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Comparative effectiveness of long term drug treatment strategies to prevent asthma exacerbations: network meta-analysis

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EDITORIAL by Cates

STUDY QUESTION

Which drug maintenance treatment is most effective at preventing asthma exacerbations in adults?

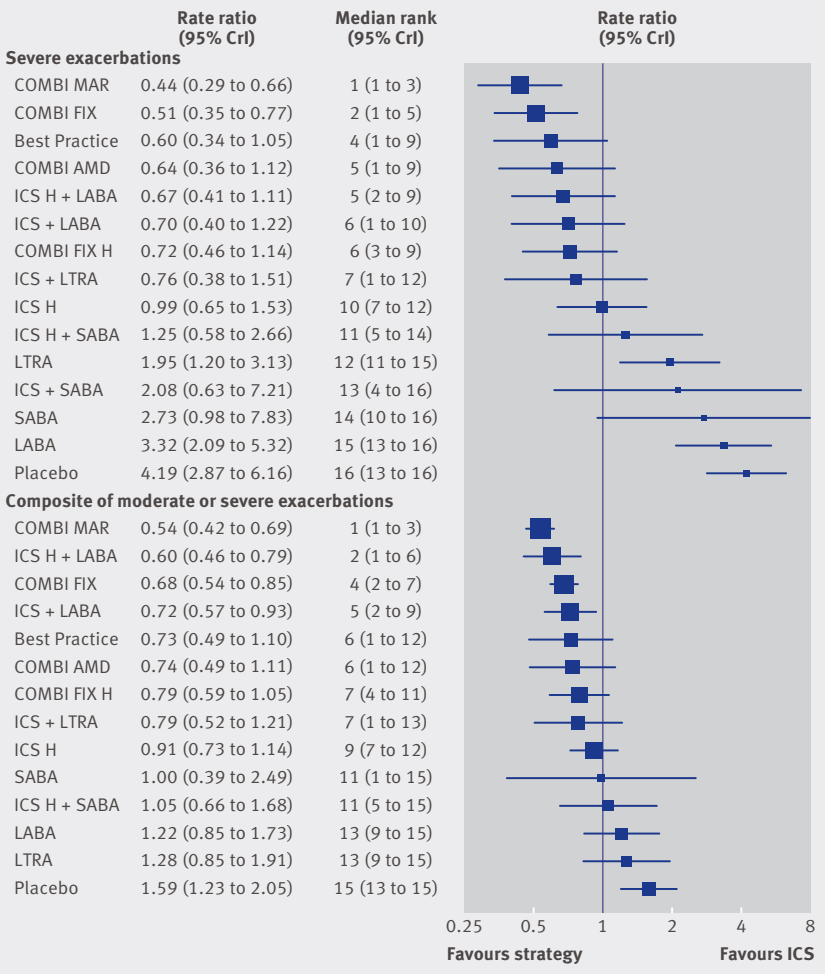
SUMMARY ANSWER

Compared with low dose inhaled corticosteroids, combined inhaled corticosteroids and long acting β agonists, either as maintenance and reliever treatment or in a fixed daily dose, significantly reduced exacerbations of asthma.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Adding long acting β agonists to asthma treatment is preferred to raising the dose of inhaled corticosteroids to prevent exacerbations, but several meta-analyses of other treatment strategies, such as leukotriene antagonists and single inhaler combination devices have been assessed.

Forest plot showing asthma exacerbation rates and median ranks for each strategy compared with low dose inhaled corticosteroids (ICS)



COMBI=combined ICS and long acting β agonist (LABA) in single inhaler; COMBI MAR=COMBI as maintenance and reliever treatment; COMBI FIX=COMBI in fixed daily dose; COMBI AMD=COMBI in adjustable maintenance dose; H=high dose; LABA=long acting β agonists, regular use; LTRA=leukotriene receptor antagonist; SABA=short acting β agonists, regular use

This network meta-analysis ranked current maintenance treatments for asthma for their potential to prevent exacerbations: combined corticosteroids and long acting β agonists as maintenance and reliever therapy or in a fixed daily dose seem to be preferred when low dose inhaled corticosteroids are not sufficient, and step-up of treatment is warranted.

Selection criteria for studies

We identified relevant trials in Cochrane systematic reviews of long term (maintenance) treatment of asthma and updated the searches when appropriate. Trial populations were adults with asthma who had been randomised to any drug maintenance treatment. We included the treatments if they occurred in full text articles reporting on exacerbations of asthma after at least 24 weeks.

Primary outcomes

Severe exacerbations according to the American Thoracic Society/European Respiratory Society recommended definition. We also analysed the composite of moderate or severe exacerbations as well as withdrawals as a result of adverse events. We compared all outcomes with the reference strategy of low dose inhaled corticosteroids after conversion in dose equivalents of beclometasone.

Main results and role of chance

In 64 trials reporting on nearly 59 622 patient years of treatment, 15 maintenance treatments for asthma exacerbations were identified and placebo. All single drug treatments were inferior to single low dose inhaled corticosteroid treatment. Combinations with inhaled corticosteroids (guideline based best practice) and high dose inhaled corticosteroids did not reduce exacerbations significantly compared with low dose inhaled corticosteroids, the reference strategy. The only two maintenance treatments that succeeded in reducing exacerbations significantly were combined corticosteroids and long acting β agonists used as maintenance and reliever treatment (ranked first out of 16 interventions, rate ratio 0.44, 95% credibility interval 0.29 to 0.66) and combined corticosteroids and long acting β agonists in a fixed daily dose (ranked second, 0.51, 0.35 to 0.77). For the composite of moderate or severe exacerbations, overall trends were similar. Safety was best for conventional best (guideline based) practice and combined maintenance and reliever treatment.

Bias, confounding, and other reasons for caution

All reports except two were funded or cowritten by pharmaceutical industries. Problems with blinding were tackled with a sensitivity analysis. Not all direct comparisons concurred with indirect comparisons in this analysis of full text reports.

Study funding/potential competing interests

See bmj.com.

Quantification of risk factors for herpes zoster: population based case-control study

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bmj.com
- Practice: Herpes zoster ophthalmicus (*BMJ* 2009;339:b2624)
- Clinical review: Herpes zoster (*BMJ* 2007;334:1211)

STUDY QUESTION

What are the effects of pre-existing clinical conditions on the risk of herpes zoster?

SUMMARY ANSWER

Conditions associated with increased risk of zoster included rheumatoid arthritis, systemic lupus erythematosus, inflammatory bowel disease, chronic obstructive pulmonary disease, asthma, chronic kidney disease, type 1 diabetes, and depression.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

A range of clinical conditions have been postulated to be associated with an increased risk of zoster, raising the possibility that some people may be at high risk and could be targeted for vaccination. People with severely immunosuppressive conditions that are currently contraindications to vaccination were at the highest risk, emphasising the need for alternative risk reduction strategies in these groups.

Participants and setting

We used primary care records from the UK Clinical Practice Research Datalink (CPRD) to identify adults diagnosed as having herpes zoster and matched them to controls on age, sex, and general practice.

Design, size, and duration

We used a case-control design, including 144 959 cases of zoster diagnosed between 2000 and 2011 and 549 336 matched controls. We used a conditional logistic regression model including all covariates to estimate adjusted odds ratios for each risk factor of interest.

Primary outcome(s), risks, exposures

We identified herpes zoster from diagnosis codes in the primary care record. Our key risk factors of interest are listed in the table. We also identified these and other covariates in the model by searching diagnosis codes recorded before the index date.

Main results and the role of chance

The median age of the cases and controls was 62 years. Factors associated with increased risk of zoster included rheumatoid arthritis (3111 (2.1%) *v* 8029 (1.5%); adjusted odds ratio 1.46, 99% confidence interval 1.38 to 1.55), inflammatory bowel disease (1851 (1.3%) *v* 5118 (0.9%); 1.36, 1.26 to 1.46), chronic obstructive pulmonary disease (6815 (4.7%) *v* 20 201 (3.7%); 1.32, 1.27 to 1.37), asthma 10 243 (7.1%) *v* 31 865 (5.8%); 1.21, 1.17 to 1.25), chronic kidney disease 8724 (6.0%) *v* 29 437 (5.4%); 1.14, 1.09 to 1.18), and depression (6830 (4.7%) *v* 22 052 (4.0%); 1.15, 1.10 to 1.20). Type 1, but not type 2, diabetes showed some association with zoster (adjusted odds ratio 1.27, 1.07 to 1.50). Severely immunosuppressive conditions, such as lymphoma (adjusted odds ratio 3.90, 3.21 to 4.74) and myeloma (2.16, 1.84 to 2.53) were the strongest risk factors for zoster.

Bias, confounding, and other reasons for caution

The study may be subject to ascertainment bias; regular general practice visits for a chronic condition may increase the likelihood of receiving a diagnosis of zoster. However, we believe that most zoster cases would present to their general practitioner, owing to the extensive rash and considerable pain associated with zoster and the fact that healthcare is free at the point of use. As with any observational study, residual confounding may exist. For example, exposure to varicella contacts, hypothesised to naturally boost varicella zoster virus specific immunity in people with latent infection and thus protect against zoster, was not available. Some misclassification of zoster is possible. In UK primary care, diagnosis of zoster is clinically based with no laboratory testing. Any misclassification is likely to be non-differential with respect to exposure status, thus leading to an underestimation of associations.

Generalisability to other populations

The CPRD has been found to be broadly representative of the UK population in terms of key demographics. Our findings are therefore likely to have good generalisibility within the UK and to similar high income settings.

Study funding/potential competing interests:

This was independent research supported by the National Institute for Health Research.

Relative risk of zoster in patients with key risk factors of interest and other covariates

	Adjusted odds ratio (99% CI)*
Key risk factors of interest	
Rheumatoid arthritis	1.46 (1.38 to 1.55)
Systemic lupus erythematosus	1.72 (1.45 to 2.04)
Inflammatory bowel disease	1.36 (1.26 to 1.46)
Chronic obstructive pulmonary disease	1.32 (1.27 to 1.37)
Asthma	1.21 (1.17 to 1.25)
Chronic kidney disease	1.14 (1.09 to 1.18)
Depression	1.15 (1.10 to 1.20)
Diabetes	1.02 (0.99 to 1.05)
Other covariates	
HIV	5.07 (3.41 to 7.54)
Leukaemia	1.78 (1.39 to 2.28)
Lymphoma	3.90 (3.21 to 4.74)
Myeloma	2.16 (1.84 to 2.53)
Haematopoietic stem cell transplantation	13.46 (2.68 to 67.60)
Other unspecified cellular immune deficiencies	1.57 (1.10 to 2.22)

*Adjusted for HIV, leukaemia, lymphoma, myeloma, haematopoietic stem cell transplantation, other unspecified cellular immune deficiencies, rheumatoid arthritis, systemic lupus erythematosus, inflammatory bowel disease, chronic obstructive pulmonary disease, asthma, chronic kidney disease, depression, diabetes, smoking, and alcohol.

Long term maintenance of weight loss with non-surgical interventions in obese adults: systematic review and meta-analyses of randomised controlled trials

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STUDY QUESTION What is the randomised controlled evidence for the effectiveness of non-surgical weight interventions for maintenance of weight loss?

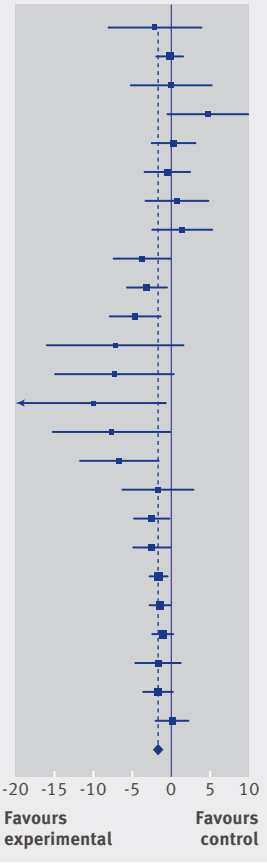
SUMMARY ANSWER Behavioural interventions covering both diet and physical activity show small but significant benefits on maintenance of weight loss. Orlistat 120 mg three times daily alongside behavioural interventions significantly adds to weight loss maintenance.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS
Behaviour change leads to moderate clinically meaningful changes in weight, but most individuals regain lost weight after initial weight loss. Behavioural interventions covering both diet and physical activity show small but significant benefits on weight loss maintenance for up to 24 months. Pharmacological support from orlistat 120 mg three times daily also shows small but significant benefits on weight loss maintenance for up to 36 months.

Difference in weight change at 12 months after initial weight loss in behavioural/lifestyle studies

Study or subgroup	Experimental Mean (SD)	Experimental Total	Control Mean (SD)	Control Total
Baum 1991	-3.63 (9.84)	15	-1.54 (6.49)	15
Cussler 2008	0.40 (5.00)	52	0.60 (4.00)	55
Harvey-Berino 2002 - FIPS	-10.40 (6.30)	32	-10.40 (9.30)	14
Harvey-Berino 2002 - Int	-5.70 (5.90)	30	-10.40 (9.30)	14
Harvey-Berino 2004 - FIPS	-3.90 (5.90)	77	-4.20 (7.90)	39
Harvey-Berino 2004 - Int	-4.70 (6.90)	77	-4.20 (7.90)	39
Kramer 1986 - WF	5.40 (5.81)	28	4.67 (6.58)	14
Kramer 1986 - SF	6.08 (4.72)	29	4.67 (6.57)	14
Perri 1984a	-5.81 (7.26)	26	-2.09 (5.03)	17
Perri 1984b	-7.50 (7.85)	48	-4.38 (5.23)	52
Perri 1986	1.54 (6.26)	35	6.16 (7.61)	32
Perri 1988 - BC	-12.88 (12.44)	19	-5.67 (6.90)	4
Perri 1988 - BCA	-12.97 (7.63)	18	-5.67 (6.90)	4
Perri 1988 - BCAS	-15.70 (14.29)	19	-5.67 (6.90)	4
Perri 1988 - BCS	-13.35 (7.37)	19	-5.67 (6.90)	4
Perri 2001 - PST	-10.80 (8.65)	23	-4.14 (4.86)	8
Perri 2001 - RPT	-5.85 (6.39)	20	-4.14 (4.86)	7
Perri 2008 - F2F	1.20 (5.47)	83	3.70 (6.22)	40
Perri 2008 - Phone	1.20 (5.94)	72	3.70 (6.22)	39
Sherwood 2013	0.77 (5.99)	210	2.40 (6.17)	209
Svetkey 2008 - F2F	-6.16 (7.66)	341	-4.73 (7.25)	170
Svetkey 2008 - Int	-5.82 (7.56)	347	-4.73 (7.25)	171
Wing 1996	3.90 (5.28)	23	5.60 (5.22)	27
Wing 2006 - F2F	1.30 (6.00)	105	3.00 (5.70)	53
Wing 2006 - Int	3.10 (7.50)	104	3.00 (5.70)	52
Total (95% CI)		1852		1097

Test for heterogeneity: τ^2=0.94, χ^2=37.39, df=24, P=0.04, I^2=36%
Test for overall effect: z=4.33, P<0.001



Selection criteria for studies
Data sources were Medline, PsycINFO, Embase, and the Cochrane Central Register of Controlled Trials. Included studies were randomised trials of interventions for maintenance of weight loss provided to initially obese adults (aged ≥18) after weight loss of ≥5% body weight with long term (≥12 months) follow-up of weight change (main outcome).

Primary outcome
Weight at 12 months after randomisation to the weight loss maintenance intervention.

Main results and role of chance
Behavioural interventions focusing on both food intake and physical activity resulted in an average of −1.56 kg (95% confidence interval −2.27 to −0.86 kg; 25 comparisons, 2949 participants) difference in weight regain compared with controls at 12 months. (In the figure the abbreviations are: BC=behaviour therapy + post-treatment therapy contact condition; BCA=behaviour therapy + post-treatment therapy contact + aerobic exercise maintenance condition; BCAS=behaviour therapy + post-treatment therapy contact + aerobic exercise maintenance + social influence maintenance programme condition; F2F=face to face condition, FIPS=frequent in-person support condition; MIPS=minimal in-person support condition; Int=internet condition; PST=problem solving therapy condition; RPT=relapse prevention training condition; SF=skill focus condition; phone=telephone condition; WF=weight focus condition.) Orlistat in combination with behavioural interventions resulted in a −1.80 kg (−2.54 to −1.06; eight comparisons, 1738 participants) difference compared with placebo at 12 months. There was a dose-response relation for treatment with orlistat, with 120 mg doses three times a day leading to greater weight loss maintenance compared with 60 mg and 30 mg three times a day (−2.34 kg (−3.03 to −1.65 kg) *v* −0.70 kg (−1.92 to 0.52 kg), P=0.02). There was no evidence for effectiveness for diet or physical activity only interventions or for using nutritional supplements or food replacements.

Bias, confounding, and other reasons for caution
All orlistat studies reported higher frequencies of adverse gastrointestinal events in the experimental compared with placebo control groups.

Study funding See bmj.com.

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Screening women for intimate partner violence in healthcare settings: abridged Cochrane systematic review and meta-analysis

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Listen to clinical advice on violence against women at bmj.com/podcast/2013/06/21/tackling-violence-against-women

STUDY QUESTION

Does screening in healthcare settings for intimate partner violence increase identification of women exposed to such violence, increase referral to support agencies, improve wellbeing, decrease further violence, or cause harm?

SUMMARY ANSWER

We found moderate evidence that screening in high income countries increases victim identification rates but not referral to support agencies. There is no evidence that screening increases wellbeing, reduces further violence, or causes harm to women.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Intimate partner violence is a breach of human rights with major public health and clinical impact. Screening all women in healthcare settings is advocated by many professional associations and is national policy in some countries. This review found no evidence that universal screening is warranted.

Selection criteria for studies

We conducted a systematic review and meta-analysis of trials assessing effectiveness of screening for intimate partner violence. We searched nine databases to July 2012 (CENTRAL, Medline, Medline(R), Embase, DARE, CINAHL, PsycINFO, Sociological Abstracts, and ASSIA) and five trials registers to 2010. We selected randomised or quasi-randomised trials of screening programmes for intimate partner violence involving all women aged 16 and above attending a healthcare setting. We included studies only where clinicians in the intervention arm personally conducted the screening or were informed of the screening result at the time of the consultation, compared with usual care (or no screening). Studies of screening programmes that were followed by structured interventions such as advocacy or therapeutic intervention were excluded.

Outcome(s)

Intervention and usual care groups were compared on identification of intimate partner violence and referral to support agencies (primary) and wellbeing, further violence, and harm (secondary).

Main results and role of chance

Eleven eligible trials (n=13 027) were identified. In six pooled studies (n=3564), screening increased the identification of intimate partner violence (risk ratio 2.33, 95% CI 1.39 to 3.89), particularly in antenatal settings (risk ratio 4.26, 1.76 to 10.31) (see figure). In three pooled studies (n=1400), we detected no increase in referrals to domestic violence support services (risk ratio 2.67, 0.99 to 7.2). Only two studies measured women's experience of violence after screening and found no reduction in intimate partner violence. One study measured physical and psychosocial outcomes; a benefit for physical health was not detected at 18 months, and there was no significant improvement in quality of life or post-traumatic stress disorder, depression, and alcohol and drug misuse. One study reported that screening does not cause harm.

Bias, confounding, and other reasons for caution

Meta-analyses were limited by heterogeneity in trial outcomes and measurement. Studies lacked attention to women's health and harm outcomes and were limited by short follow-up after screening. Nine studies minimised the risk of selection bias through effective random sequence allocation. Lack of blinding of participants and providers (performance bias), and the associated potential for differential behaviour across study groups, was the most consistent threat to validity.

Study funding/potential competing interests

La Trobe University (Melbourne) funded work undertaken towards the original review. KH and GF were members of the development group for the WHO guidelines on responding to intimate partner violence and sexual violence against women. GF chaired the programme development group of the UK NICE domestic violence and abuse guidelines.

This article is based on a Cochrane Review 2013, Issue 4, doi:10.1002/14651858.CD007007 (see www.thecochranelibrary.com for information). Cochrane Reviews are regularly updated as new evidence emerges and in response to feedback, and the Cochrane Database of Systematic Reviews should be consulted for the most recent version of the review.

Effect of screening on identification of intimate partner violence by healthcare setting