%) corroborated by a protection index of 49% (95% CI: 47–51) against a decrease in PEFR (range 33–66%).

Dosage sensitivity analyses

Although no definite trend was noted when comparing low, moderate or high doses of NCS, note that few trials investigated a low (≤ 2 mg, n=3) or a high (>4 mg, n=1) dose and this prevented any meaningful analyses for a dose-response effect. The recommended clinical dose of 4 mg was used in 16/20 studies.

Duration of effect. Three trials [40, 43, 44] recorded the mean maximum per cent fall FEV₁ on 2 or 3 repeated challenges to evaluate NCS for its duration of effect (fig. 5). No significant benefit of NCS over placebo was demonstrated beyond the first challenge. WMD = 5.9% (95% CI: 1.0–12.9; n=3), and WMD = 5.7% (95% CI: 2.8–14.2; n=2) at 2–2.5 h and 4–4.5 h respectively.

Time course analysis. In the 13 studies that reported the mean per cent fall in FEV₁ at seven time points during the immediate postexercise period following both therapies, statistically significant improvements in FEV₁ measures favouring NCS were noted at all times up to 30 min postexercise (p<0.001) (fig. 6). The return to normal lung function (*i.e.* <10% change from baseline) occurred within 10 min postexercise using NCS compared to 30 min using placebo.

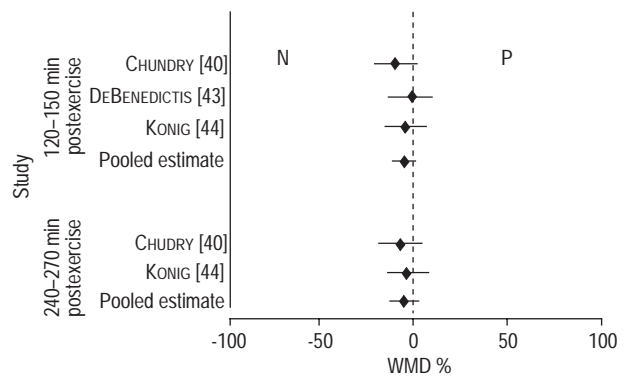


Fig. 5. – The weighted mean difference (WMD, ◆) in the maximum per cent fall in forced expiratory volume in one second (FEV₁) between nedocromil (N) and placebo (P): duration. The horizontal bars represent the 95% confidence interval. Values either side of 0% favour either N or P, as shown.

Discussion

This large systematic review is the first of its kind to examine the efficacy of NCS in preventing the bronchoconstriction typically observed in EIA. The results of this review clearly document the benefit of NCS in attenuating the maximum per cent fall in pulmonary function, blunting the entire EIA response, and identifying a more rapid return to baseline lung function. This effect is consistent across a wide variety of studies regardless of the subgroup and sensitivity comparisons performed. Furthermore, this attenuation is both statistically and clinically important.

There does not appear to be a dose response curve associated with NCS delivery, however, there were insufficient data for a meaningful comparison. The degree of protection is most impressive in those patients with more severe EIA. The drug appears to be well tolerated, is simple to use, and may be delivered by MDI with or without a spacer device.

Clearly, the statistically and clinically important effects of NCS indicate that it should be considered for use in EIA. While other agents are available to treat the disorder, the relative merits of one drug compared to another are not well established. From a clinical perspective, NCS was

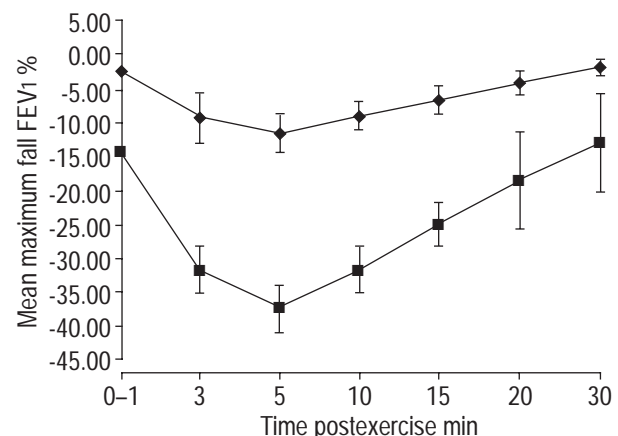


Fig. 6. – Treatment effect of nedocromil and placebo on the time-course of exercise-induced asthma. Data are mean maximum fall in forced expiratory volume in one second (FEV₁) and 95% confidence interval. ■: placebo; ◆: nedocromil.

well tolerated and adverse effects were minor, therefore, it may be useful for patients who dislike the autonomic side-effects of β_2 -agonists or the adverse effects of other choices. It may also have a role in combination therapy for people who experience EIA symptoms despite premedication with another drug [47].

There are a variety of issues that must be addressed to produce a valid systematic review or meta-analysis. Most importantly, systemic reviews must address the issues of study publication and selection bias. This review employed comprehensive search strategies that identified published, unpublished, and foreign language literature, in addition to employing an unbiased selection process to decide on inclusion. There remains the possibility of publication bias due to having missed retrieving unpublished negative trials. If this is the case, the pooled effect of NCS therapy may be overestimated.

Comparisons in trial design, populations, interventions studied, and methods of outcome reporting are also important issues in systemic review methodology. In this review, only randomized controlled trials were included, ensuring the highest level of evidence was incorporated. Studies were pooled only after similarities in populations, interventions and outcomes were determined, and pooling was accomplished using accepted mathematical approaches.

Despite the methodological care taken, some limitations to generalizability remain. To assess the efficacy of NCS it was necessary for the exercise challenges to take place in laboratories with controlled environments. To assess the effectiveness of the drug under normal conditions, the drug needs to be evaluated by asthmatics during regular exercise where environmental conditions have greater variability.

To control for variations in baseline severity of EIA on the magnitude of drug effect, the reviewers selected the mean maximum per cent fall index on the placebo challenge for comparison. This was the only subgroup analysis that demonstrated a significant difference in effect size. In planning a new primary study, stratifying by this variable may reveal additional information on who could best benefit from pretreatment with NCS. Studying an increasing dose-effect in nonresponders and known responders could also reveal important information.

All studies in this review used the crossover design. Future studies using the crossover method must concentrate on complete reporting of results by period and sequence to assure that readers' concerns over "carry-over" and "period effects" have been addressed. The reviewers believed the potential for a carry-over effect to be negligible for two reasons. Firstly, NCS is a short acting agent (half-life 1.5–2 h) with topical effects. While the drug is well absorbed from the lung, it does not accumulate systemically, has no known systemic effects, is rapidly cleared from the body, and has few side-effects [15, 16, 48]. Secondly, the exercise challenges were conducted on separate days, thus the trialists adhered to the recommended wash-out time of 5–10 times the half-life of a drug [49, 50] in the unlikely event of systemic effects. Had there been a period effect in every study, there is no reason to believe that a systematic bias favours any one challenge period. The large number of studies included should ensure an equal distribution of period effects if they exist. By averaging the estimates, any effect would disappear leaving an unbiased estimate of the treatment contrast [51].

Finally, data on symptom scores, exercise performance, or subject satisfaction were not included in the studies. The patient's own assessment of NCS is clearly an important consideration in choosing one treatment over another.

In conclusion, this review of 20 randomized trials with 280 adults and children across eight countries over 10 yrs, supports the single dose use of nedocromil as an effective pharmaceutical option for the management of exercise-induced asthma. When nedocromil was taken within an hour of an intense, prolonged exercise challenge, the severity of bronchoconstriction, measured by the change in forced expiratory volume in one second or peak expiratory flow rate, was significantly reduced. There was evidence to indicate that the exercise-induced asthma response was blunted over the entire immediate postexercise period and that, on average, people returned to normal lung function within 10 min of completing the exercise challenge. Considering the methodological rigour, consistency of findings over subgroup and sensitivity analyses, the reviewers feel that the results of this review are valid. Moreover, they should be generalizable to a broad range of patients with exercise-induced asthma.

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References

1. Anderson SD. Issues in exercise-induced asthma. *J Allergy Clin Immunol* 1985; 76: 763–772.
2. Anderson SD, Silverman M, Konig P, Godfrey S. Exercise-induced asthma. *Br J Dis Chest* 1975; 69: 1–39.
3. Kattan M, Keens TG, Mellis CM, Levison H. The response to exercise in normal and asthmatic children. *J Pediatr* 1978; 92: 718–721.
4. Virant FS. Exercise-induced bronchospasm: epidemiology, pathophysiology, and therapy. *Med Sci Sports Exerc* 1992; 24: 851–855.
5. Rupp NT. Diagnosis and management of exercise-induced asthma. *Phys Sportsmed* 1996; 24: 77–87.
6. Anderson SD. Specific problems: exercise-induced asthma. In: O'Byrne P, Thomson NC, eds. *Manual of Asthma Management*. London, UK, WB Saunders Co. Ltd, 1995; pp. 621–643.
7. Nastasi KJ, Heinly TL, Blaiss MS. Exercise-induced asthma and the athlete. *J Asthma* 1995; 32: 249–257.
8. Spector SL. Update on exercise-induced asthma. *Ann Allergy* 1993; 71: 571–577.
9. Hogshead N, Couzens GS. *Asthma and Exercise*. New York, NY, USA, Henry Holt and Company, 1989; pp. 1–114.
10. Pierson WE, Voy RO. Exercise-induced bronchospasm in the XXIII summer Olympic Games. *N Engl Reg Allergy Proc* 1988; 9: 209–213.

11. McFadden ER, Gilbert IA. Exercise-induced asthma. *N Engl J Med* 1994; 330: 1362–1367.
12. Hendrickson CD, Lynch JM, Gleeson K. Exercise induced asthma: a clinical perspective. *Lung* 1993; 172: 1–14.
13. Du Buske LM, Horan RF, Sheffer AL. Exercise-induced allergy syndromes. In: Weiler JM, ed. *Allergic and Respiratory Disease in Sports Medicine*. New York, NY, USA, Marcel Dekker, Inc., 1997; pp. 253–278.
14. Anderson SD, Daviskas E. Pathophysiology of exercise-induced asthma: the role of respiratory water loss in allergic and respiratory disease. In: Weiler JM, ed. *Allergic and Respiratory Disease in Sports Medicine*. New York, NY, USA, Marcel Dekker, Inc., 1997; pp. 87–114.
15. Holgate ST. Clinical evaluation of nedocromil sodium in asthma. *Eur J Respir Dis* 1986; 69: Suppl. 147, 149–159.
16. Auty RM. The Clinical development of a new agent for the treatment of airway inflammation, nedocromil sodium (Tilade[®]). *Eur J Respir Dis* 1986; 69: Suppl. 147, 120–131.
17. Canadian Thoracic Society. Canadian Asthma Consensus Conference: Summary of recommendations. *Can Respir J* 1996; 3: 89–100.
18. American Thoracic Society. Guidelines for the evaluation of impairment/disability in patients with asthma. *Am Rev Respir Dis* 1993; 147: 1056–1061.
19. Bara A, Milan S, Jones PW. Identifying asthma RCTs with Medline and Embase. 3rd Annual Cochrane Colloquium. Oslo, Norway, 1995.
20. The Cochrane Collaboration. *Cochrane Collaboration Handbook*. The Cochrane Library [database on disk and CDROM]. updated Mar 1997. Oxford, UK, Update Software, 1997.
21. Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomised clinical trials: is blinding necessary? *Control Clin Trials* 1996; 17: 1–12.
22. Senn S. The AB/BA crossover: past, present and future? *Stat Methods Med Res* 1994; 3: 303–324.
23. Kenward MG, Jones B. The analysis of data from 2 × 2 crossover trials with baseline measurements. *Stat Med* 1987; 6: 911–926.
24. Petitti DB. *Meta-analysis, Decision analysis, and cost-effectiveness analysis: methods for quantitative synthesis in medicine*. New York, NY, USA, Oxford University Press, 1994; pp. 90–110.
25. Follman D, Elliott P, Suh I, Cutler J. Variance imputation for overviews of clinical trials with continuous response. *J Clin Epidemiol* 1992; 45: 769–773.
26. Boner AL, Miglioranza P, Piacentini GL, Peroni DG, Andreoli A. Effects of nedocromil sodium pressurized aerosol on exercise challenge using a spacer device and the normal adapter. *Pediatr Asthma Allergy Immunol* 1988; 2: 207–213.
27. Boner AL, Vallone G, Bennati D. Nedocromil sodium in exercise-induced bronchoconstriction in children. *Ann Allergy* 1989; 62: 38–41.
28. Debelic M. Nedocromil sodium and exercise-induced asthma in adolescents. *Eur J Respir Dis* 1986; 69 (Suppl 147): 266–267.
29. DeBenedictis FM, Tuteri G, Bertotto A, Bruni L, Vaccaro R. Comparison of the protective effects of cromolyn sodium and nedocromil sodium in the treatment of exercise-induced asthma in children. *J Allergy Clin Immunol* 1994; 94: 684–688.
30. Henriksen JM. Effect of nedocromil sodium on exercise-induced bronchoconstriction in children. *Allergy* 1988; 43: 449–453.
31. Morton AR, Ogle SL, Fitch KD. Effects of nedocromil sodium, cromolyn sodium, and a placebo in exercise-induced asthma. *Ann Allergy* 1992; 68: 143–148.
32. Novembre E, Frongia GF, Veneruso G, Vierucci A. Inhibition of exercise-induced asthma (EIA) by nedocromil sodium and sodium cromoglycate in children. *Pediatr Allergy Immunol* 1994; 5: 107–110.
33. Novembre E, Frongia GF, Lombardi E, Veneruso G, Vierucci A. The preventive effect of nedocromil or furosemide alone or in combination on exercise-induced asthma in children. *J Allergy Clin Immunol* 1994; 94: 201–206.
34. Oseid S, Mellbye E, Hem E. Effect of nedocromil sodium on exercise-induced bronchoconstriction exacerbated by inhalation of cold air. *Scan J Med Sci Sports* 1995; 5: 88–93.
35. Roberts JA, Thomson NC. Attenuation of exercise-induced asthma by pretreatment with nedocromil sodium and minocromil. *Clin Allergy* 1985; 15: 377–381.
36. Shaw RJ, Kay AB. Nedocromil, a mucosal and connective tissue mast cell stabilizer, inhibits exercise-induced asthma. *Br J Dis Chest* 1985; 79: 385–389.
37. Sinclair DG, Winfield CR. Attenuation of exercise-induced asthma by nedocromil sodium and sodium cromoglycate. *J Royal Army Med Corps* 1990; 136: 105–106.
38. Todaro A, Faina M, Alippi B, Dal Monte A, Ruggieri F. Nedocromil sodium in the prevention of exercise-induced bronchospasm in athletes with asthma. *J Sports Med Phys Fitness* 1993; 33: 137–145.
39. Bundgaard A, Enehjelm SD, Schmidt A. A comparative study of the effects of two different doses of nedocromil sodium and placebo given by pressurised aerosol in exercise-induced bronchoconstriction. *Eur J Allergy Clin Immunol* 1988; 43: 493–496.
40. Chudry N, Correa F, Silverman M. Nedocromil sodium and exercise induced asthma. *Arch Dis Child* 1987; 62: 412–414.
41. Comis A, Valletta EA, Sette L, Andreoli A, Boner AL. Comparison of nedocromil sodium and sodium cromoglycate administered by pressurised aerosol, with and without a spacer device in exercise-induced asthma in children. *Eur Respir J* 1993; 6: 523–526.
42. DeBenedictis FM, Tuteri G, Niccoli A, Mezzetti D, Rossi L, Bruni L. The effect of cromolyn sodium and nedocromil sodium administered by a pressurised aerosol with a spacer device on exercise-induced asthma in children. *Mediators Inflamm* 1994; 3 Suppl. 1, S35–S37.
43. DeBenedictis FM, Tuteri G, Pazzelli P, Bertotto A, Bruni L, Vaccaro R. Cromolyn versus nedocromil: duration of action in exercise-induced asthma in children. *J Allergy Clin Immunol* 1995; 96: 510–514.
44. Konig P, Hordvik NL, Kreutz C. The preventive effect and duration of action of nedocromil sodium and cromolyn sodium on exercise-induced asthma (EIA) in adults. *J Allergy Clin Immunol* 1987; 79: 64–68.
45. Vilsvik J, Schaanning J. A comparative study of the effect of three doses of nedocromil sodium and placebo given by pressurised aerosol to asthmatics with exercise-induced bronchoconstriction. *Ann Allergy* 1988; 61: 67–70.
46. Mihalyka MS, Anderson SD, Corte P. Nedocromil sodium in exercise induced asthma. *Aust NZ Med* 1987; 17: Suppl. 2, 524.
47. DeBenedictis FM, Tuteri G, Pazzelli P, Solinas LF, Niccoli A, Parente C. Combination drug therapy for the prevention of exercise-induced bronchoconstriction in children. *Ann Allergy Asthma Immunol* 1998; 80: 352–356.
48. Canadian Pharmaceutical Association. *Compendium of Pharmaceuticals and Specialties*. 32 ed. Ottawa, Canada, Canadian Pharmaceutical Association, 1997.
49. Lloyd J. Clinical trial design. In: Lloyd J, Raven A, eds. *Handbook of Clinical Research* 2 ed. Edinburgh, UK, Churchill Livingstone, 1994; pp. 92–113.
50. Shapiro SH, Louis TA. *Clinical Trials: Issues and Approaches*. New York, NY, USA, Marcel Dekker Inc., 1983.
51. Senn S, Hildebrand H. Crossover trials, degrees of freedom, the carryover problem and its dual. *Stat Med* 1991; 10: 1361–1374.