April 2020

Interventions to prevent asthma deaths: Maintenance and Reliever Therapy (MART) for people with asthma who may overuse short-acting beta-agonists (SABA)

Cochrane Airways Scoping Search Report

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Introduction to the scoping search report

This scoping search report describes the methods and results of scoping activities undertaken by Cochrane Airways on interventions to prevent asthma deaths. This topic was identified as priority by the Cochrane Airways Priority Setting Group (CAPSG) as part of the Cochrane Airways 'whole of scope' priority setting exercise conducted in 2019/2020.

One of the ways an 'at risk' patient may be identified is when they are overusing their short-acting beta-agonist (SABA) inhaler. This may be addressed by moving people onto a combined inhaler containing both a beta-agonist (formoterol) and an inhaled steroid. This is known as Maintenance and Reliever Therapy (MART).

There is a related Cochrane review on this topic: Cates CJ, Lasserson TJ. Combination formoterol and inhaled steroid versus beta$_2$-agonist as relief medication for chronic asthma in adults and children. Cochrane Database of Systematic Reviews 2009, Issue 1. Art. No.: CD007085. DOI: 10.1002/14651858.CD007085.pub2.

This scoping search report does not attempt to appraise or synthesise the included studies. It provides a summary of the existing evidence on this topic.

Purpose

The purpose of this scoping search report is:

- to assess what evidence exists for this topic
- to inform the development of future Cochrane Review titles
- to provide a transparent record of scoping work undertaken by Cochrane Airways

Study inclusion criteria

Population: people with asthma who have been identified as overusing their SABA inhaler

Intervention: combination inhaler containing formoterol and an inhaled steroid (MART)

Comparator: SABA reliever medication

Outcomes: any

Study design: Randomised controlled trials (RCTs)

Literature search

A limited literature search was conducted to identify relevant systematic reviews and trials. A search was conducted in the Cochrane Airways Trials Register and CENTRAL to identify relevant RCTs and quasi-RCTs. The search strategies can be found in the appendix. Searches were conducted on 29th April 2020.

Assessment of search results

The database search retrieved 32 references after duplicates were removed. One member of the Cochrane Airways team (LS) screened the titles and abstracts using the Cochrane Register of Studies triage function. A short-list of 12 references were screened by a second team member (CJC).

Included studies

The search identified 1 RCTs (6 references). The studies are summarised in **Table 1**. The primary reference for the study is listed in the References section.

Table 1: Summary of studies

Study ID	Trial Registration	Population	Intervention(s)	Comparator	No. participants randomized	Country
Patel 2013	ACTRN12610000515099	Patients (aged 16-65 years) with a recent asthma exacerbation	Two actuations of budesonide-formoterol (200 µg and 6 µg, respectively, per actuation) twice daily, delivered through a combination metered dose inhaler (MDI), with one extra actuation as needed for relief of symptoms	Two actuations of budesonide-formoterol (200 µg and 6 µg, respectively, per actuation) twice daily through a combination MDI with one to two actuations of salbutamol (100 µg per actuation) by MDI as needed for relief of symptoms	303	New Zealand

References

Randomized controlled trials

Patel M, Pilcher J, Pritchard A, Perrin K, Travers J, Shaw D, Holt S, Harwood M, Black P, Weatherall M, Beasley R, SMARTStudy Group. Efficacy and safety of maintenance and reliever combination budesonide-formoterol inhaler in patients with asthma at risk of severe exacerbations: a randomised controlled trial *The Lancet. Respiratory medicine* **2013:** 1 (1) ; 32-42

BACKGROUND: The Single combination budesonide-formoterol inhaler Maintenance And Reliever Therapy (SMART) regimen reduces severe asthma exacerbations in patients, but whether the high doses of corticosteroid and beta agonist increase the risk of adverse effects with both short-term and cumulative exposure is not certain. Our aim was to investigate whether the SMART regimen would reduce the risk of overuse of beta agonist, reduce the likelihood of patients to seek medical review when such episodes occurred, and if any reduction in severe asthma exacerbations would be at the cost of a higher burden of systemic corticosteroid. METHODS: In this 24-week trial undertaken at four primary health-care practices and one hospital in New Zealand, patients (aged 16-65 years) with a recent asthma exacerbation were randomly assigned in a 1:1 ratio to the SMART or standard fixed-dose regimen. Treatment in the SMART group consisted of two actuations of budesonide-formoterol (200 mug and 6 mug, respectively, per actuation) twice daily, delivered through a combination metered dose inhaler (MDI), with one extra actuation as needed for relief of symptoms; treatment in the standard group consisted of two actuations of budesonide-formoterol (200 mug and 6 mug, respectively, per actuation) twice daily through a combination MDI with one to two actuations of salbutamol (100 mug per actuation) by MDI as needed for relief of symptoms. MDIs were monitored electronically to measure actual use of medication. The allocation sequence for randomisation was computer generated, with a block size of eight per site. Participants, investigators, and the statistician were not masked to group assignment. The primary outcome was the proportion of participants with at least one high-use episode of beta agonist (more than eight actuations per day of budesonide-formoterol in addition to the four maintenance doses in the SMART group or more than 16 actuations per day of salbutamol in the standard group). Analysis was by intention to treat. This trial is registered with the Australian New Zealand Clinical Trials Registry, number ACTRN12610000515099. FINDINGS: 303 patients were randomly assigned to the SMART (n=151) or standard group (n=152). No significant difference was noted between the SMART and standard groups in the proportion of participants with at least one high-use episode of beta agonist (84 [56%] vs 68 [45%], respectively, relative risk 124 [95% CI 099-156]; p=0058). There were fewer days of high use in the SMART group (mean 51 days [SD 143] vs 89 days [209], relative rate 058 [039-088]; p=001). Of the patients who had at least one high-use episode, those in the SMART group had fewer days of high use without medical review (85 days [178] vs 183 days [248], 049 [031-075]; p=0001). The SMART regimen resulted in higher inhaled corticosteroid exposure (9435 mug budesonide per day [15025] vs 6843 mug budesonide per day [3905], respectively; ratio of means 122 [106-141]; p=0006), but reduced oral corticosteroid exposure (775 mg prednisone [2405] vs 1266 mg prednisone [3821], respectively; p=0011), with no significant difference in composite systemic corticosteroid exposure (7937 mg prednisone equivalent per year [8931] vs 7721 mg prednisone equivalent per year [10627], respectively; 103 [086-122]; p=076). Participants in the SMART group had fewer severe asthma exacerbations (35 [weighted mean rate per year 053] vs 66 [097]; relative rate 054 [036-082]; p=0004). INTERPRETATION: The SMART regimen has a favourable risk-to-benefit profile and can be recommended for use in adults at risk of severe asthma exacerbations. FUNDING: Health Research Council of New Zealand

Appendix: Database search strategies

Cochrane Airways Register of Trials via The Cochrane Register of Studies

1	MESH DESCRIPTOR Asthma EXPLODE ALL AND INSEGMENT	21327
2	asthma*:ti,ab AND INSEGMENT	60767
3	#1 OR #2	62474
4	(albuterol OR terbutaline OR salbutamol):ti,ab AND INSEGMENT	6424
5	ventolin:ti,ab AND INSEGMENT	174
6	SABA:ti,ab AND INSEGMENT	483
7	(relief* or reliever*):ti,ab AND INSEGMENT	3150
8	#4 OR #5 OR #6 OR #7	9619
9	(overuse* OR over-use*):ti,ab AND INSEGMENT	453
10	(over-relian*):ti,ab AND INSEGMENT	18
11	#9 OR #10	466
12	#3 AND #8 AND #11	66
13	INREGISTER	43080
14	#12 AND #13	14

CENTRAL via the Cochrane Register of studies

1	MESH DESCRIPTOR Asthma EXPLODE ALL AND CENTRAL:TARGET	11895
2	asthma*:ti,ab AND CENTRAL:TARGET	31396
3	#1 OR #2 AND CENTRAL:TARGET	32077
4	(albuterol OR terbutaline OR salbutamol):ti,ab AND CENTRAL:TARGET	6650
5	ventolin:ti,ab AND CENTRAL:TARGET	201
6	SABA:ti,ab AND CENTRAL:TARGET	311
7	(relief* or reliever*):ti,ab AND CENTRAL:TARGET	26649
8	#4 OR #5 OR #6 OR #7 AND CENTRAL:TARGET	33235
9	(overuse* OR over-use*):ti,ab AND CENTRAL:TARGET	1138
10	(over-relian*):ti,ab AND CENTRAL:TARGET	18
11	#9 OR #10 AND CENTRAL:TARGET	1156
12	#3 AND #8 AND #11 AND CENTRAL:TARGET	32