

Summary of findings tables

Question 1 [profile 1]

Date: 2007-06-04

Question: Should exclusive breastfeeding for at least 3 months be used in infants for the prevention of allergy?

Bibliography: 1. Gdalevich M, Mimouni D, David M, Mimouni M. Breast-feeding and the onset of atopic dermatitis in childhood: a systematic review and meta-analysis of prospective studies. J Am Acad Dermatol. 2001;45(4):520-7. 2. Gdalevich M, Mimouni D, Mimouni M. Breast-feeding and the risk of bronchial asthma in childhood: a systematic review with meta-analysis of prospective studies. J Pediatr. 2001;139(2):261-6. 3. Mimouni Bloch A, Mimouni D, Mimouni M, Gdalevich M. Does breastfeeding protect against allergic rhinitis during childhood? A meta-analysis of prospective studies. Acta Paediatr. 2002;91(3):275-9.

Quality assessment							Summary of findings				Importance	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients		Effect			Quality
							breastfeeding	control	Relative (95% CI)	Absolute		
Atopic dermatitis (follow-up mean 2.9 years¹)												
18	observational study ²	no serious limitations ³	no serious inconsistency	no serious indirectness	no serious imprecision ⁴	none	-/2079 ⁵	-/2079 ⁵	OR 0.77 (0.6 to 0.98)		⊕⊕⊕⊕ LOW	CRITICAL
Atopic dermatitis (high risk children) (follow-up mean 2.36 years¹)												
14 ²	observational study	no serious limitations ³	no serious inconsistency ⁶	no serious indirectness	no serious imprecision ⁴	none	-/668 ⁷	-/668 ⁷	OR 0.58 (0.41 to 0.92)		⊕⊕⊕⊕ LOW	CRITICAL
Atopic dermatitis (low risk + general population) (follow-up mean 3.14 years¹)												
7	observational study ²	no serious limitations ³	no serious inconsistency ⁶	no serious indirectness	serious ⁸	none	-/1410 ⁹	-/1410 ⁹	OR 0.84 (0.59 to 1.19)		⊕⊕⊕⊕ VERY LOW	CRITICAL
Allergic rhinitis (follow-up mean 2.25 years¹)												
6	observational study ²	no serious limitations ³	no serious inconsistency	no serious indirectness	serious ¹⁰	none	-/1651 ¹¹	-/1651 ¹¹	OR 0.74 (0.54 to 1.01)		⊕⊕⊕⊕ VERY LOW	CRITICAL
Allergic rhinitis (high risk only) (follow-up mean 2.4 years¹)												
4	observational study ²	no serious limitations	no serious inconsistency	no serious indirectness	serious ⁸	none	-/397 ¹²	-/397	RR 0.87 (0.48 to 1.58)		⊕⊕⊕⊕ VERY LOW	CRITICAL
Allergic rhinitis (low risk + general population) (follow-up mean 2.7 years¹)												
3	observational study ²	no serious limitations	no serious inconsistency	no serious indirectness	serious ¹⁰	none	-/1254 ¹³	-/1254 ¹³	RR 0.68 (0.47 to 0.99)		⊕⊕⊕⊕ VERY LOW	CRITICAL
Asthma (follow-up 1.5 to 8.4 years)												
12	observational study ²	no serious limitations ³	no serious inconsistency	no serious indirectness	no serious imprecision	none	-/4091 ¹⁴	-/4091 ¹⁴	RR 0.70 (0.6 to 0.81)		⊕⊕⊕⊕ LOW	CRITICAL
Asthma (high risk) (follow-up 1.5 to 8.4 years)												
7	observational study	no serious limitations ³	no serious inconsistency	no serious indirectness	no serious imprecision	none	-/620 ¹⁵	-/620 ¹⁵	RR 0.52 (0.35 to 0.79)		⊕⊕⊕⊕ LOW	CRITICAL
Asthma (low risk + general population) (follow-up 2 to 8.4 years)												
9	observational study	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	-/3471 ¹⁶	-/3471 ¹⁶	RR 0.73 (0.62 to 0.86)		⊕⊕⊕⊕ LOW	CRITICAL
Asthma (low risk) (follow-up 3 to 8.4 years)												

4	observational study	no serious limitations	no serious inconsistency	no serious indirectness	serious ⁸	none	-/957 ¹⁷	-/957 ¹⁷	RR 0.99 (0.48 to 2.03)		⊕○○○ VERY LOW	CRITICAL
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¹ Mean age at the end of follow-up.

² "prospective studies"

³ We assumed no serious limitations, but detailed information was not provided in the systematic review.

⁴ Results do not exclude almost no effect or a moderate effect.

⁵ There were 4158 children overall. Authors of the review did not report the number of children in each of the groups or the number of events per group.

⁶ We did not downgrade for inconsistency, since we already downgraded for imprecision.

⁷ There were 1337 children overall. Authors of the review did not report the number of children in each of the groups or the number of events per group.

⁸ Results include both important benefit and harm.

⁹ There were 2821 children overall. Authors of the review did not report the number of children in each of the groups or the number of events per group.

¹⁰ Results include an important benefit or no effect.

¹¹ There were 3303 children overall. Authors of the review did not report the number of children in each of the groups or the number of events per group.

¹² There were 794 children overall. Authors of the review did not report the number of children in each of the groups or the number of events per group.

¹³ There were 2509 children overall. Authors of the review did not report the number of children in each of the groups or the number of events per group.

¹⁴ There were 8183 children overall. Authors of the review did not report the number of children in each of the groups or the number of events per group.

¹⁵ There were 1241 children overall. Authors of the review did not report the number of children in each of the groups or the number of events per group.

¹⁶ There were 6942 children overall. Authors of the review did not report the number of children in each of the groups or the number of events per group.

¹⁷ There were 1915 children overall. Authors of the review did not report the number of children in each of the groups or the number of events per group.

Question 1 [profile 2]

Date: 2007-08-29

Question: Should exclusive breastfeeding for 3 to 7 months vs breastfeeding for up to 3 months be used in infants for the prevention of allergy?

Settings: developed countries

Bibliography: Kramer MS, Kakuma R. Optimal duration of exclusive breastfeeding. Cochrane Database of Systematic Reviews 2002, Issue 1. Art. No.: CD003517. DOI: 10.1002/14651858.CD003517.

Quality assessment							Summary of findings					Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients		Effect		Quality	
							exclusive breastfeeding for 3 to 7 months	breastfeeding for up to 3 months	Relative (95% CI)	Absolute		
Atopic eczema (follow-up 1 and 5 years)												
2	observational study	serious ¹	no serious inconsistency ²	no serious indirectness	serious ³	none	27/691	101/2927	RR 0.73 (0.49 to 1.08)	9 fewer per 1000 (from 18 fewer to 3 more)	⊕○○○ VERY LOW	CRITICAL
Pollen allergy (follow-up 5 years)												
1	observational study	serious ¹	no serious inconsistency	no serious indirectness ⁴	serious ^{3,5}	none	10/51	23/62	RR 0.53 (0.28 to 1.01)	174 fewer per 1000 (from 267 fewer to 4 more)	⊕○○○ VERY LOW	IMPORTANT
Asthma (follow-up 5 to 6 years)												
2	observational study	serious ¹	no serious inconsistency	no serious indirectness	serious ⁶	none	37/258	46/294	RR 0.91 (0.61 to 1.36)	14 fewer per 1000 (from 61 fewer to 56 more)	⊕○○○ VERY LOW	CRITICAL
Death (follow-up 12 months)												
1	observational study ⁷	no serious limitations	no serious inconsistency	no serious indirectness	very serious ^{6,8}	none	1/621	2/2862	RR 2.30 (0.21 to 25.37)	1 more per 1000 (from 1 fewer to 24 more)	⊕○○○ VERY LOW	CRITICAL
Other adverse outcomes												
20 ⁹	observational study	not assessed	not assessed	not assessed	not assessed	none	-	-	-	-	-	

¹ One small study had inadequate blinding and follow-up.

² We did not downgrade for inconsistency, since we already downgraded for limitations in execution and imprecision.

³ Results do not exclude important benefit or no effect.

⁴ We did not downgrade for indirectness although there is some uncertainty what "pollen allergy" means.

⁵ One very small study with few outcomes.

⁶ Results do not exclude important benefit or harm.

⁷ prospective cohort nested in a randomised trial

⁸ Only 3 event in both groups.

⁹ Nine studies were from developing countries (two of which were experimental trials) and 11 from developed countries. Studies do not suggest that infants who continue to be exclusively breastfed for six months, instead of three months, show deficits in weight or length gain, although results were imprecise and did not exclude modest risk of undernutrition. Based primarily on the analysis of a large cohort study nested in a randomized trial in Belarus, infants who continued exclusive breastfeeding for at least six months appear to have reduced risk of gastrointestinal infection. Data from the two Honduran trials suggest that exclusive breastfeeding through six months is associated with delayed resumption of menses and more rapid postpartum weight loss in the mother.

Question 2

Date: 2007-06-28

Question: Should antigen avoidance diet be used in pregnant or breastfeeding women to prevent development of allergy in children?

Bibliography: Kramer MS, Kakuma R. Maternal dietary antigen avoidance during pregnancy or lactation, or both, for preventing or treating atopic disease in the child. Cochrane Database of Systematic Reviews 2006, Issue 3. Art. No.: CD000133. DOI: 10.1002/14651858.CD000133.pub2.

Quality assessment							Summary of findings					Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients		Effect		Quality	
							antigen avoidance diet	control	Relative (95% CI)	Absolute		
Atopic eczema in first 12-18 months (follow-up 12-18 months)												
2	randomised trial	serious ¹	no serious inconsistency	serious ²	serious	none	35/157	39/177	RR 1.01 (0.57 to 1.79)	2 more per 1000 (from 95 fewer to 174 more)	⊕○○○ VERY LOW	CRITICAL
Asthma in first 18 months (follow-up 18 months)												
2	randomised trial	serious ¹	no serious inconsistency	serious ²	serious	none	4/157	2/177	RR 2.22 (0.39 to 12.67)	13 more per 1000 (from 7 fewer to 128 more)	⊕○○○ VERY LOW	CRITICAL
Allergic rhinitis/conjunctivitis in first 18 months (follow-up 18 months)												
1	randomised trial	serious ¹	no serious inconsistency	serious ²	very serious ³	none	0/81	0/82	not estimable ³	not estimable ³	⊕○○○ VERY LOW	CRITICAL
Allergic urticaria in first 18 months (follow-up 18 months)												
1	randomised trial	serious ¹	no serious inconsistency	serious ²	very serious ⁴	none	3/81	3/82	RR 1.01 (0.21 to 4.87)	0 more per 100 (from 3 fewer to 14 more)	⊕○○○ VERY LOW	CRITICAL
Any atopic condition in first 18 months (follow-up 18 months)												
1	randomised trial	serious ¹	no serious inconsistency	serious ²	serious ⁵	none	15/81	20/82	RR 0.76 (0.42 to 1.38)	59 fewer per 1000 (from 93 fewer to 142 more)	⊕○○○ VERY LOW	CRITICAL
Preterm birth												
2	randomised trial	serious ¹	no serious inconsistency	no serious indirectness	very serious ⁶	none	3/98	0/138	RR 10.06 (0.53 to 192.26)	0 more per 1000 (from 0 fewer to 0 more)	⊕○○○ VERY LOW	CRITICAL
Birth weight (measured with: grams; Better indicated by more)												
2	randomised trial	serious ¹	no serious inconsistency	serious ⁷	no serious imprecision	none	98	138	-	WMD -83 (-221 to 55)	⊕⊕○○ LOW	IMPORTANT

¹ "intention-to-treat" principle not followed, and in one trial randomisation was not described, there were inconsistencies in reporting of the number of randomised women, concealment not adequate, analysis based on individual subjects despite cluster randomization, large differences at baseline in type of allergy raises question about randomization

² only 18 months of observation

³ 1 trial with no events

⁴ one trial with 163 patients and 3 events

⁵ only one trial with 163 patients 45 events

⁶ two small trials, one with no events and another with 3 events in experimental group

⁷ uncertainty if birth weight is a reliable indicator of malnutrition

Question 4

Date: 2007-08-15

Question: Should methods aimed at reducing exposure to house dust mites vs no such methods be used in infants and preschool children?

Settings: home

Bibliography: [1] Chan-Yeung M, Ferguson A, Watson W, Dimich-Ward H, Rousseau R, Lilley M, et al. The Canadian Childhood Asthma Primary Prevention Study: outcomes at 7 years of age. *J Allergy Clin Immunol* 2005;116(1):49-55. [2] Chan-Yeung M, Manfreda J, Dimich-Ward H, Ferguson A, Watson W, Becker A. A randomized controlled study on the effectiveness of a multifaceted intervention program in the primary prevention of asthma in high-risk infants. *Arch Pediatr Adolesc Med* 2000;154(7):657-63. [3] Becker A, Watson W, Ferguson A, Dimich-Ward H, Chan-Yeung M. The Canadian asthma primary prevention study: outcomes at 2 years of age. *J Allergy Clin Immunol* 2004;113(4):650-6. [4] Schonberger HJ, Dompeling E, Knottnerus JA, Maas T, Muris JW, van Weel C, et al. The PREVASC study: the clinical effect of a multifaceted educational intervention to prevent childhood asthma. *Eur Respir J* 2005;25(4):660-70. [5] Halmerbauer G, Gartner C, Schierl M, Arshad H, Dean T, Koller DY, et al. Study on the Prevention of Allergy in Children in Europe (SPACE): allergic sensitization at 1 year of age in a controlled trial of allergen avoidance from birth. *Pediatr Allergy Immunol* 2003;14(1):10-7. [6] Horak F, Jr., Matthews S, Ihorst G, Arshad SH, Frischer T, Kuehr J, et al. Effect of mite-impermeable mattress encasings and an educational package on the development of allergies in a multinational randomized, controlled birth-cohort study -- 24 months results of the Study of Prevention of Allergy in Children in Europe. *Clin Exp Allergy* 2004;34(8):1220-5. [7] Arshad SH, Bateman B, Matthews SM. Primary prevention of asthma and atopy during childhood by allergen avoidance in infancy: a randomised controlled study. *Thorax* 2003;58(6):489-93. [8] Arshad SH, Bateman B, Sadeghnejad A, Gant C, Matthews SM. Prevention of allergic disease during childhood by allergen avoidance: the Isle of Wight prevention study. *J Allergy Clin Immunol* 2007;119(2):307-13. [9] Marks GB, Mahrshahi S, Kemp AS, Tovey ER, Webb K, Almqvist C, et al. Prevention of asthma during the first 5 years of life: a randomized controlled trial. *J Allergy Clin Immunol* 2006;118(1):53-61. [10] Mahrshahi S, Peat JK, Marks GB, Mellis CM, Tovey ER, Webb K, et al. Eighteen-month outcomes of house dust mite avoidance and dietary fatty acid modification in the Childhood Asthma Prevention Study (CAPS). *J Allergy Clin Immunol* 2003;111(1):162-8. [11] Corver K, Kerkhof M, Brussee JE, Brunekreef B, van Strien RT, Vos AP, et al. House dust mite allergen reduction and allergy at 4 yr: follow up of the PIAMA-study. *Pediatr Allergy Immunol* 2006;17(5):329-36. [12] Koopman LP, van Strien RT, Kerkhof M, Wijga A, Smit HA, de Jongste JC, et al. Placebo-controlled trial of house dust mite-impermeable mattress covers: effect on symptoms in early childhood. *Am J Respir Crit Care Med* 2002;166(3):307-13. [13] van Strien RT, Koopman LP, Kerkhof M, Oldenwening M, de Jongste JC, Gerritsen J, et al. Mattress encasings and mite allergen levels in the Prevention and Incidence of Asthma and Mite Allergy study. *Clin Exp Allergy* 2003;33(4):490-5. [14] van Strien RT, Koopman LP, Kerkhof M, Spithoven J, de Jongste JC, Gerritsen J, et al. Mite and pet allergen levels in homes of children born to allergic and nonallergic parents: the PIAMA study. *Environ Health Perspect* 2002;110(11):A693-8. [15] Simpson A, Simpson B, Custovic A, Craven M, Woodcock A. Stringent environmental control in pregnancy and early life: the long-term effects on mite, cat and dog allergen. *Clin Exp Allergy* 2003;33(9):1183-9. [16] Woodcock A, Lowe LA, Murray CS, Simpson BM, Pipis SD, Kissen P, et al. Early life environmental control: effect on symptoms, sensitization, and lung function at age 3 years. *Am J Respir Crit Care Med* 2004;170(4):433-9.

Quality assessment							Summary of findings				Quality	Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients		Effect			
							methods aimed at reducing exposure to house dust mites	no such methods	Relative (95% CI)	Absolute		
Rhinitis at 2 years of follow-up (follow-up 24 months)												
3	randomised trial	no serious limitations	no serious inconsistency	serious ⁴	serious ¹	none	128/637	162/619	RR 0.72 (0.49 to 1.06)	73 fewer per 1000 (from 134 fewer to 16 more)	⊕⊕○○ LOW	CRITICAL
Allergic rhinitis (diagnosed) or rhinitis after 3-8 years (follow-up 3 to 8 years)												
5	randomised trial	no serious limitations	no serious inconsistency	serious ⁴	serious ²	none	226/968	213/890	RR 1.03 (0.88 to 1.2)	7 more per 1000 (from 29 fewer to 48 more)	⊕⊕○○ LOW	CRITICAL
Eczema (atopic dermatitis) at 2 years of follow-up (follow-up 24 months)												
5	randomised trial	no serious limitations	no serious inconsistency	serious ⁴	serious ²	none	278/1308	262/1276	RR 1.02 (0.82 to 1.24)	4 more per 1000 (from 37 fewer to 49 more)	⊕⊕○○ LOW	CRITICAL
Eczema (atopic dermatitis) after 3-8 years (follow-up 3 to 8 years)												
5	randomised trial	no serious limitations	no serious inconsistency	serious ⁴	serious ²	none	163/968	161/890	RR 0.91 (0.7 to 1.2)	16 fewer per 1000 (from 54 fewer to 36 more)	⊕⊕○○ LOW	CRITICAL
Wheezing at 2 years (follow-up 24 months)												
4	randomised trial	no serious limitations	no serious inconsistency	serious ⁴	serious ³	none	199/1223	181/1193	RR 1.08 (0.87 to 1.34)	12 more per 1000 (from 20 fewer to 52 more)	⊕⊕○○ LOW	CRITICAL
Wheezing at 3-7 years (follow-up 3 to 7 years)												
4	randomised trial	no serious limitations	no serious inconsistency	serious ⁴	serious ²	none	118/910	144/828	RR 0.77 (0.62 to 0.98)	40 fewer per 1000 (from 66 fewer to 3 more)	⊕⊕○○ LOW	CRITICAL
Asthma at 2 years (follow-up 24 months)												

4	randomised trial	no serious limitations	no serious inconsistency	serious ⁴	serious ¹	none	121/856	143/826	RR 0.81 (0.61 to 1.06)	33 fewer per 1000 (from 67 fewer to 10 more)	⊕⊕○○ LOW	CRITICAL
Asthma at 3-8 years (follow-up 3 to 8 years)												
4	randomised trial	no serious limitations	no serious inconsistency	serious ⁴	serious ²	none	121/644	144/611	RR 0.82 (0.66 to 1.01)	42 fewer per 1000 (from 80 fewer to 2 more)	⊕⊕○○ LOW	CRITICAL

¹ Plausible results include no benefit as well as large benefit from the intervention.

² Plausible results include no benefit as well as benefit from the intervention in the context of the results for other outcomes.

³ Plausible results do not exclude important harm, although this seems unlikely given the other results.

⁴ The included trials used different interventions and it is not clear which parts of the multifaceted interventions would exert an effect.

Question 5

Date: 2007-08-15

Question: Should avoidance of pet allergens vs no such avoidance be used in non-allergic infants or preschool children?

Settings: population-based birth cohorts

Bibliography: 1. Chan-Yeung M., Ferguson A., Watson W., Dimich-Ward H., Rousseau R., Lilley M., Dybuncio A., Becker A. The Canadian Childhood Asthma Primary Prevention Study: outcomes at 7 years of age. *J Allergy Clin Immunol*, 2005;116:49-55. 2. Chan-Yeung M., Manfreda J., Dimich-Ward H., Ferguson A., Watson W., Becker A. A randomized controlled study on the effectiveness of a multifaceted intervention program in the primary prevention of asthma in high-risk infants. *Arch Pediatr Adolesc Med*, 2000;154:657-663. 3. Becker A., Watson W., Ferguson A., Dimich-Ward H., Chan-Yeung M. The Canadian asthma primary prevention study: outcomes at 2 years of age. *J Allergy Clin Immunol*, 2004;113:650-656. 4. Schonberger H.J., Dompeling E., Knottnerus J.A., Maas T., Muris J.W., van Weel C., van Schayck C.P. The PREVASC study: the clinical effect of a multifaceted educational intervention to prevent childhood asthma. *Eur Respir J*, 2005;25:660-670. 5. Halmerbauer G., Gartner C., Schierl M., Arshad H., Dean T., Koller D.Y., Karmaus W., Kuehr J., Forster J., Urbanek R., Frischer T. Study on the Prevention of Allergy in Children in Europe (SPACE): allergic sensitization at 1 year of age in a controlled trial of allergen avoidance from birth. *Pediatr Allergy Immunol*, 2003;14:10-17. 6. Horak F., Jr., Matthews S., Ithorst G., Arshad S.H., Frischer T., Kuehr J., Schwieger A., Forster J. Effect of mite-impermeable mattress encasings and an educational package on the development of allergies in a multinational randomized, controlled birth-cohort study -- 24 months results of the Study of Prevention of Allergy in Children in Europe. *Clin Exp Allergy*, 2004;34:1220-1225.

Quality assessment							Summary of findings				Importance	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients		Effect			Quality
							avoidance of pet allergens	no such avoidance	Relative (95% CI)	Absolute		
Rhinitis at 2 years of follow-up (follow-up 24 months)												
2	randomised trial	no serious limitations	no serious inconsistency	serious ¹	serious ²	none	126/579	155/557	RR 0.74 (0.52 to 1.11)	72 fewer per 1000 (from 133 fewer to 31 more)	⊕⊕○○ LOW	CRITICAL
Allergic rhinitis (diagnosis) at 7 years of follow-up (follow-up 7 years)												
1	randomised trial	no serious limitations	no serious inconsistency	serious ¹	serious ^{3,4}	none	64/202	49/178	RR 1.13 (0.71 to 1.81)	36 more per 1000 (from 80 fewer to 223 more)	⊕⊕○○ LOW	CRITICAL
Eczema (atopic dermatitis) at 2 years of follow-up (follow-up 24 months)												
2	randomised trial	no serious limitations	no serious inconsistency	serious ¹	serious ³	none	123/558	118/542	RR 1.02 (0.77 to 1.35)	4 more per 1000 (from 50 fewer to 76 more)	⊕⊕○○ LOW	CRITICAL
Eczema (atopic dermatitis: diagnosis) at 7 years of follow-up (follow-up 7 years)												
1	randomised trial	no serious limitations	no serious inconsistency	serious ¹	serious ^{3,4}	none	25/202	24/178	RR 0.92 (0.49 to 1.73)	11 fewer per 1000 (from 99 fewer to 69 more)	⊕⊕○○ LOW	CRITICAL
Wheezing (recurrent) at 2 years of follow-up (follow-up 24 months)												
2	randomised trial	no serious limitations	no serious inconsistency	serious ¹	no serious imprecision ³	none	85/531	83/521	RR 1.00 (0.77 to 1.32)	0 fewer per 1000 (from 37 fewer to 51 more)	⊕⊕⊕○ MODERATE	CRITICAL
Asthma at 2 years of follow-up (follow-up 24 months)												
2 ⁵	randomised trial	no serious limitations	no serious inconsistency	serious ¹	serious ^{3,4}	none	72/552	73/534	RR 1.01 (0.59 to 1.72)	1 more per 1000 (from 56 fewer to 99 more)	⊕⊕○○ LOW	CRITICAL
Asthma (diagnosis) at 7 years of follow-up (follow-up 7 years)												
1	randomised trial	no serious limitations	no serious inconsistency	serious ¹	serious ⁴	none	30/202	41/178	RR 0.44 (0.25 to 0.79)	129 fewer per 1000 (from 172 fewer to 48 fewer)	⊕⊕○○ LOW	CRITICAL

¹ Studies used multiple interventions directed at multiple potential risk factors.

² Results do not exclude a important benefit or no benefit.

³ Results do not exclude a important benefit or important harm, although the point estimate suggests no effect.

⁴ Small number of events.

⁵ We used definitions of "Asthma diagnosed by physician" or "asthma"

Question 7 [profile 1]

Date: 2007-07-31

Question: Should high efficiency particulate air filters be used for perennial allergic rhinitis?

Bibliography: Sheikh A, Hurwitz B, Shehata Y. House dust mite avoidance measures for perennial allergic rhinitis. Cochrane Database of Systematic Reviews 2007, Issue 1.

Quality assessment							Summary of findings					Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients		Effect		Quality	
							high efficiency particulate air filters	control	Relative (95% CI)	Absolute		
Quality of Life - not measured¹												
0	-	²	-	-	³	none ³	0	0	-	-		CRITICAL
Rhinitis symptoms (follow-up 2 to 8 weeks; Better indicated by less)												
2	randomised trial	very serious ²	serious ⁴	no serious indirectness	very serious ⁵	none ³	41	41	-	not pooled	⊕○○○ VERY LOW	CRITICAL
Days off/sick leave - not measured¹												
0	-	-	-	-	-	none	0/0	0/0	-	-		IMPORTANT
medication usage (follow-up 2 weeks; Better indicated by less)												
1	randomised trial	very serious ²	no serious inconsistency	no serious indirectness	very serious ⁵	none ³	32	32	-	- ⁶	⊕○○○ VERY LOW	IMPORTANT
adverse effects (follow-up 8 weeks)												
1	randomised trial	very serious ²	no serious inconsistency	no serious indirectness	very serious ⁵	none ³	0/9	0/9	not pooled	not pooled	⊕○○○ VERY LOW	IMPORTANT

¹ Outcome was not measured in the included studies

² allocation concealment and randomisation unclear or inadequate, power calculations with small samples not provided, outcome measures not validated.

³ Reporting bias not assessed.

⁴ Significant results in 1 trial and non-significant results in other trial not explained.

⁵ Very few patients.

⁶ Effect sizes not reported but analyses found significant reduction in medication usage.

Question 7 [profile 2]

Date: 2007-07-31

Question: Should acaricides be used for perennial allergic rhinitis?

Settings: Home

Bibliography: Sheikh A, Hurwitz B, Shehata Y. House dust mite avoidance measures for perennial allergic rhinitis. Cochrane Database of Systematic Reviews 2007, Issue 1.

Quality assessment							Summary of findings				Quality	Importance
							No of patients		Effect			
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	acaricides	control	Relative (95% CI)	Absolute		
Quality of Life - not measured¹												
0	-	-	-	-	-	none	0/0	0/0	-	-		CRITICAL
rhinitis symptoms (follow-up 6 to 12 months; Better indicated by less)												
2	randomised trial	serious ²	no serious inconsistency	no serious indirectness	very serious ³	none ⁴	27	25	-	not pooled ⁵	⊕○○○ VERY LOW	CRITICAL
Days off/sick leave - not measured¹												
0	-	-	-	-	-	none	0/0	0/0	-	-		IMPORTANT
Adverse effects (follow-up 12 months)												
1	randomised trial	serious ²	no serious inconsistency	no serious indirectness	very serious ³	none	0/10	0/10	not pooled ⁶	not pooled ⁶	⊕○○○ VERY LOW	IMPORTANT

¹ Outcome was not measured in the included studies.

² allocation concealment and randomisation unclear or inadequate, power calculations with small samples not provided,.

³ Very few patients.

⁴ Reporting bias not assessed.

⁵ 1 trial significant reduction of symptoms, 1 trial reduction of symptoms but significance unknown.

⁶ there were no events in both groups

Question 7 [profile 3]

Date: 2007-07-31

Question: Should barrier bedding be used for perennial allergic rhinitis?

Settings: Home

Bibliography: Sheikh A, Hurwitz B, Shehata Y. House dust mite avoidance measures for perennial allergic rhinitis. Cochrane Database of Systematic Reviews 2007, Issue 1.

Quality assessment							Summary of findings				Quality	Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients		Effect			
							barrier bedding	control	Relative (95% CI)	Absolute		
Quality of Life - not measured¹												
0	-	-	-	-	-	none	0/0	0/0	-	-		CRITICAL
Rhinitis symptoms (follow-up 12 months; measured with: Daily symptom scale; range of scores: 0-3; Better indicated by less)												
1	randomised trial	no serious limitations ²	no serious inconsistency	no serious indirectness	serious ³	none ⁴	100 ³	98	-	WMD 0.15 (-0.26 to 0.56)	⊕⊕⊕○ MODERATE	CRITICAL
Days off/sick leave - not measured¹												
0	-	-	-	-	-	none	0	0	-	-		IMPORTANT
Medication usage (follow-up 9 to 11 weeks; Better indicated by less)												
1	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	very serious ^{5,6}	none ⁴	30	30	-	not pooled ⁵	⊕⊕○○ LOW	IMPORTANT
Adverse effects - not reported												
0	-	-	-	-	-	none	-	-	-	-		NOT IMPORTANT

¹ Outcome was not measured

² Intent-to-treat analysis was not performed

³ The confidence interval crosses no difference and does not rule out a small increase.

⁴ Reporting bias not assessed.

⁵ No difference was found but the values were not reported.

⁶ Very few patients.

Question 7 [profile 4]

Date: 2009-03-28

Question: Should chemical methods to reduce house dust mite allergens be used in patients with asthma allergic to mites?

Settings: home

Bibliography: Gøtzsche PC, Johansen HK. House dust mite control measures for asthma. Cochrane Database of Systematic Reviews 2008, Issue 2. Art. No.: CD001187. DOI: 10.1002/14651858.CD001187.pub3.

Quality assessment							Summary of findings				Quality	Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients		Effect			
							chemical methods to reduce house dust mite allergens	control	Relative (95% CI)	Absolute		
Asthma symptoms (follow-up 3 to 12 months; Better indicated by lower values)												
4 ¹	randomised trials	serious ²	no serious inconsistency	no serious indirectness	serious ³	none ⁴	59	66	-	SMD 0.39 higher (0.04 to 0.75 higher)	⊕⊕○○ LOW	CRITICAL
Improvement of asthma (follow-up 6 to 12 months)												
3 ⁵	randomised trials	very serious ⁶	no serious inconsistency	no serious indirectness	serious ⁷	none ⁴	38/65 (58.5%)	45/73 (61.6%)	RR 0.94 (0.72 to 1.24)	37 fewer per 1000 (from 173 fewer to 148 more)	⊕○○○ VERY LOW	CRITICAL
Medication use (follow-up 12 months; Better indicated by lower values)												
1	randomised trials	serious ²	no serious inconsistency	no serious indirectness	serious ⁸	none ⁴	11	12	-	SMD 0.89 higher (0.02 to 1.75 higher)	⊕⊕○○ LOW	IMPORTANT
Adverse effects - not measured												
0	-	-	-	-	-	none	-	-	-	-		CRITICAL

¹ All studies included children; two also included adults.

² Randomisation method and allocation concealment not described, 88% follow-up.

³ No explanation was provided

⁴ Most trials were very small, and results may have been influenced by publication bias, which would exaggerate the effect of treatment.

⁵ All studies included children; one study also included adults.

⁶ Randomisation method and allocation concealment described in one study; 62% follow-up.

⁷ Few events and patients. Results do not exclude appreciable benefit or harm.

⁸ Very few patients.

Question 7 [profile 5]

Date: 2009-03-28

Question: Should physical methods to reduce house dust mite allergens be used in patients with asthma allergic to mites?

Settings: home

Bibliography: Gøtzsche PC, Johansen HK. House dust mite control measures for asthma. Cochrane Database of Systematic Reviews 2008, Issue 2. Art. No.: CD001187. DOI: 10.1002/14651858.CD001187.pub3.

Quality assessment							Summary of findings				Quality	Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients		Effect			
							physical methods to reduce house dust mite allergens	control	Relative (95% CI)	Absolute		
Asthma symptoms (follow-up 3 to 24 months; Better indicated by lower values)												
10	randomised trials	serious ¹	no serious inconsistency ²	no serious indirectness	no serious imprecision ³	none ⁴	513	485	-	SMD 0.07 lower (0.20 lower to 0.05 higher)	⊕⊕⊕○ MODERATE	CRITICAL
Improvement of asthma (follow-up 8 weeks)												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness ⁵	very serious ⁶	none	16/26 (61.5%)	15/27 (55.6%)	RR 1.11 (0.7 to 1.74)	61 more per 1000 (from 167 fewer to 411 more)	⊕⊕○○ LOW	CRITICAL
Medication use (follow-up 3 to 24 months⁷; Better indicated by lower values)												
6	randomised trials	serious ^{1,8}	no serious inconsistency	no serious indirectness	no serious imprecision	none	464	456	-	SMD 0.07 lower (0.20 lower to 0.06 higher)	⊕⊕⊕○ MODERATE	IMPORTANT
Unscheduled hospital visit or course of oral steroids (follow-up 6 months)												
1	randomised trials	serious ^{1,9}	no serious inconsistency	no serious indirectness	serious ¹⁰	none	38/315 (12.1%)	27/310 (8.7%)	RR 1.39 (0.87 to 2.20)	34 more per 1000 (from 11 fewer to 105 more)	⊕⊕○○ LOW	CRITICAL
Adverse effects - not measured												
0	-	-	-	-	-	none	0/0 (0%)	0/0 (0%)	-	-		CRITICAL

¹ Randomisation and allocation concealment were not described in 6 studies. Large loss to follow-up in most studies. Largest study showing no effect provided only a subgroup analysis.

² One open label small study (n=24) sponsored by air cleaner manufacturer showed very large effect; results of other studies were consistent.

³ Results do not exclude small benefit, however this is unlikely.

⁴ Most trials were small, and results may have been influenced by publication bias, which would exaggerate the effect of treatment.

⁵ There is some concern about directness since 50% of patients improved with placebo treatment (visit by nurse).

⁶ Very few events and patients. Results do not exclude an appreciable benefit or harm.

⁷ median: 12 months.

⁸ Randomisation and allocation concealment were not described in 2 studies. Only 3 studies were blinded. Large loss to follow-up in most studies. Largest study showing no effect provided only a subgroup analysis.

⁹ Subgroup analysis of one study. Most studies did not measure or report these obvious outcomes.

¹⁰ Few events.

Question 7 [profile 6]

Date: 2009-03-28

Question: Should a combination of physical and chemical methods to reduce house dust mite allergens be used in patients with asthma allergic to mite?

Settings: Home

Bibliography: Gøtzsche PC, Johansen HK. House dust mite control measures for asthma. Cochrane Database of Systematic Reviews 2008, Issue 2. Art. No.: CD001187. DOI: 10.1002/14651858.CD001187.pub3.

Quality assessment							Summary of findings					Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients		Effect		Quality	
							a combination of physical and chemical methods to reduce house dust mite allergens	control	Relative (95% CI)	Absolute		
Asthma symptoms (follow-up 4 to 6 weeks; range of scores: 0-0; Better indicated by lower values)												
2 ¹	randomised trials	serious ²	no serious inconsistency	no serious indirectness	serious ³	none ⁴	93	99	-	SMD 0.01 lower (0.29 lower to 0.28 higher)	⊕⊕○○ LOW	CRITICAL
Improvement of asthma (follow-up 24 weeks)												
1 ⁵	randomised trials	serious ²	no serious inconsistency	no serious indirectness	serious ³	none	3/23 (13%)	4/26 (15.4%)	RR 0.85 (0.21 to 3.4)	23 fewer per 1000 (from 122 fewer to 369 more)	⊕⊕○○ LOW	CRITICAL
Medication use - not measured												
0	-	-	-	-	-	none	0	0	-	-		IMPORTANT
Adverse effects - not measured												
0	-	-	-	-	-	none	0/0 (0%)	0/0 (0%)	-	-		CRITICAL

¹ Adults only.

² allocation concealment and randomisation unclear

³ Few patients. Results do not exclude small benefit or small harm.

⁴ Studies were small, and results may have been influenced by publication bias, which would exaggerate the effect of treatment.

⁵ Children only.

Question 9 [profile 1]

Date: 2007-08-17

Question: Should avoidance of exposure to pet allergens be used in patient with allergic rhinitis sensitive to these allergens?

Bibliography: Bjornsdottir US, Jakobinudottir S, Runarsdottir V, Juliusson S. The effect of reducing levels of cat allergen (Fel d 1) on clinical symptoms in patients with cat allergy. Ann Allergy Asthma Immunol. 2003;91(2):189-94.

Quality assessment							Summary of findings					Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients		Effect		Quality	
							avoidance of exposure to pet allergens	control	Relative (95% CI)	Absolute		
nasal congestion (follow-up 8 months; measured with: 11-point scale (0: no symptoms; 10: worst symptoms experienced)range of scores: 0-10; Better indicated by less)												
1	randomised trial	serious ¹	no serious inconsistency	serious ²	very serious ³	none	15	16	-		⊕000 VERY LOW	CRITICAL
Rhinorrhoea (follow-up 8 months; measured with: 11-point scale (0: no symptoms; 10: worst symptoms experienced)range of scores: 0-10; Better indicated by less)												
1	randomised trial	serious ¹	no serious inconsistency	serious ²	very serious ³	none	15	16	-		⊕000 VERY LOW	CRITICAL
nasal itching (follow-up 8 months; measured with: 11-point scale (0: no symptoms; 10: worst symptoms experienced)range of scores: 0-10; Better indicated by less)												
1	randomised trial	serious ¹	no serious inconsistency	serious ²	very serious ³	none	15	16	-		⊕000 VERY LOW	CRITICAL
Quality of life - not measured⁴												
0	-	-	-	-	-	none	0	0	-	-		CRITICAL

¹ 22% did not complete the study.

² Patients used multiple interventions that might also decrease house dust mite allergens.

³ One very small trial.

⁴ Quality of life was not measured in available studies.

Question 9 [profile 2]

Date: 2007-08-17

Question: Should avoidance of exposure to pet allergens be used in patient with asthma sensitive to these allergens?

Bibliography: Kilburn S, Lasserson TJ, McKean M. Pet allergen control measures for allergic asthma in children and adults. Cochrane Database Syst Rev. 2003(1):CD002989.

Quality assessment							Summary of findings					Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients		Effect		Quality	
							avoidance of exposure to pet allergens	control	Relative (95% CI)	Absolute		
Nasal symptoms (follow-up 3 months; Better indicated by less)												
1 ¹	randomised trial	no serious limitations	no serious inconsistency	serious ²	very serious ³	none	18	17	-	WMD 0 (0 to 0) ⁴	⊕⊕⊕⊕ VERY LOW	CRITICAL
Asthma symptoms (follow-up 3 months; Better indicated by less)												
2	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	very serious ⁵	none	40 ⁶	39 ⁶	-	not pooled ⁷	⊕⊕⊕⊕ LOW	CRITICAL
Medication usage (follow-up 3 months; Better indicated by less)												
2	randomised trial	no serious limitations	no serious inconsistency	serious ⁸	very serious ⁵	none	40 ⁶	39 ⁶	-	not pooled ⁹	⊕⊕⊕⊕ VERY LOW	IMPORTANT
Sleeping difficulty (follow-up 3 months)												
1	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	very serious ¹⁰	none	4/9	12/14	RR 0.21 (0.04 to 0.94)	677 fewer per 1000 (from 51 fewer to 823 fewer)	⊕⊕⊕⊕ LOW	CRITICAL
Quality of life - not measured¹¹												
0	-	-	-	-	-	none	0	0	-	-		CRITICAL

¹ trials used air filtration units

² only 7 of 35 patients had rhinitis

³ very small study; 7 patients had allergic rhinitis

⁴ Authors reported no important change in morning, afternoon and night nasal symptom scores in both groups.

⁵ Two very small trials.

⁶ one study had a cross-over design

⁷ Authors of one study did not report numerical values for changes in symptoms. Authors of both studies reported no important changes in symptoms in both groups.

⁸ There is some uncertainty about the directness of outcome measure.

⁹ One study did not detect any important difference in either maintenance or as-needed medication usage in the active or placebo groups. Other study withdrew the data contributed by participants who embarked new therapies or who came off existing therapies during the study; no medication usage scores were reported.

¹⁰ one very small trial

¹¹ Quality of life was not measured in available studies.

Question 11 [profile 1]

Date: 2007-08-20

Question: Should oral H1-antihistamines be used in patients with perennial or persistent allergic rhinitis?

Bibliography: Hore I., Georgalas C., Scadding G. Oral antihistamines for the symptom of nasal obstruction in persistent allergic rhinitis--a systematic review of randomized controlled trials. Clin Exp Allergy, 2005;35:207-212.

Quality assessment							Summary of findings				Importance	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients		Effect			Quality
							oral H1-antihistamines	control	Relative (95% CI)	Absolute		
Nasal obstruction (patient-assessed) (follow-up 2 to 12 weeks; measured with: 4-point scale; range of scores: 0-3; Better indicated by less)												
4	randomised trial	no serious limitations ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	142	126	-	WMD -0.52 (-0.31 to -0.73) ²	⊕⊕⊕⊕ HIGH	CRITICAL
Nasal obstruction (healthcare worker-assessed) (follow-up 2 to 12 weeks; measured with: 4-point scale range of scores: 0-3; Better indicated by less)												
4	randomised trial	no serious limitations ¹	no serious inconsistency	serious ³	no serious imprecision	none	190	181	-	WMD -0.33 (-0.16 to -0.49)	⊕⊕⊕○ MODERATE	IMPORTANT
Adverse effects (follow-up 2 to 12 weeks)												
7	randomised trial					none	0/0	0/0	not pooled ⁴	not pooled ⁴		IMPORTANT
Quality of life - not measured⁵												
0						none	0	0	-	-		

¹ there was little information on the methodological quality of the included studies; follow-up was from 84% to 98%

² Three studies presented data in a way that could not be pooled; one found no statistically significant reduction in "stiffness" in patients on antihistamine compared with placebo, second found that nasal stuffiness improved in 50% patients on loratadine and 13% on placebo, and the third found a statistically significant reduction in "stiffness" in patients on cetirizine 20 mg (but not 10 mg) daily compared with placebo.

³ there is uncertainty if the clinician assessment of the effect corresponds to the patients'

⁴ Headache was the most common adverse event, but there was no statistically significant difference between the groups; one study found statistically significant increase in fatigue in the antihistamine group with cetirizine 20 mg once daily, and one study found a statistically significant increase in tiredness in the placebo group, compared with loratidine 10 mg once daily.

⁵ Outcome was not measured in the included studies

Question 11 [profile 2]

Date: 2007-08-25

Question: Should oral H1-antihistamines be used in patients with seasonal allergic rhinitis?

Bibliography: see guideline document

Quality assessment							Summary of findings				Quality	Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients		Effect			
							oral H1-antihistamines	control	Relative (95% CI)	Absolute		
Nasal symptoms (Better indicated by less)												
80 ¹	randomised trial	no serious limitations ²	serious ³	no serious indirectness ⁴	no serious imprecision ⁵	none	-	-	-	-	⊕⊕⊕O MODERATE	CRITICAL
Quality of life (Better indicated by less)												
80 ¹	randomised trial	no serious limitations ²	serious ³	no serious indirectness ⁴	no serious imprecision ⁵	reporting bias ⁶	-	-	-	-	⊕⊕OO LOW	CRITICAL
Adverse effects												
80 ¹	randomised trial	no serious limitations ²	serious ³	no serious indirectness	no serious imprecision ⁵	reporting bias ⁷	-	-	-	-	⊕⊕OO LOW	CRITICAL

¹ An estimate based on the studies identified by ARIA group members

² We assumed most of the studies would have no serious limitations.

³ We assumed, there would be serious inconsistency in the results due to different effect of various H1-antihistamines or dosing schedules

⁴ We did not downgrade for indirectness, because we already downgraded for inconsistency, however different effect of particular medications and dosing may also be considered as influencing directness

⁵ We assumed, that with that many trials that will be no imprecision in the results

⁶ We assumed, based on the systematic reviews of other interventions, that many trials would not measure or report quality of life.

⁷ We assumed, based on the systematic reviews of other interventions in allergic rhinitis, that many trials would not measure or report adverse events.

Question 13

Date: 2007-06-13

Question: Should oral H1-antihistamines vs placebo be used for prevention of asthma in children at high risk?

Bibliography: 1. Allergic factors associated with the development of asthma and the influence of cetirizine in a double-blind, randomised, placebo-controlled trial: first results of ETAC. Early Treatment of the Atopic Child. *Pediatr Allergy Immunol.* 1998 Aug;9(3):116-24. 2. Bustos GJ, Bustos D, Bustos GJ, Romero O. Prevention of asthma with ketotifen in preasthmatic children: a three-year follow-up study. *Clin Exp Allergy.* 1995 Jun;25(6):568-73. 3. Iikura Y, Naspitz CK, Mikawa H, Talaricoficho S, Baba M, Sole D, Nishima S. Prevention of asthma by ketotifen in infants with atopic dermatitis. *Ann Allergy.* 1992 Mar;68(3):233-6.

Quality assessment							Summary of findings					Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients		Effect		Quality	
							oral H1-antihistamines	placebo	Relative (95% CI)	Absolute		
development of asthma (all trials) (follow-up 1 to 3 years)												
3	randomised trial	serious ¹	serious ²	no serious indirectness	serious ³	none	162/509	190/507	RR 0.48 (0.18 to 1.27)	20 fewer per 100 (from 10 fewer to 31 more)	⊕○○○ VERY LOW	CRITICAL
development of asthma (ketotifen only) (follow-up 1 to 3 years)												
2	randomised trial	serious ¹	no serious inconsistency	no serious indirectness	serious ⁴	none	12/111	39/110	RR 0.31 (0.17 to 0.55)	24 fewer per 100 (from 16 fewer to 29 fewer)	⊕○○○ LOW	CRITICAL
development of asthma (cetirizine only; all children) (follow-up 18 months)												
1	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	150/398	151/397	RR 0.99 (0.83 to 1.18)	4 fewer per 1000 (from 65 fewer to 68 more)	⊕⊕⊕⊕ HIGH	CRITICAL
development of asthma (cetirizine only; subgroup allergic to pollen and house dust mites) (follow-up 18 months)												
2	randomised trial	serious ⁵	no serious inconsistency	no serious indirectness	very serious ⁶	none	26/76	44/82	RR 0.64 (0.44 to 0.92)	193 fewer per 1000 (from 43 fewer to 301 fewer)	⊕○○○ VERY LOW	CRITICAL
Adverse effects (ketotifen) (follow-up 1 to 3 years)												
2	randomised trial	serious ¹	no serious inconsistency	no serious indirectness	very serious ⁴	none	0/0	0/0	not pooled ⁷	not pooled	⊕○○○ VERY LOW	CRITICAL
Adverse effects (cetirizine) (follow-up 18 months)												
1	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/0	0/0	not pooled	not pooled	⊕⊕⊕⊕ HIGH	

¹ no information on method of randomisation, blinding, concealment, and ITT in 2 trials, 15% lost to follow-up in one trial and no info on lost to follow-up in another

² One big trial showing no effect and 2 small ones showing benefit

³ Pooled relative risk = 0,46 (95% CI 0,17 to 1,26)

⁴ two small trials with small number with events

⁵ post hoc analysis of a subgroup

⁶ results do not exclude a large effect or negligible effect; few events

⁷ in one trial there were three cases of sedation, one case of vomiting, and one case of alopecia in ketotifen group, and no side effects in placebo group; second trial did not report adverse events

Question 14 [profile 1]

Date: 2009-03-04

Question: Should intranasal azelastine 0.56 mg/d vs placebo be used in adults with seasonal allergic rhinitis?

Bibliography: 1. Arcimowicz M, Samolinski B, Zawisza E. Clinical assessment of azelastine nasal spray in seasonal allergic rhinitis. Pol Merkuriusz Lekarski 1998;5(30):363-7. 2. Ciprandi G, Ricca V, Passalacqua G, Truffelli T, Bertolini C, Fiorino N, et al. Seasonal rhinitis and azelastine: long- or short-term treatment? J Allergy Clin Immunol 1997;99(3):301-7. 3. LaForce C, Dockhorn RJ, Prenner BM, Chu TJ, Kraemer MJ, Widlitz MD, et al. Safety and efficacy of azelastine nasal spray (Astelin NS) for seasonal allergic rhinitis: a 4-week comparative multicenter trial [see comments]. Ann Allergy Asthma Immunol 1996;76(2):181-8. 4. Lumry W, Prenner B, Corren J, Wheeler W. Efficacy and safety of azelastine nasal spray at a dose of 1 spray per nostril twice daily. Ann Allergy Asthma Immunol 2007;99(3):267-72. 5. Newson-Smith G, Powell M, Baehre M, Garnham SP, MacMahon MT. A placebo controlled study comparing the efficacy of intranasal azelastine and beclomethasone in the treatment of seasonal allergic rhinitis. Eur Arch Otorhinolaryngol 1997;254(5):236-41. 6. Pelucchi A, Chiapparino A, Mastropasqua B, Marazzini L, Hernandez A, Foresi A. Effect of intranasal azelastine and beclomethasone dipropionate on nasal symptoms, nasal cytology, and bronchial responsiveness to methacholine in allergic rhinitis in response to grass pollens. J Allergy Clin Immunol 1995;95(2):515-23. 7. Ratner PH, Findlay SR, Hampel F, Jr., van-Bavel J, Widlitz MD, Freitag JJ. A double-blind, controlled trial to assess the safety and efficacy of azelastine nasal spray in seasonal allergic rhinitis. J Allergy Clin Immunol 1994;94(5):818-25. 8. Storms WW, Pearlman DS, Chervinsky P, Grossman J, Halverson PC, Freitag JJ, et al. Effectiveness of azelastine nasal solution in seasonal allergic rhinitis. Ear Nose Throat J 1994;73(6):382-386, 390-394.

Quality assessment							Summary of findings					Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients		Effect		Quality	
							intranasal azelastine 0.56 mg/d	placebo	Relative (95% CI)	Absolute		
nasal symptoms (follow-up 2 to 12 weeks¹; Better indicated by lower values)												
8	randomised trials	serious ^{2,3}	serious ⁴	no serious indirectness	no serious imprecision ⁵	none	444	448	-	not pooled ^{3,4}	⊕⊕○○ LOW	CRITICAL
quality of life - not reported⁶												
0	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
adverse effects (bitter taste) (follow-up 2 to 12 weeks¹)												
5	randomised trials	serious ²	no serious inconsistency	no serious indirectness	no serious imprecision ⁷	strong association	78/414 (18.8%)	1/393 (0.3%)	RR 19.95 (6.38 to 62.36)	48 more per 1000 (from 14 more to 156 more)	⊕⊕⊕⊕ HIGH	IMPORTANT
adverse effects (somnia/fatigue) (follow-up 2 weeks)												
3	randomised trials	serious ²	no serious inconsistency	no serious indirectness	serious ⁸	none	11/404 (2.7%)	5/409 (1.2%)	RR 1.83 (0.69 to 4.85)	10 more per 1000 (from 4 fewer to 47 more)	⊕⊕○○ LOW	CRITICAL

¹ Most studies followed patients for 2-4 weeks

² Only 2 studies reported adherence to the intention to treat principle and none reported concealment of allocation.

³ Most studies did not report variability in results so no combined estimate could be calculated.

⁴ Five of 7 studies did not report variability in results. Point estimates showed 3% to 30% difference in symptom scores favouring azelastine. Results of 3 studies were not statistically significant.

⁵ We did not downgrade for imprecision, because we already downgraded for inconsistency. It was not possible to estimate precision since most studies did not report variability in results.

⁶ One study measured quality of life in 20-30% of patients and found no significant difference between azelastine and placebo-treated groups.

⁷ We did not downgrade for imprecision despite only 79 events, since this outcome was observed only in azelastine group. Studies that used 0.56 mg/d and 1.12 mg per day gave very consistent results; combining them would give 128 events and a RR of 21.07 (95% CI: 8.68 to 51.13).

⁸ Results do not exclude serious increase in somnolence/fatigue, or no effect.

Question 14 [profile 2]

Date: 2009-03-04

Question: Should intranasal azelastine 1.12 mg/d vs placebo be used in adults with seasonal allergic rhinitis?

Bibliography: 1. Berger WE, White MV. Efficacy of azelastine nasal spray in patients with an unsatisfactory response to loratadine. *Ann Allergy Asthma Immunol* 2003;91(2):205-11. 2. Ghimire A, Das BP, Mishra SC. Comparative efficacy of steroid nasal spray versus antihistamine nasal spray in allergic rhinitis. *Nepal Med Coll J* 2007;9(1):17-21. 3. LaForce C, Dockhorn RJ, Prenner BM, Chu TJ, Kraemer MJ, Widlitz MD, et al. Safety and efficacy of azelastine nasal spray (Astelin NS) for seasonal allergic rhinitis: a 4-week comparative multicenter trial [see comments]. *Ann Allergy Asthma Immunol* 1996;76(2):181-8. 4. LaForce CF, Corren J, Wheeler WJ, Berger WE. Efficacy of azelastine nasal spray in seasonal allergic rhinitis patients who remain symptomatic after treatment with fexofenadine. *Ann Allergy Asthma Immunol* 2004;93(2):154-9. 5. Newson-Smith G, Powell M, Baehre M, Garnham SP, MacMahon MT. A placebo controlled study comparing the efficacy of intranasal azelastine and beclomethasone in the treatment of seasonal allergic rhinitis. *Eur Arch Otorhinolaryngol* 1997;254(5):236-41. 6. Ratner PH, Findlay SR, Hampel F, Jr., van-Bavel J, Widlitz MD, Freitag JJ. A double-blind, controlled trial to assess the safety and efficacy of azelastine nasal spray in seasonal allergic rhinitis. *J Allergy Clin Immunol* 1994;94(5):818-25. 7. Storms WW, Pearlman DS, Chervinsky P, Grossman J, Halverson PC, Freitag JJ, et al. Effectiveness of azelastine nasal solution in seasonal allergic rhinitis. *Ear Nose Throat J* 1994;73(6):382-386, 390-394.

Quality assessment							Summary of findings				Quality	Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients		Effect			
							intranasal azelastine 1.12 mg/d	placebo	Relative (95% CI)	Absolute		
nasal symptoms (follow-up 2 weeks¹; Better indicated by lower values)												
7	randomised trials	serious ^{2,3}	no serious inconsistency ⁴	no serious indirectness	serious ⁵	none	457	455	-	not pooled ^{3,4}	⊕⊕○○	CRITICAL
quality of life - not measured												
0	-	-	-	-	-	none	0	0	-	-		CRITICAL
adverse effects (bitter taste) (follow-up 2 to 12 weeks)												
5	randomised trials	serious ²	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	49/369 (13.3%)	0.01% ⁶	RR 22.91 (5.59 to 93.95)	2 more per 1000 (from 0 more to 9 more)	⊕⊕⊕⊕	IMPORTANT
adverse effects (somnolence/fatigue) (follow-up 2 weeks)												
6	randomised trials	serious ²	no serious inconsistency	no serious indirectness	serious ⁷	none	16/444 (3.6%)	6/442 (1.4%)	RR 2.17 (0.93 to 5.08)	16 more per 1000 (from 1 fewer to 55 more)	⊕⊕○○	CRITICAL

¹ One study followed patients for 4 weeks

² One study was not blinded, 3/7 did not report adherence to the intention to treat principle and none reported concealment of allocation.

³ Most studies did not report variability in results so no combined estimate could be calculated.

⁴ Five of 7 studies did not report variability in results. Point estimates showed 8% to 30% difference in symptom scores favouring azelastine. Results of 2 studies were not statistically significant.

⁵ We downgraded for imprecision, because it was not possible to estimate precision since most studies did not report variability in results.

⁶ No event occurred in control groups. We assumed a baseline risk of 1 per 10,000 to estimate the absolute effect.

⁷ Results do not exclude important harm or no effect.

Question 14 [profile 3]

Date: 2009-03-04

Question: Should intranasal azelastine 0.56 mg/d vs placebo be used in adults with perennial/persistent allergic rhinitis?

Bibliography: 1. Davies RJ, Lund VJ, Harten-Ash VJ. The effect of intranasal azelastine and beclomethasone on the symptoms and signs of nasal allergy in patients with perennial allergic rhinitis. *Rhinology* 1993;31(4):159-64.

2. Stern MA, Wade AG, Ridout SM, Cambell LM. Nasal budesonide offers superior symptom relief in perennial allergic rhinitis in comparison to nasal azelastine. *Ann Allergy Asthma Immunol* 1998;81(4):354-8.

Quality assessment							Summary of findings				Importance	
							No of patients		Effect			Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	intranasal azelastine 0.56 mg/d	placebo	Relative (95% CI)	Absolute		
nasal symptoms (follow-up 6 weeks; Better indicated by lower values)												
2	randomised trials	serious ¹	serious ²	no serious indirectness	no serious imprecision ³	none	110	87	-	not pooled ⁴	⊕⊕○○ LOW	CRITICAL
quality of life - not measured												
0	-	-	-	-	-	none	0	0	-	-		CRITICAL
adverse effects (follow-up 6 weeks; bitter taste⁵)												
1 ⁶	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ⁷	none	22/45 (48.9%)	0/22	RR 22.5 (1.4 to 354.6)	490 more per 1000 ⁸	⊕⊕○○ LOW	IMPORTANT

¹ One study was not blinded, none reported concealment of allocation or adherence to intention to treat principle. In one trial only 78% of patients finished the study and the other did not report follow-up.

² Both studies reported their results on graphs only with no measure of variability. However, one reported a statistically significant benefit with azelastine and the other reported no difference.

³ We did not downgrade for imprecision, because we already downgraded for inconsistency. Precision of the results could not be evaluated, because no measure of variability was reported.

⁴ One study reported a statistically significant benefit with azelastine and the other reported no difference. Data were reported as graphs only with no measure of variability.

⁵ nausea and vomiting, sore throat, and intolerance to nasal spray were also more common in azelastine treated patients

⁶ One study did not report any adverse effects

⁷ One small study with few events.

⁸ No events occurred in control group. Therefore, it was not possible to estimate the precision of the absolute effect.

Question 14 [profile 4]

Date: 2009-03-04

Question: Should intranasal azelastine 1.12 mg/d vs placebo be used in adults with perennial/persistent allergic rhinitis?

Bibliography: Golden S, Teets SJ, Lehman EB, Mauger EA, Chinchilli V, Berlin JM, et al. Effect of topical nasal azelastine on the symptoms of rhinitis, sleep, and daytime somnolence in perennial allergic rhinitis. Ann Allergy Asthma Immunol 2000;85(1):53-7.

Quality assessment							Summary of findings				Importance	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients		Effect			Quality
							intranasal azelastine 1.12 mg/d	placebo	Relative (95% CI)	Absolute		
nasal symptoms (follow-up 8 weeks; measured with: 5-point scale; range of scores: 0-4; Better indicated by lower values)												
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	very serious ²	none	8	11	-	mean 0.48 lower (1.43 lower to 0.48 higher) ³	⊕○○○ VERY LOW	CRITICAL
quality of life - not measured												
0	-	-	-	-	-	none	0/0 (0%)	0/0 (0%)	-	-		CRITICAL
adverse effects (withdrawal from the study)												
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	very serious ⁴	none	3/12 (25%)	0/12	RR 7.0 (0.4 to 122)	250 more per 1000 ⁵	⊕○○○ VERY LOW	CRITICAL

¹ Sample size calculation was based on an erroneous assumption that the effect of azelastine would be the same as intranasal steroid. 79% of patients completed the study.

² One very small study with results not excluding important benefit or harm.

³ point estimate favours azelastine

⁴ One very small study with results not excluding important harm.

⁵ No events occurred in control group. Therefore, it was not possible to estimate the precision of the absolute effect.

Question 14 [profile 5]

Date: 2009-03-04

Question: Should intranasal azelastine 0.56 mg/d vs placebo be used in children with perennial allergic rhinitis?

Bibliography: Herman D, Garay R, Le-Gal M. A randomized double-blind placebo controlled study of azelastine nasal spray in children with perennial rhinitis. Int J Pediatr Otorhinolaryngol 1997;39(1):1-8.

Quality assessment							Summary of findings				Quality	Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients		Effect			
							intranasal azelastine 0.56 mg/d	placebo	Relative (95% CI)	Absolute		
nasal symptoms (follow-up 6 weeks; Better indicated by lower values)												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	very serious ¹	none	58	59	-	not pooled ²	⊕⊕○○ LOW	CRITICAL
quality of life - not measured												
0	-	-	-	-	-	none	0	0	-	-		CRITICAL
adverse effects												
1	randomised trials	no serious limitations ³	no serious inconsistency	no serious indirectness	serious ⁴	none	17/64 (26.6%) ⁵	19/61 (31.1%) ⁵	not pooled	not pooled	⊕⊕⊕○ MODERATE	CRITICAL

¹ Single study with 125 participants; no measure of variability was provided.

² Authors reported results on a graph with no measure of variability, but on average a difference of 10 to 15% between azelastine and placebo was observed and the p-value for the difference was <0.0001.

³ Authors did not report somnolence and bitter taste which one could expect to occur.

⁴ Single study with 125 participants; there were only 29 events in total. Some adverse events that one would expect to occur (e.g. bitter taste) were not reported.

⁵ Assuming that adverse events were independent, i.e. none occurred in the same patient twice. Only number of events not number of patients with an event were reported.

Question 14 [profile 6]

Date: 2009-03-07

Question: Should intranasal levocabastine vs placebo be used in adults with seasonal allergic rhinitis?

Bibliography: 1. Dahl R., Pedersen B., Larsen B. Intranasal levocabastine for the treatment of seasonal allergic rhinitis: a multicentre, double-blind, placebo-controlled trial. *Rhinology*, 1995;33:121-125. 2. Di Lorenzo G., Gervasi F., Drago A., Esposito Pellitteri M., Di Salvo A., Cosentino D., Potestio M., Colombo A., Candore G., Mansueto S., Caruso C. Comparison of the effects of fluticasone propionate, aqueous nasal spray and levocabastine on inflammatory cells in nasal lavage and clinical activity during the pollen season in seasonal rhinitis. *Clin Exp Allergy*, 1999;29:1367-1377. 3. Hampel F., Jr., Martin B.G., Dolen J., Travers S., Karcher K., Holton D. Efficacy and safety of levocabastine nasal spray for seasonal allergic rhinitis. *Am J Rhinol*, 1999;13:55-62. 4. Ortolani C., Foresi A., Di Lorenzo G., Bagnato G., Bonifazi F., Crimi N., Emmi L., Prandini M., Senna G.E., Tursi A., Mirone C., Leone C., Fina P., Testi R. A double-blind, placebo-controlled comparison of treatment with fluticasone propionate and levocabastine in patients with seasonal allergic rhinitis. FLNCO2 Italian Study Group. *Allergy*, 1999;54:1173-1180. 5. Schata M., Jorde W., Richarz-Barthauer U. Levocabastine nasal spray better than sodium cromoglycate and placebo in the topical treatment of seasonal allergic rhinitis. *The Journal of allergy and clinical immunology*, 1991;87:873-878. 6. Svensson C., Andersson M., Greiff L., Blychert L.O., Persson C.G. Effects of topical budesonide and levocabastine on nasal symptoms and plasma exudation responses in seasonal allergic rhinitis. *Allergy*, 1998;53:367-374.

Quality assessment							Summary of findings					Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients		Effect		Quality	
							intranasal levocabastine	placebo	Relative (95% CI)	Absolute		
nasal symptoms (follow-up 4 to 6 weeks; Better indicated by lower values)												
6	randomised trials	no serious limitations ¹	no serious inconsistency	no serious indirectness	no serious imprecision ²	none	242	233	-	SMD 0.48 lower (0.15 to 0.81 lower) ³	⊕⊕⊕⊕ HIGH	CRITICAL
nasal symptoms (global assessment of efficacy) (follow-up 2 to 4 weeks; rating: excellent or good)												
2	randomised trials	no serious limitations ⁴	no serious inconsistency	no serious indirectness	serious ⁵	none	89/150 (59.3%)	53/149 (35.6%)	RR 1.83 (1.16 to 2.89)	30 more per 100 (from 6 more to 67 more)	⊕⊕⊕○ MODERATE	CRITICAL
ocular symptoms (follow-up 2 to 6 weeks; Better indicated by lower values)												
4	randomised trials	no serious limitations ⁶	no serious inconsistency	no serious indirectness	serious ⁷	none	262	253	-	not pooled ⁸	⊕⊕⊕○ MODERATE	IMPORTANT
quality of life - not measured												
0	-	-	-	-	-	none	0	0	-	-		CRITICAL
adverse effects (follow-up 2 to 4 weeks; somnolence/fatigue⁹)												
2	randomised trials	serious ^{9,10}	no serious inconsistency	no serious indirectness	serious ¹¹	none	4/151 (2.6%)	1/157 (0.6%)	RR 3.17 (0.51 to 19.71)	14 more per 1000 (from 3 fewer to 119 more)	⊕⊕○○ LOW	CRITICAL

¹ One study blinded patients only and 2 did not report type of analysis (overall 10% of patients did not complete these studies)

² Results do not exclude small or large effect.

³ Other 3 trials did not report variability in results so it was not possible to combine their results. However, all reported statistically significant difference favouring levocabastine (one showed a difference of ~12% and the other of ~28%; the third trial did not report the scale or variability in results).

⁴ In one study 25% patients did not complete treatment.

⁵ Results do not exclude a large effect or a negligible one. Only 142 events.

⁶ One study blinded patients only, 2 did not report type of analysis, and only one study reported variability in results.

⁷ It was not possible to estimate the precision of the findings since only one study provided variability in results.

⁸ One study reported -18% difference vs placebo, second reported 71.4% days free of eye symptoms compared to 56.1% with placebo, third reported a change in symptoms -1.92 vs -0.19 on a 4-point scale, and the last reported an effect size of -0.28 (95% CI: -1.10 to 0.54) favouring levocabastine.

⁹ Other adverse effects were poorly reported. In one study 4 vs 3 patients withdrew due to unspecified adverse effects, one reported that there were no adverse effects, one provided a detailed table but there were no differences and 2 studies did not report adverse effects at all.

¹⁰ 15% patients did not complete the studies

¹¹ Results do not exclude a large harm or a benefit. Very few events.

Question 14 [profile 7]

Date: 2009-03-07

Question: Should intranasal olopatadine 0.4% vs placebo be used in adults with seasonal allergic rhinitis?

Bibliography: 1. Fairchild CJ, Meltzer EO, Roland PS, Wells D, Drake M, Wall GM. Comprehensive report of the efficacy, safety, quality of life, and work impact of Olopatadine 0.6% and Olopatadine 0.4% treatment in patients with seasonal allergic rhinitis. Allergy Asthma Proc 2007;28(6):716-23. 2. Hampel FC, Jr., Ratner PH, Amar NJ, van Bavel JH, Mohar D, Fairchild CJ, et al. Improved quality of life among seasonal allergic rhinitis patients treated with olopatadine HCl nasal spray 0.4% and olopatadine HCl nasal spray 0.6% compared with vehicle placebo. Allergy Asthma Proc 2006;27(3):202-7. 3. Meltzer EO, Hampel FC, Ratner PH, Bernstein DL, Larsen LV, Berger WE, et al. Safety and efficacy of olopatadine hydrochloride nasal spray for the treatment of seasonal allergic rhinitis. Ann Allergy Asthma Immunol 2005;95(6):600-6. 4. Ratner PH, Hampel FC, Amar NJ, van Bavel JH, Mohar D, Marple BF, et al. Safety and efficacy of olopatadine hydrochloride nasal spray for the treatment of seasonal allergic rhinitis to mountain cedar. Ann Allergy Asthma Immunol 2005;95(5):474-9.

Quality assessment							Summary of findings				Importance	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients		Effect			Quality
							intranasal olopatadine 0.4%	placebo	Relative (95% CI)	Absolute		
nasal symptoms (follow-up 2 weeks; measured with: % change from baseline; Better indicated by lower values)												
2	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias ¹	418	416	-	MD 8.87 lower (5.55 to 12.18 lower) ²	⊕⊕⊕○ MODERATE	CRITICAL
quality of life (follow-up 2 weeks; measured with: change in Rhinoconjunctivitis Quality-of-Life Questionnaire (RQLQ); range of scores: 0-6; Better indicated by lower values)												
2	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious ³	reporting bias ¹	418	416	-	MD 0.35 lower ^{4,5}	⊕⊕○○ LOW	CRITICAL
eye symptoms (follow-up 2 weeks; measured with: percent change from baseline; Better indicated by lower values)												
2	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious ³	reporting bias ¹	418	416	-	MD 9.1 lower (1.26 to 16.93 lower) ⁶	⊕⊕○○ LOW	IMPORTANT
adverse effects (somnolence) (follow-up 2 weeks)												
2	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious ⁷	none	4/418 (1%)	1/416 (0.2%)	RR 2.97 (0.47 to 18.76)	5 more per 1000 (from 1 fewer to 43 more)	⊕⊕⊕○ MODERATE	CRITICAL
adverse effects (bitter taste) (follow-up 2 weeks)												
2	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	strong association ⁸	31/418 (7.4%)	2/417 (0.5%)	RR 15.46 (4.13 to 58.25)	69 more per 1000 (from 15 more to 275 more)	⊕⊕⊕⊕ HIGH	IMPORTANT

¹ There are only 2 studies available. Results of these two studies were published as 4 separate papers and all were supported by the manufacturer of olopatadine.

² Mean change from baseline in the placebo group was -22.5%.

³ Results do not exclude a moderate effect or no effect.

⁴ Mean change from baseline in the RQLQ score combined from both studies was -1.15 points in the olopatadine 0.4% and -0.8 points the placebo group. Authors did not provide a measure of variability for the total score combined from both studies. Based on the results of one of these studies that reported variability in results, a mean difference between olopatadine 0.4% and placebo in RQLQ score would be -0.30 points (95% CI: -0.06 to -0.54). Assuming a minimal important difference for RQLQ is 0.5 points, a mean change is most likely lower than the MID.

⁵ Mean change from baseline in the placebo group was -0.8 points.

⁶ Mean change from baseline in the placebo group was -23.6%.

⁷ Results do not exclude no effect or important harm.

⁸ lower limit of 95% CI is 4.0.

Question 14 [profile 8]

Date: 2009-03-07

Question: Should intranasal olopatadine 0.6% vs placebo be used in adults with seasonal allergic rhinitis?

Bibliography: 1. Fairchild CJ, Meltzer EO, Roland PS, Wells D, Drake M, Wall GM. Comprehensive report of the efficacy, safety, quality of life, and work impact of Olopatadine 0.6% and Olopatadine 0.4% treatment in patients with seasonal allergic rhinitis. Allergy Asthma Proc 2007;28(6):716-23. 2. Hampel FC, Jr., Ratner PH, Amar NJ, van Bavel JH, Mohar D, Fairchild CJ, et al. Improved quality of life among seasonal allergic rhinitis patients treated with olopatadine HCl nasal spray 0.4% and olopatadine HCl nasal spray 0.6% compared with vehicle placebo. Allergy Asthma Proc 2006;27(3):202-7. 3. Meltzer EO, Hampel FC, Ratner PH, Bernstein DI, Larsen LV, Berger WE, et al. Safety and efficacy of olopatadine hydrochloride nasal spray for the treatment of seasonal allergic rhinitis. Ann Allergy Asthma Immunol 2005;95(6):600-6. 4. Ratner PH, Hampel FC, Amar NJ, van Bavel JH, Mohar D, Marple BF, et al. Safety and efficacy of olopatadine hydrochloride nasal spray for the treatment of seasonal allergic rhinitis to mountain cedar. Ann Allergy Asthma Immunol 2005;95(5):474-9.

Quality assessment							Summary of findings				Importance	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients		Effect			Quality
							intranasal olopatadine 0.6%	placebo	Relative (95% CI)	Absolute		
nasal symptoms (follow-up 2 weeks; measured with: percentage change from baseline; Better indicated by lower values)												
2	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias ¹	406	416	-	MD 11.73 lower (8.17 to 15.30 lower) ²	⊕⊕⊕○ MODERATE	CRITICAL
quality of life (follow-up 2 weeks; measured with: change in Rhinoconjunctivitis Quality-of-Life Questionnaire (RQLQ); range of scores: 0-6; Better indicated by lower values)												
2	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious ³	reporting bias ¹	406	416	-	MD 0.45 lower ^{4,5}	⊕⊕○○ LOW	CRITICAL
eye symptoms (follow-up 2 days; measured with: percentage change from baseline; Better indicated by lower values)												
2	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias ¹	406	416	-	MD 14.51 lower (7.47 to 21.54 lower) ⁶	⊕⊕⊕○ MODERATE	IMPORTANT
adverse effects (somnolence) (follow-up 2 weeks)												
2	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious ⁷	none	4/406 (1%)	1/417 (0.2%)	RR 4.11 (0.62 to 27.27)	7 more per 1000 (from 1 fewer to 63 more)	⊕⊕⊕○ MODERATE	CRITICAL
adverse effects (bitter taste) (follow-up 2 weeks)												
2	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	very strong association ⁸	53/406 (13.1%)	2/417 (0.5%)	RR 27.22 (7.39 to 101.0)	126 more per 1000 (from 31 more to 480 more)	⊕⊕⊕⊕ HIGH	IMPORTANT

¹ There are only 2 studies available. Results of these two studies were published as 4 separate papers and all were supported by the manufacturer of olopatadine. The only conference abstracts we identified that also reported this outcome was also supported by the manufacturer.

² Mean change from baseline in the placebo group was -22.5%.

³ Results do not exclude a moderate or negligible effect.

⁴ Mean change from baseline in the placebo group was -0.8 points.

⁵ Mean change from baseline in the RQLQ score combined from both studies was -1.25 points in the olopatadine 0.6% and -0.8 points the placebo group. Authors did not provide a measure of variability for the total score combined from both studies. Based on the results of one of these studies that reported variability in results, a mean difference between olopatadine 0.6% and placebo in RQLQ score would be -0.40 points (95% CI: -0.15 to -0.65). Assuming a minimal important difference for RQLQ is 0.5 points, a fair proportion of patients might have benefited from the treatment at least minimally.

⁶ Mean change from baseline in the placebo group was -23.6%.

⁷ Results do not exclude important harm or no effect.

⁸ Lower limit of 95% CI is 7.4.

Question 15 [profile 1]

Date: 2009-03-10

Question: Should intranasal H1-antihistamines vs oral H1-antihistamines be used in adults with seasonal allergic rhinitis?

Bibliography: 1. Berger W, Hampel F, Jr., Bernstein J, Shah S, Sacks H, Meltzer EO. Impact of azelastine nasal spray on symptoms and quality of life compared with cetirizine oral tablets in patients with seasonal allergic rhinitis. *Ann Allergy Asthma Immunol* 2006;97(3):375-81. 2. Berger WE, White MV. Efficacy of azelastine nasal spray in patients with an unsatisfactory response to loratadine. *Ann Allergy Asthma Immunol* 2003;91(2):205-11. 3. Charpin D, Godard P, Garay RP, Baehre M, Herman D, Michel FB. A multicenter clinical study of the efficacy and tolerability of azelastine nasal spray in the treatment of seasonal allergic rhinitis: a comparison with oral cetirizine. *Eur Arch Otorhinolaryngol* 1995;252(8):455-8. 4. Conde Hernandez DJ, Palma Aqilar JL, Delgado Romero J. Comparison of azelastine nasal spray and oral ebastine in treating seasonal allergic rhinitis. *Curr Med Res Opin* 1995;13(6):299-304. 5. Corren J, Storms W, Bernstein J, Berger W, Nayak A, Sacks H, et al. Effectiveness of azelastine nasal spray compared with oral cetirizine in patients with seasonal allergic rhinitis. *Clin Ther* 2005;27(5):543-53. 6. Gambardella R. A comparison of the efficacy of azelastine nasal spray and loratidine tablets in the treatment of seasonal allergic rhinitis. *J Int Med Res* 1993;21(5):268-75. 7. Swedish GP Allergy Team. Topical levocabastine compared with oral loratidine for the treatment of seasonal allergic rhinoconjunctivitis. *Allergy* 1994;49(8):611-5.

Quality assessment							Summary of findings				Importance	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients		Effect			Quality
							intranasal H1-antihistamines	oral H1-antihistamines	Relative (95% CI)	Absolute		
nasal symptoms (change from baseline) (follow-up 2 weeks; Better indicated by higher values)												
2 ¹	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious ²	none	330	330	-	SMD 0.21 higher (0.06 to 0.36 higher) ³	⊕⊕⊕○ MODERATE	CRITICAL
nasal symptoms (symptom score) (follow-up 2 to 6 weeks; Better indicated by lower values)												
4	randomised trials	no serious limitations ⁴	no serious inconsistency	no serious indirectness	serious ^{5,6}	none	144	147	-	not pooled ^{5,7}	⊕⊕⊕○ MODERATE	CRITICAL
treatment efficacy (follow-up 2 to 6 weeks; rated as excellent or good [as opposed to moderate or poor])												
4	randomised trials	no serious limitations ⁴	no serious inconsistency	no serious indirectness ⁸	serious ⁹	none	102/144 (70.8%)	100/147 (68%)	RR 1.04 (0.89 to 1.20)	27 more per 1000 (from 75 fewer to 136 more)	⊕⊕⊕○ MODERATE	CRITICAL
								50%		20 more per 1000 (from 55 fewer to 100 more)		
ocular symptoms (follow-up 2 to 6 weeks; Better indicated by lower values)												
4	randomised trials	no serious limitations ⁴	no serious inconsistency	no serious indirectness	serious ^{5,6}	none	144	147	-	not pooled ^{5,10}	⊕⊕⊕○ MODERATE	IMPORTANT
adverse effects (somnolence)												
5	randomised trials	no serious limitations ⁴	no serious inconsistency ¹¹	no serious indirectness	serious ¹²	none	6/369 (1.6%)	18/379 (4.7%)	RR 0.39 (0.16 to 0.98) ¹³	29 fewer per 1000 (from 1 fewer to 40 fewer)	⊕⊕⊕○ MODERATE	CRITICAL
								1%		6 fewer per 1000 (from 0 fewer to 8 fewer)		

¹ Both studies compared intranasal azelastine 1.12 mg/d with oral cetirizine 10 mg/d.

² Results do not exclude a small effect favouring cetirizine or no difference.

³ Favouring cetirizine (control)

⁴ One study was not blinded and 2 did not report if they followed intention to treat principle during the analysis.

⁵ Only 1 of these 4 studies reported variability in results.

⁶ Only 291 patients.

⁷ The only study that reported variability in results compared intranasal levocabastine to oral loratidine and found a negligible difference between the groups of -0.02 points (95% CI: -0.27 to 0.23) on a 4-point scale, but the symptom scores in both groups were very low during whole study (average 0.7 points).

⁸ In one study (blinded) the evaluation of the efficacy of treatment was done by investigators not by patients.

⁹ Results do not exclude important benefit with either treatment.

¹⁰ The only study that reported variability in results compared intranasal levocabastine to oral loratadine and found a negligible difference between the groups of -0.01 points (95% CI: -0.21 to 0.23) on a 4-point scale, but the symptom scores in both groups were very low during whole study (average 0.48 points). No other study found any difference between the two treatments.

¹¹ Increased somnolence with oral compared to intranasal H1-antihistamines was observed in studies that used ebastine and cetirizine. In one study that used desloratadine there was only one event of somnolence in 111 patients. However, any conclusions that desloratadine causes less somnolence than cetirizine or ebastine should not be drawn based on the results of these studies, since the comparison is indirect and there were very few events.

¹² Very few events. Results do not exclude serious harm from oral compared to intranasal H1-antihistamines or no difference.

¹³ Favours intranasal H1-antihistamines

Question 15 [profile 2]

Date: 2009-03-11

Question: Should intranasal H1-antihistamines vs newer oral H1-antihistamines be used in adults with perennial/persistent allergic rhinitis?

Bibliography: Passali D, Piragine F. A comparison of azelastine nasal spray and cetirizine tablets in the treatment of allergic rhinitis. J Int Med Res 1994;22(1):17-23.

Quality assessment							Summary of findings				Quality	Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients		Effect			
							intranasal H1-antihistamines	newer oral H1-antihistamines	Relative (95% CI)	Absolute		
nasal symptoms (follow-up 8 weeks; Better indicated by lower values)												
1	randomised trials	no serious limitations ¹	no serious inconsistency	serious ²	very serious ^{2,3,4}	none	19	18	-	mean 24% lower ⁵	⊕○○○ VERY LOW	CRITICAL
treatment efficacy (follow-up 8 weeks)												
1	randomised trials	no serious limitations ¹	no serious inconsistency	serious ⁶	very serious ^{4,7}	none	14/19 (73.7%)	10/18 (55.6%)	RR 1.33 (0.81 to 2.17)	183 more per 1000 (from 106 fewer to 650 more)	⊕○○○ VERY LOW	CRITICAL
adverse effects (somnolence) (follow-up 8 weeks)												
1	randomised trials	no serious limitations ¹	no serious inconsistency	no serious indirectness	very serious ^{4,7}	none	0/19 (0%)	3/18 (16.7%)	RR 0.14 (0.01 to 2.46) ⁸	143 fewer per 1000 (from 165 fewer to 243 more)	⊕⊕○○ LOW	CRITICAL

¹ Authors did not report if the allocation was concealed or if they followed intention to treat principle during analysis.

² Authors did not report the scale of measurement so it is not possible to evaluate the magnitude of this finding.

³ No measure of variability was reported.

⁴ Only 40 patients.

⁵ mean total symptom score was 24% lower in azelastine compared with cetirizine group, but authors reported neither the scale on which symptom score was measured nor the variability in these results.

⁶ Efficacy was rated the investigators not patients themselves.

⁷ Results do not exclude important benefit with either treatment.

⁸ Favours intranasal azelastine.

Question 15 [profile 3]

Date: 2009-03-11

Question: Should intranasal H1-antihistamines vs newer oral H1-antihistamines be used in children with perennial allergic rhinitis?

Bibliography: Arreguin Osuna L, Garcia Caballero R, Montero Cortes MT, Ortiz Aldana I. Levocabastina contra cetirizina en niños con rinitis alergica perenne. Rev Alerg Mex 1998;45(3):7-11.

Quality assessment							Summary of findings				Importance	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients		Effect			Quality
							intranasal H1-antihistamines	newer oral H1-antihistamines	Relative (95% CI)	Absolute		
nasal symptoms (follow-up 2 weeks; measured with: Total Symptom Score; range of scores: 0-15; Better indicated by lower values)												
1	randomised trials	serious ¹	no serious inconsistency	serious ²	very serious ^{3,4}	none	13	17	-	mean 0.54 higher (1.79 lower to 2.87 higher)	⊕○○○ VERY LOW	CRITICAL
ocular symptoms (follow-up 2 weeks; measured with: symptom score; range of scores: 0-3; Better indicated by lower values)												
1	randomised trials	serious ¹	no serious inconsistency	serious ²	very serious ^{3,4}	none	13	17	-	mean 0.15 lower (0.64 lower to 0.34 higher)	⊕○○○ VERY LOW	IMPORTANT
adverse effects												
1	randomised trials	serious ¹	no serious inconsistency	serious ²	serious ⁴	none	-	-	- ⁵	-	⊕○○○ VERY LOW	CRITICAL

¹ Authors did not report allocation concealment or intention to treat analysis. Study was not blinded, the outcomes were assessed by the investigators.

² Treatment was administered for 2 weeks only. Most investigators agree that follow-up in studies in perennial allergic rhinitis should be at least 4 weeks (Krouse 2005).

³ Results do not exclude an important benefit from either treatment.

⁴ Only 30 patients.

⁵ One patient in cetirizine group reported somnolence, one increase in appetite and one epistaxis. In the levocabastine group one child reported feeling of facial edema.

Question 16 [profile 1]

Date: 2007-08-11

Question: Should oral leukotriene receptor antagonists vs placebo be used for treatment of seasonal allergic rhinitis?

Bibliography: Rodrigo G.J., Yanez A. The role of antileukotriene therapy in seasonal allergic rhinitis: a systematic review of randomized trials. Ann Allergy Asthma Immunol, 2006;96:779-786.

Quality assessment							Summary of findings					Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients		Effect		Quality	
							oral leukotriene receptor antagonists	placebo	Relative (95% CI)	Absolute		
Daytime nasal symptoms (follow-up 2 to 4 weeks; Better indicated by less)												
6	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	2512 ¹	2512 ¹	-	SMD -0.24 (-0.16 to -0.33)	⊕⊕⊕⊕ HIGH	CRITICAL
Night-time nasal symptoms (follow-up 2 to 4 weeks; Better indicated by less)												
6	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	2512 ¹	2512 ¹	-	SMD -0.23 (-0.16 to -0.3)	⊕⊕⊕⊕ HIGH	CRITICAL
Quality of life (follow-up 2 to 4 weeks; measured with: Rhinoconjunctivitis quality of life questionnaire (RQLQ) Better indicated by less)												
5	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	2481 ²	2481 ²	-	SMD -0.27 (-0.19 to -0.34)	⊕⊕⊕⊕ HIGH	CRITICAL
Eye symptoms (follow-up 2 to 4 weeks; Better indicated by less)												
3	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	1376 ³	1376 ³	-	SMD -0.17 (-0.08 to -0.27)	⊕⊕⊕⊕ HIGH	IMPORTANT
Adverse effects												
4	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision ⁴	publication bias ⁵	0/0	0/0	not pooled ⁶	not pooled ⁶	⊕⊕⊕○ MODERATE	IMPORTANT

¹ Number of patients in each group was not stated. There were altogether 5024 patients in both intervention and control groups.

² Number of patients in each group was not stated. There were altogether 4962 patients in both intervention and control groups.

³ Number of patients in each group was not stated. There were altogether 2753 patients in both intervention and control groups.

⁴ we did not downgrade for imprecision since we already downgraded for reporting bias

⁵ results were not pooled and were not reported in one study suggesting a reporting bias

⁶ Adverse effects were not pooled because of insufficient information to combine the results of different studies. A low incidence of adverse effects was observed in 4 studies. Most adverse events were rated mild, and there was no difference between groups. One of the most frequently reported adverse events was headache (3%–5% of patients treated with oral leukotriene receptor antagonists).

Question 16 [profile 2]

Date: 2007-08-11

Question: Should oral leukotriene receptor antagonists vs placebo be used in adults with perennial allergic rhinitis?

Bibliography: 1. Patel P., Philip G., Yang W., et al. Randomized, double-blind, placebo-controlled study of montelukast for treating perennial allergic rhinitis. Ann Allergy Asthma Immunol, 2005;95:551-557. 2. Philip G., Williams-Herman D., Patel P., et al. Efficacy of montelukast for treating perennial allergic rhinitis. Allergy Asthma Proc, 2007;28:296-304.

Quality assessment							Summary of findings				Importance	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients		Effect			Quality
							oral leukotriene receptor antagonists	placebo	Relative (95% CI)	Absolute		
Daytime nasal symptoms (change from baseline) (follow-up 6 weeks; Better indicated by less)												
2	randomised trial	no serious limitations	no serious inconsistency	serious	no serious imprecision	none	1632	1603	-	SMD -0.08 (-0.11 to -0.05)	⊕⊕⊕⊕ HIGH	CRITICAL
Nighttime symptoms (change from baseline) (follow-up 6 weeks; measured with: 4-point scale (0 - none; 3 - severe)range of scores: 0-3; Better indicated by less)												
1	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	1002	990	-	mean -0.06 (-0.02 to -0.1) ¹	⊕⊕⊕⊕ HIGH	CRITICAL
Quality of life (follow-up 6 weeks; measured with: rhinoconjunctivitis quality-of-life questionnaire range of scores: 0-6; Better indicated by more)												
2	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	1632	1603	-	not pooled ²	⊕⊕⊕⊕ HIGH	CRITICAL
Quality of life (% with meaningful improvement) (follow-up 6 weeks)												
1	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	570/977	514/969	RR 1.1 (1.02 to 1.19)	53 more per 1000 (from 11 more to 101 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Daytime eye symptoms (follow-up 6 weeks; Better indicated by less)												
1	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	serious ^{3,4}	none	630	613	-	not pooled ⁴	⊕⊕⊕○ MODERATE	IMPORTANT
Adverse effects (Upper respiratory infection) (follow-up 6 weeks)												
2	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	63/1632	45/1603	RR 1.37 (0.94 to 2)	10 more per 1000 (from 2 fewer to 28 more)	⊕⊕⊕⊕ HIGH	IMPORTANT
Adverse effects (Headache) (follow-up 6 weeks)												
2	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	61/1632	72/1603	RR 0.83 (0.6 to 1.16)	8 fewer per 1000 (from 18 fewer to 7 more)	⊕⊕⊕⊕ HIGH	IMPORTANT
Adverse effects (other) (follow-up 6 weeks)												
2	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	-/1632	-/1603	not pooled ⁵	not pooled	⊕⊕⊕⊕ HIGH	IMPORTANT

¹ A second trial reported only that there was no statistically significant difference between the groups

² change in RQLQ from baseline was -0,15 (95% CI: -0.06 to -0.24) in one study, and -0,13 (95% CI: 0.00 to -0,25) in another.

³ one trial

⁴ authors stated only that there was no difference between the groups

⁵ There were many different adverse effects of uncertain relation to treatment and importance to patients; it was also uncertain how many occurred per patient.

Question 16 [profile 3]

Date: 2007-08-11

Question: Should oral leukotriene receptor antagonists vs placebo be used in children with perennial allergic rhinitis?

Bibliography: Chen S.T., Lu K.H., Sun H.L., et al. Randomized placebo-controlled trial comparing montelukast and cetirizine for treating perennial allergic rhinitis in children aged 2-6 yr. *Pediatr Allergy Immunol*, 2006;17:49-54.

Quality assessment							Summary of findings					Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients		Effect		Quality	
							oral leukotriene receptor antagonists	placebo	Relative (95% CI)	Absolute		
Total nasal symptoms (follow-up 12 weeks; measured with: mean of eight symptoms; range of scores: 0-3; Better indicated by less)												
1	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	very serious ¹	none ²	20	20	-	mean -0.32 (-0.21 to -0.43)	⊕⊕⊕⊕ LOW	CRITICAL
Night sleeping quality (follow-up 12 weeks; measured with: 0 - slept well to 3 - slept very poorly or woke up >3 times; range of scores: 0-3; Better indicated by less)												
1	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	very serious ¹	none	20	20	-	mean -0.37 (-0.29 to -0.45)	⊕⊕⊕⊕ LOW	CRITICAL
Quality of life (follow-up 12 weeks; measured with: Pediatric Rhinoconjunctivitis Quality of Life Questionnaire (23 items; 7-point scale each); range of scores: 0-138; Better indicated by less)												
1	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	very serious ¹	none	20	20	-	mean 15.3 (5.9 to 24.7)	⊕⊕⊕⊕ LOW	CRITICAL
Adverse events (follow-up 12 weeks)												
1	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	very serious ³	none ²	0/20	0/20	not pooled ⁴	not pooled	⊕⊕⊕⊕ LOW	IMPORTANT

¹ Very limited data.

² we did not downgrade for publication bias, because we already downgraded for very serious imprecision

³ one very small study

⁴ Authors stated only that "no serious adverse events were observed".

Question 17 [profile 1]

Date: 2007-08-11

Question: Should oral leukotriene receptor antagonists vs oral histamine H1 antagonists be used for seasonal allergic rhinitis?

Bibliography: Rodrigo G.J., Yanez A. The role of antileukotriene therapy in seasonal allergic rhinitis: a systematic review of randomized trials. Ann Allergy Asthma Immunol, 2006;96:779-786.

Quality assessment							Summary of findings					Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients		Effect		Quality	
							oral leukotriene receptor antagonists	oral histamine H1 antagonists	Relative (95% CI)	Absolute		
Daytime and night-time nasal symptoms (follow-up 2 to 4 weeks; Better indicated by less)												
5	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	2481 ¹	2481 ¹	-	SMD 0.04 (-0.04 to 0.11) (favours H1 antagonist)	⊕⊕⊕⊕ HIGH	CRITICAL
Quality of life (follow-up 2 to 4 weeks; measured with: Rhinoconjunctivitis quality of life questionnaire (RQLQ); Better indicated by less)												
5	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	2481 ¹	2481 ¹	-	SMD 0.04 (-0.04 to 0.12) (favours H1 antagonist)	⊕⊕⊕⊕ HIGH	CRITICAL
Eye symptoms (follow-up 2 to 4 weeks; Better indicated by less)												
3	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	1376 ²	1376 ²	-	SMD -0.02 (-0.09 to 0.13) (favours LTRA)	⊕⊕⊕⊕ HIGH	IMPORTANT
Adverse effects												
4	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision ³	reporting bias ⁴	_ ⁵	_ ⁵	not pooled ⁵	not pooled ⁵	⊕⊕⊕○ MODERATE	IMPORTANT

¹ Number of patients in each group was not stated. There were altogether 4962 patients in both intervention and control groups.

² Number of patients in each group was not stated. There were altogether 2753 patients in both intervention and control groups.

³ We did not downgrade for imprecision since we already downgraded for reporting bias.

⁴ Only 3 of 5 trials reported adverse events.

⁵ insufficient information to combine the results of adverse effects in different studies. A low incidence of adverse effects was observed in 4 studies. Most adverse events were rated mild, and there was no difference between groups. One of the most frequently reported adverse events was headache (3-5% of patients treated with oral leukotriene receptor antagonists).

Question 17 [profile 2]

Date: 2007-08-11

Question: Should oral leukotriene receptor antagonists vs oral histamine H1 antagonists be used in adults with perennial allergic rhinitis?

Bibliography: Philip G., Williams-Herman D., Patel P., et al. Efficacy of montelukast for treating perennial allergic rhinitis. Allergy Asthma Proc, 2007;28:296-304.

Quality assessment							Summary of findings				Importance	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients		Effect			Quality
							oral leukotriene receptor antagonists	oral histamine H1 antagonists	Relative (95% CI)	Absolute		
Daytime nasal symptoms (follow-up 6 weeks; measured with: four-point scale; range of scores: 0-3; Better indicated by lower values)												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	630	122	-	mean 0.03 higher (0.07 lower to 0.12 higher)	⊕⊕⊕⊕ HIGH	CRITICAL
Nighttime symptoms - not reported¹												
0	-	-	-	-	-	none	630	122	-	-		CRITICAL
Daytime eye symptoms - not reported¹												
0	-	-	-	-	- ¹	none	630	122	-	-		IMPORTANT
Quality of life - not reported¹												
0	-	-	-	-	-	none	630	122	-	-		CRITICAL
Adverse effects (follow-up 6 weeks; somnolence²)												
1 ³	randomised trials	no serious limitations	no serious inconsistency	serious ^{3,4}	serious ⁵	none	5/630 (0.8%)	6/122 (4.9%)	RR 0.06 (0.02 to 0.19)	46 fewer per 1000 (from 40 fewer to 48 fewer)	⊕⊕○○ LOW	CRITICAL

¹ Actual values not reported. Authors only stated that the difference was not statistically significant.

² Various other adverse events were reported, but they were rare and the difference between montelukast and cetirizine was not statistically significant for any of them. However, there was a trend towards more fatigue, dry mouth and dry nose in the cetirizine group, compared to montelukast. Quality of evidence for these outcomes would also be low, because of indirect comparison and imprecision.

³ Data on adverse effects were reported as pooled from two studies of montelukast in perennial allergic rhinitis (Patel 2005 and Philip 2007), but cetirizine was used in only one of them.

⁴ Indirect comparison. Adverse effects in montelukast group are pooled from two studies whereas data on cetirizine are from one study only.

⁵ Very few events.

Question 17 [profile 3]

Date: 2007-08-12

Question: Should oral leukotriene receptor antagonists vs oral histamine H1 antagonists be used in children with perennial allergic rhinitis?

Bibliography: Chen S.T., Lu K.H., Sun H.L., et al. Randomized placebo-controlled trial comparing montelukast and cetirizine for treating perennial allergic rhinitis in children aged 2-6 yr. *Pediatr Allergy Immunol*, 2006;17:49-54.

Quality assessment							Summary of findings				Importance	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients		Effect			Quality
							oral leukotriene receptor antagonists	oral histamine H1 antagonists	Relative (95% CI)	Absolute		
Total nasal symptoms (follow-up 12 weeks; measured with: mean of eight symptoms; range of scores: 0-3; Better indicated by less)												
1	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	very serious ¹	none	20	20	-	mean 0.17 (0.02 to 0.32)	⊕⊕○○ LOW	CRITICAL
Night sleep quality (follow-up 12 weeks; measured with: 0 - slept well to 3 - slept very poorly or woke up >3 times; range of scores: 0-3; Better indicated by less)												
1	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	very serious ¹	none	20	20	-	mean -0.13 (-0.03 to -0.23)	⊕⊕○○ LOW	CRITICAL
Quality of life (follow-up 12 weeks; measured with: Pediatric Rhinoconjunctivitis Quality of Life Questionnaire (23 items; 7-point scale each); range of scores: 0-138; Better indicated by less)												
1	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	very serious ¹	none	20	20	-	mean 0.17 (0.02 to 0.32)	⊕⊕○○ LOW	CRITICAL
Adverse effects (follow-up 12 weeks)												
1	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	very serious ¹	none ²	0/20	2/20 ³	Not pooled ³	- ³	⊕⊕○○ LOW	IMPORTANT

¹ Small study that did not exclude no effect or a moderate effect.

² We did not downgrade for reporting bias, because we already downgraded for very serious imprecision

³ Authors stated, that "only mild medication-induced sedation was noted in two of children treated with cetirizine".

Question 18

Date: 2008-12-09

Question: Should intranasal glucocorticosteroids vs no intranasal glucocorticosteroids be used in patients with allergic rhinitis?¹

Bibliography: Penagos M., Compalati E., Tarantini F., Baena-Cagnani C.E., Passalacqua G., Canonica G.W. Efficacy of mometasone furoate nasal spray in the treatment of allergic rhinitis. Meta-analysis of randomized, double-blind, placebo-controlled, clinical trials. Allergy, 2008;63:1280-1291.

Quality assessment							Summary of findings				Importance	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients		Effect			Quality
							intranasal mometasone	no intranasal mometasone	Relative (95% CI)	Absolute		
Nasal symptoms (adults) (follow-up 2 to 12 weeks; measured with: Total Nasal Symptom Score (TNSS); Better indicated by lower values)												
10 ²	randomised trials	no serious limitations ³	no serious inconsistency	no serious indirectness	no serious imprecision	none	967	911	-	SMD 0.56 lower (0.41 to 0.71 lower) ⁴	⊕⊕⊕⊕ HIGH	CRITICAL
Nasal symptoms (children) (follow-up 4 weeks; measured with: Total Nasal Symptom Score (TNSS); Better indicated by lower values)												
1 ⁵	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision ⁶	none	135	136	-	SMD 0.41 lower (0.17 to 0.65 lower) ⁴	⊕⊕⊕⊕ HIGH	CRITICAL
Congestion (follow-up 2 to 12 weeks; Better indicated by lower values)												
7	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	812	770	-	SMD 0.41 lower (0.27 to 0.56 lower)	⊕⊕⊕⊕ HIGH	CRITICAL
Rhinorrhea (follow-up 2 to 12 weeks; Better indicated by lower values)												
7	randomised trials	no serious limitations	no serious inconsistency ⁷	no serious indirectness	no serious imprecision	none	812	770	-	SMD 0.44 lower (0.21 to 0.66 lower)	⊕⊕⊕⊕ HIGH	CRITICAL
Sneezing (follow-up 2 to 12 weeks; Better indicated by lower values)												
7	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	812	770	-	SMD 0.40 lower (0.23 to 0.57 lower)	⊕⊕⊕⊕ HIGH	IMPORTANT
Nasal itching (follow-up 2 to 12 weeks; Better indicated by lower values)												
7	randomised trials	no serious limitations	no serious inconsistency ⁸	no serious indirectness	no serious imprecision	none	812	770	-	SMD 0.39 lower (0.25 to 0.53 lower)	⊕⊕⊕⊕ HIGH	IMPORTANT
Quality of life - not reported⁹												
0	-	-	-	-	-	none	-	-	-	-		CRITICAL
Adverse events (follow-up 2 to 12 weeks)												
9	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	335/1041 (32.2%)	333/1031 (32.3%)	RR 0.99 (0.86 to 1.20)	3 fewer per 1000 (from 45 fewer to 65 more)	⊕⊕⊕⊕ HIGH	CRITICAL ¹⁰

¹ systematic review is available for mometasone fuorate trials only

² Four of these studies were done in patients with perennial/persistent allergic rhinitis. Authors of the review performed a sensitivity analysis and their results showed the effect similar to the remaining studies in patients with seasonal allergic rhinitis.

³ Based on Jadad score these were high quality studies. Out of 14 studies only 3 lost to follow-up more than 10% of subjects and only one lost ~23%. Median loss to follow-up was 3.5%. Authors of the review did not report the type of analysis (intention-to-treat vs per protocol), although they stated that they used ITT data when possible.

⁴ Favours mometasone

⁵ This study was done in children with seasonal allergic rhinitis.

⁶ Results do not exclude small or moderate effect. We did not downgrade for imprecision despite only 271 patients were studied. This evidence is consistent with the effect in adults.

⁷ We did not downgrade for inconsistency, because it would not influence the decision to use or not to use mometasone. However some heterogeneity was observed ($I^2 = 79%$) and could not be explained by differences in population, intervention or study quality.

⁸ As could be expected, the effect seemed more pronounced in patients with seasonal compared to perennial allergic rhinitis.

⁹ Studies either not measured or not reported quality of life or the systematic review did not provide any information on this outcome. There are however recent studies suggesting improved quality of life in patients with rhinitis using mometasone (Bachert C, and Meltzer E.O. Effect of mometasone furoate nasal spray on quality of life of patients with acute rhinosinusitis. *Rhinology*. 2007 Sep;45:190-196).

¹⁰ There is some uncertainty about the importance of adverse effects, since authors of the systematic review did not report what they were. However, they commented that "epistaxis, headache, and pharyngitis were the most common adverse effects".

Question 19 [profile 1]

Date: 2007-08-13

Question: Should intranasal glucocorticosteroids vs oral H1-antihistamines be used in adults with seasonal allergic rhinitis?

Bibliography: 1. Long A., McFadden C., DeVine D., Chew P., Kupelnick B., Lau J. (Agency for Healthcare Research and Quality). Management of Allergic and Nonallergic Rhinitis. Evidence Report/Technology Assessment No. 54 (Prepared by New England Medical Center Evidence-based Practice Center under Contract No. 290-97-0019). 2002. 2. Kaszuba S.M., Baroody F.M., deTineo M., Haney L., Blair C., Naclerio R.M. Superiority of an intranasal corticosteroid compared with an oral antihistamine in the as-needed treatment of seasonal allergic rhinitis. Arch Intern Med, 2001;161:2581-2587.

Quality assessment							Summary of findings					Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients		Effect		Quality	
							Intranasal glucocorticosteroids	oral H1-antihistamines	Relative (95% CI)	Absolute		
Nasal symptoms (follow-up 14 to 60 days; Better indicated by less)												
8	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	serious ^{1,2}	none	0 ³	0 ³	-	not pooled ^{1,4}	⊕⊕⊕O MODERATE	CRITICAL
Quality of life (follow-up 14 to 60 days; measured with: Rhinoconjunctivitis Quality of Life Questionnaire; range of scores: 0-6; Better indicated by more)												
3	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	serious ^{1,2}	none	0 ³	0 ³	-	not pooled ^{1,5}	⊕⊕⊕O MODERATE	CRITICAL
Adverse events												
8	randomised trial	no serious limitations	serious ⁶	no serious indirectness	serious ¹	none	0/0 ³	0/0 ³	not pooled ⁷	not pooled ⁷	⊕⊕OO LOW	CRITICAL

¹ No systematic review available. Results were not pooled.

² No overall estimate of the effect.

³ There were 1788 patients altogether in all 8 trials

⁴ Seven studies favoured intranasal glucocorticosteroids over oral H1-antihistamines, and one favoured oral H1-antihistamine. On average the effect was moderate.

⁵ Patients in the intranasal corticosteroid group reported statistically significantly better scores in the selected domains and overall score of RQLQ.

⁶ Studies have reported from 0 to 40% incidence of headaches. Other side effects were also inconsistent.

⁷ There were no major adverse effects reported in the included studies. Minor adverse effects were headache and pharyngitis that were inconsistent across the studies. In one study that used chlorpheniramine sedation and dry mouth were most frequently reported adverse effects of an oral H1-antihistamine.

Question 19 [profile 2]

Date: 2007-08-13

Question: Should intranasal glucocorticosteroids vs oral H1-antihistamines be used in adults with perennial allergic rhinitis?

Bibliography: Rinne J., Simola M., Malmberg H., Haahtela T. Early treatment of perennial rhinitis with budesonide or cetirizine and its effect on long-term outcome. J Allergy Clin Immunol, 2002;109:426-432.

Quality assessment							Summary of findings				Importance	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients		Effect			Quality
							intranasal glucocorticosteroids	oral H1-antihistamines	Relative (95% CI)	Absolute		
Nasal symptoms (follow-up 12 months; measured with: 3 symptoms on 6-point scale (0 = no symptoms; 5 = very severe symptoms)range of scores: 0-15; Better indicated by less)												
1	randomised trial	no serious limitations ¹	no serious inconsistency	no serious indirectness	serious ²	none	71	72	-	WMD -1.08 (-1.72 to -0.44) ³	⊕⊕⊕○ MODERATE	CRITICAL
Eye symptoms (measured with: 6-point scale (0 = no symptoms; 5 = very severe symptoms)range of scores: 0-5; Better indicated by less)												
1	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	serious ^{2,4}	none	71	72	-	WMD 0.31 (0 to 0) ⁴	⊕⊕⊕○ MODERATE	CRITICAL
Quality of Life - not measured												
0	-	-	-	-	-	none	0/0	0/0	-	-		
viral upper respiratory tract infections (follow-up 12 months)												
1	randomised trial	no serious limitations ¹	no serious inconsistency	no serious indirectness	serious ²	none	48/71	52/72	RR 0.94 (0.75 to 1.16) ⁵	43 fewer per 1000 (from 116 fewer to 180 more)	⊕⊕⊕○ MODERATE	IMPORTANT
Blood in nasal secretion (follow-up 12 months)												
1	randomised trial	no serious limitations ¹	no serious inconsistency	no serious indirectness	serious ²	none	19/71	9/72	RR 2.14 (1.04 to 4.41)	143 more per 1000 (from 5 more to 426 more)	⊕⊕⊕○ MODERATE	IMPORTANT
conjunctivitis (follow-up 12 months)												
1	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	serious ²	none	8/71	5/72	RR 1.62 (0.56 to 4.72) ⁵	43 more per 1000 (from 30 fewer to 257 more)	⊕⊕⊕○ MODERATE	IMPORTANT
Headache												
1	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	very serious ²	none	6/71	1/72	RR 6.08 (0.75 to 49.27) ⁵	71 more per 1000 (from 3 fewer to 676 more)	⊕⊕○○ LOW	IMPORTANT
Sinusitis												
1	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	very serious ²	none	2/71	1/72	RR 2.03 (0.19 to 21.87) ⁵	14 more per 1000 (from 11 fewer to 292 more)	⊕⊕○○ LOW	IMPORTANT

¹ Allocation concealment unknown; randomised; ITT conducted; adequate follow-up;

² One small study.

³ The percentage of rhinitis-free days was also higher in the budesonide group (45.1%) compared to cetirizine group (25.9%).

⁴ Authors stated only that there was no important difference between the groups in eye symptoms.

⁵ The confidence interval crosses no difference and does not rule out a small increase with glucocorticosteroids

Question 19 [profile 3]

Date: 2007-08-13

Question: Should intranasal glucocorticosteroids vs oral H1-antihistamines be used in children with seasonal allergic rhinitis?

Settings: home

Bibliography: Bender B.G., Milgrom H. Comparison of the effects of fluticasone propionate aqueous nasal spray and loratadine on daytime alertness and performance in children with seasonal allergic rhinitis. Ann Allergy Asthma Immunol, 2004;92:344-349.

Quality assessment							Summary of findings					Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients		Effect		Quality	
							intranasal glucocorticosteroids	oral H1-antihistamines	Relative (95% CI)	Absolute		
Nasal symptoms (follow-up 2 weeks; measured with: 5-point scale (0 - very little; 4 - very much) ¹range of scores: 0-4; Better indicated by more)												
1 ²	randomised trial	serious ³	no serious inconsistency	serious ^{1,4}	serious ^{5,6}	none	20 ⁷	20 ⁷	-	WMD 0.55 (0.17 to 0.93) ^{8,9}	⊕○○○ VERY LOW	CRITICAL
Quality of life (follow-up 2 weeks; measured with: Adolescent Rhinoconjunctivitis Quality of Life Questionnaire; range of scores: 0-6; Better indicated by less)												
1 ²	randomised trial	serious ³	no serious inconsistency	serious ⁴	serious ⁵	none	20 ⁷	20 ⁷	-	WMD 0 (0 to 0) ¹⁰	⊕○○○ VERY LOW	CRITICAL
Memory (follow-up 22 days; measured with: California Verbal Learning Test[®] "Children's Version"¹¹; Better indicated by more)												
1 ²	randomised trial	serious ³	no serious inconsistency	serious ^{11,12}	serious ^{6,11}	none	20 ⁷	20 ⁷	-	WMD 4.25 (-0.71 to 9.21) ⁹	⊕○○○ VERY LOW	CRITICAL
Adverse events - not reported¹³												
0	-	-	-	-	-	none	0/0	0/0	-	-		

¹ Parents were rating the symptoms answering the question: How do you feel that the study drug has controlled your child's allergic rhinitis symptoms in the last week?

² Children were 8-17 year old.

³ Allocation concealment, ITT, and follow-up not reported; outcomes poorly reported

⁴ Parents were rating the symptoms of their 8-17 year old children.

⁵ results do not exclude important benefit from intranasal glucocorticosteroid or a negligible difference.

⁶ one small trial

⁷ Exact numbers of children in each group were not stated. There were 60 children altogether randomised into 3 groups.

⁸ The confidence interval crosses no difference and does not rule out a small increase with glucocorticosteroids

⁹ 95% CI was estimated with an assumption of 20 children in each group.

¹⁰ Overall score not provided; individual scores all not statistically significantly different between groups.

¹¹ no information on the interpretation of the results measured with a used scale

¹² There is serious uncertainty about the real-life meaning of the results of the used scale

¹³ Adverse events were measured in the trial but not reported in the results

Question 19 [profile 4]

Date: 2007-08-13

Question: Should intranasal glucocorticosteroids vs oral H1-antihistamines be used in children with perennial allergic rhinitis?

Settings: home

Bibliography: Fokkens W.J., Scadding G.K. Perennial rhinitis in the under 4s: a difficult problem to treat safely and effectively? A comparison of intranasal fluticasone propionate and ketotifen in the treatment of 2-4-year-old children with perennial rhinitis. *Pediatr Allergy Immunol*, 2004;15:261-266.

Quality assessment							Summary of findings				Quality	Importance
							No of patients		Effect			
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	intranasal glucocorticosteroids	oral H1-antihistamines	Relative (95% CI)	Absolute		
Nasal symptoms - daytime score (follow-up 6 weeks; measured with: parent assessment of symptoms¹; Better indicated by less)												
1 ²	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	very serious ³	none	11	12	-	WMD -1.90 (-3.56 to -0.24)	⊕⊕○○ LOW	CRITICAL
Nasal symptoms - night time scores (follow-up 6 weeks; measured with: parent assessment of symptoms¹; Better indicated by less)												
1	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	very serious ³	none	11	12	-	WMD -2.30 (-4.24 to -0.36)	⊕⊕○○ LOW	CRITICAL
Quality of Life - not measured												
0	-	-	-	-	-	none	0/0	0/0	-	-		
Adverse events (follow-up 6 weeks)												
1	randomised trial	serious ^{4,5}	no serious inconsistency	no serious indirectness	very serious ^{3,4}	none	0/11	0/12	RR 0 (0 to 0) ⁴		⊕○○○ VERY LOW	IMPORTANT

¹ no description of the scale was provided

² Children were 2 to 4 years old

³ one very small trial

⁴ Authors stated only that there were no reports of serious adverse events. The incidence of adverse events that were assessed as being related to the drug treatment was very low and with no statistical difference between the groups.

⁵ poorly reported

Question 19 [profile 5] and **question 21** [profile 2]

Date: 2007-08-13

Question: Should intranasal glucocorticosteroids vs combined oral H1-antihistamines plus oral leukotriene receptor antagonists be used in patients with allergic rhinitis?

Bibliography: Rodrigo G.J., Yanez A. The role of antileukotriene therapy in seasonal allergic rhinitis: a systematic review of randomized trials. Ann Allergy Asthma Immunol, 2006;96:779-786.

Quality assessment							Summary of findings					Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients		Effect		Quality	
							Intranasal glucocorticosteroids	combined oral H1-antihistamines plus oral leukotriene receptor antagonists	Relative (95% CI)	Absolute		
Nasal symptoms (follow-up 2 weeks; Better indicated by less)												
5	randomised trial	no serious limitations ¹	no serious inconsistency	no serious indirectness	serious ²	none	134 ³	134 ³	-	SMD -0.23 (-0.6 to 0.13)	⊕⊕⊕O MODERATE	CRITICAL
Nasal congestion (follow-up 2 weeks; Better indicated by less)												
5	randomised trial	no serious limitations	no serious inconsistency ⁴	no serious indirectness	very serious ⁵	none	134 ³	134 ³	-	SMD -0.97 (-1.92 to -0.01)	⊕⊕OO LOW	CRITICAL
Quality of life - not reported⁶												
0	-	-	-	-	-	none	0	0	-	-		CRITICAL
Adverse events - not reported⁷												
0	-	-	-	-	-	none	0/0	0/0	-	-		

¹ Two of the 5 trials had Jadad score of 2.

² There is possibility of no difference or a moderately better effect of intranasal glucocorticosteroids.

³ Authors did not provide the number of patients per group. There were altogether 268 patients in all 5 studies.

⁴ There was very serious heterogeneity in results ($I^2 = 88\%$) due to two studies being of low methodological quality.

⁵ There is possibility of no difference or a large benefit with intranasal glucocorticosteroids.

⁶ Quality of life was not reported in the review. There was insufficient information in the individual trials.

⁷ Authors of the review did not mention if adverse events were reported in individual studies.

Question 20 [profile 1]

Date: 2007-07-18

Question: Should intranasal corticosteroids vs intranasal H1-antihistamines be used in patients with allergic rhinitis?

Bibliography: Yanez A, Rodrigo GJ. Intranasal corticosteroids versus topical H1 receptor antagonists for the treatment of allergic rhinitis: a systematic review with meta-analysis. Ann Allergy Asthma Immunol. 2002;89(5):479-84.

Quality assessment							Summary of findings				Importance	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients		Effect			Quality
							intranasal corticosteroids	intranasal H1-antihistamines	Relative (95% CI)	Absolute		
Total nasal symptom score (follow-up 2 to 6 weeks; Better indicated by less)												
6	randomised trial	no serious limitations	no serious inconsistency ¹	no serious indirectness	no serious imprecision	none	0 ²	0 ²	-	SMD -0.36 (-0.14 to -0.57) ¹	⊕⊕⊕⊕ HIGH	CRITICAL
Sneezing (follow-up 2 to 8 weeks; Better indicated by less)												
7	randomised trial	no serious limitations	no serious inconsistency ³	no serious indirectness	no serious imprecision	none	0 ⁴	0 ⁴	-	SMD -0.41 (-0.24 to -0.57)	⊕⊕⊕⊕ HIGH	CRITICAL
Rhinorrhea (follow-up 2 to 8 weeks; Better indicated by less)												
6	randomised trial	no serious limitations	no serious inconsistency ³	no serious indirectness	no serious imprecision	none	0 ⁵	0 ⁵	-	SMD -0.47 (-0.29 to -0.64)	⊕⊕⊕⊕ HIGH	CRITICAL
Itching (follow-up 2 to 6 weeks; Better indicated by less)												
5	randomised trial	no serious limitations	no serious inconsistency ³	no serious indirectness	no serious imprecision	none	0 ⁶	0 ⁶	-	SMD -0.38 (-0.19 to -0.56)	⊕⊕⊕⊕ HIGH	IMPORTANT
Nasal blockage (follow-up 6 weeks; Better indicated by less)												
4	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	0	0	-	SMD -0.86 (-0.64 to -1.07)	⊕⊕⊕⊕ HIGH	CRITICAL
Nasal congestion (follow-up 2 and 8 weeks; Better indicated by less)												
2	randomised trial	serious ⁷	no serious inconsistency	no serious indirectness	very serious ⁸	none	0 ⁹	0 ⁹	-	SMD -0.01 (-0.56 to 0.53)	⊕○○○ VERY LOW	IMPORTANT
Ocular symptoms (Better indicated by less)												
4		no serious limitations	serious ¹⁰	no serious indirectness	serious ¹¹	none	0 ¹²	0 ¹²	-	SMD -0.07 (0.12 to -0.27)	⊕○○○ LOW	IMPORTANT
Quality of life - not measured¹³												
0	-	-	-	-	-	none	-	-	-	-		CRITICAL
Adverse effects¹⁴												
4	randomised trial	-	-	-	-	none	-	-	not pooled	not pooled	-	IMPORTANT

¹ Five high quality studies showed substantial decrease in total nasal symptom score compared with the one study of low quality (SMD: -0.42, 95% CI: 0.63 to 0.20 vs 0.55, 95% CI: 0.53 to 1.62). Five studies among patients with seasonal rhinitis showed slightly more benefit than the one study of patients with perennial rhinitis (SMD: -0.38, 95% CI: -0.64 to -0.13 vs -0.33, 95% CI: -0.73 to 0.07).

² Total number of participants in the 6 studies was 346

³ One small (n = 14) and methodologically weak study showed different effect than the other studies.

⁴ Total number of participants in these studies was 594

⁵ Total number of participants in these studies was 523

⁶ Total number of participants in these studies was 460

⁷ Two small studies with Jadad score of 2.

⁸ 95% confidence interval includes appreciable benefit from both treatments.

⁹ Total number of participants in these studies was 52

¹⁰ There was significant heterogeneity, with two studies showing greater benefit from intranasal corticosteroids (both used azelastine as comparator) and two showing the opposite (both used levocabastine as comparator).

¹¹ If studies comparing different H1-antihistamines were considered separately there may have been an appreciable benefit from intranasal corticosteroids compared to azelastine.

¹² Total number of participants in these studies was 428

¹³ None of the studies measured quality of life.

¹⁴ Authors stated only that a low incidence of adverse effects was observed and there was no difference between groups; most adverse events were rated as mild or moderate, and the most frequently reported adverse events were respiratory symptoms, headache, epistaxis, and taste perversion with intranasal H1-antihistamine.

Question 21 [profile 1]

Date: 2007-08-11

Question: Should oral leukotriene receptor antagonists vs intranasal glucocorticosteroids be used for allergic rhinitis?

Bibliography: Rodrigo G.J., Yanez A. The role of antileukotriene therapy in seasonal allergic rhinitis: a systematic review of randomized trials. Ann Allergy Asthma Immunol, 2006;96:779-786.

Quality assessment							Summary of findings					Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients		Effect		Quality	
							oral leukotriene receptor antagonists	intranasal glucocorticosteroids	Relative (95% CI)	Absolute		
Daytime nasal symptoms (follow-up 2 to 4 weeks; Better indicated by less)												
2	randomised trial	serious ¹	no serious inconsistency	no serious indirectness	serious ²	none	414 ³	414 ³	-	SMD 0.41 (0.27 to 0.56) (favours steroids)	⊕⊕⊕⊕ LOW	CRITICAL
Night-time nasal symptoms (follow-up 2 to 4 weeks; Better indicated by less)												
2	randomised trial	serious ¹	no serious inconsistency	no serious indirectness	serious ²	none	414 ³	414 ³	-	SMD 0.33 (0.18 to 0.48) (favours steroids)	⊕⊕⊕⊕ LOW	CRITICAL
Quality of life - not measured												
0	-	-	-	-	-	none	0	0	-	-		CRITICAL
Adverse effects - not reported⁴												
0	-	-	-	-	-	none	0/0	0/0	-	-		IMPORTANT

¹ Jadad score of both trials was 2.

² 95% CI around SMD did not exclude small and negligible effect or a moderate and possibly clinically important effect.

³ Number of patients in each group was not stated. There were altogether 767 patients in both intervention and control groups.

⁴ Adverse effects were not pooled because only one study reported them. Authors of the review did not report any adverse events of intranasal glucocorticosteroids.

Question 23

Date: 2007-08-14

Question: Should intramuscular glucocorticosteroids be used for seasonal allergic rhinitis?

Bibliography: Østergaard M.S., Østrem A., Söderström M. Hay fever and a single intramuscular injection of corticosteroids: a systematic review. Primary Care Resp J, 2005;14:123-130.

Quality assessment							Summary of findings				Quality	Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients		Effect			
							intramuscular glucocorticosteroids	control	Relative (95% CI)	Absolute		
Symptoms of allergic rhinitis (vs placebo in randomised trials) (measured with: global satisfaction scale¹ Better indicated by more)												
5	randomised trial	serious ²	no serious inconsistency	no serious indirectness	no serious imprecision ³	none	128 ⁴	128 ⁴	-	not pooled ³	⊕⊕⊕O MODERATE	CRITICAL
Clinical side effects (vs placebo in randomised trials)												
4	randomised trial	serious ²	no serious inconsistency	no serious indirectness	serious ⁵	none	-128 ⁴	-128 ⁴	not pooled ⁶	not pooled ⁶	⊕⊕OO LOW	CRITICAL
Physiological side effects (vs placebo in randomised trials)												
1 ⁷	randomised trial	serious ⁸	no serious inconsistency	serious ⁹	serious ⁷	none	-47 ¹⁰	-47 ¹⁰	- ¹¹	-	⊕OOO VERY LOW	IMPORTANT
Symptoms of allergic rhinitis (vs intranasal corticosteroids in randomised trials) (follow-up 3 to 4 weeks; Better indicated by more)												
2	randomised trial	no serious limitations	serious ¹²	no serious indirectness	serious ^{12,13}	none	24	25	-	not pooled ¹²	⊕⊕OO LOW	CRITICAL

¹ In all studies the clinical effect was rated on different scales, i.e. either as "no symptoms, slight or moderate symptoms, severe symptoms", or "restored/improved or unimproved" or using an "excellent, good, poor or none effect" scale. Specific symptoms such as nasal blockage, nasal itching and eye symptoms were measured by grading them and by counting the occurrence.

² Not explicitly assessed in the review, but studies were conducted between 1960 and 1988 rising high possibility of lower methodological quality.

³ All studies showed statistically significant and large effect with i.m. glucocorticosteroids lasting from the second day after injection until 3-5 weeks.

⁴ Exact numbers in each group were not provided. There was altogether 257 patients in both groups in all 5 trials.

⁵ Only 5 trials with few events.

⁶ All reported clinical side effects were considered minor. There were no statistically significant differences in side effects between the groups, not even in one study with patients being given three consecutive i.m. injections of methylprednisolone 80 mg at weekly intervals.

⁷ Only one of 5 studies measured physiological side effects.

⁸ Not explicitly assessed in the review, but study was conducted in 1960 rising high possibility of lower methodological quality.

⁹ There is a high uncertainty about directness of physiological side effects.

¹⁰ Exact numbers in each group were not provided. There was altogether 95 patients in both groups in this trial.

¹¹ Glycosuria was observed in 1 of 90 patients. Weight and blood pressure were unaffected.

¹² Single injection of intramuscular glucocorticosteroid (2 or 5 mg betametasone disodium phosphate or 80 mg methylprednisolone) proved to be importantly superior to intranasal beclomethasone 100 µg twice daily in one study, and equally effective when compared to intranasal budesonide 400 µg once daily (with increased use of supplementary medicines in the nasal steroid group).

¹³ Two small trials with few patients.

Question 28

Date: 2007-08-23

Question: Should oral decongestant vs placebo be used for seasonal allergic rhinitis?

Bibliography: 1. Bronsky E, Boggs P, Findlay S, et al. Comparative efficacy and safety of a once-daily loratadine-pseudoephedrine combination versus its components alone and placebo in the management of seasonal allergic rhinitis. J Allergy Clin Immunol. 1995;96(2):139-47. 2. Storms WW, Bodman SF, Nathan RA, et al. SCH 434: a new antihistamine/decongestant for seasonal allergic rhinitis. J Allergy Clin Immunol. 1989;83(6):1083-90. 3. Dockhorn RJ, Williams BO, Sanders RL. Efficacy of acrivastine with pseudoephedrine in treatment of allergic rhinitis due to ragweed. Ann Allergy Asthma Immunol. 1996;76(2):204-8. 4. Williams BO, Hull H, McSorley P, Frosolono MF, Sanders RL. Efficacy of acrivastine plus pseudoephedrine for symptomatic relief of seasonal allergic rhinitis due to mountain cedar. Ann Allergy Asthma Immunol. 1996;76(5):432-8.

Quality assessment							Summary of findings					Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients		Effect		Quality	
							oral decongestant	placebo	Relative (95% CI)	Absolute		
Nasal and eye symptoms (follow-up 2 weeks; measured with: Total nasal and non-nasal symptom scores; Better indicated by less)												
4	randomised trial	no serious limitations	no serious inconsistency ¹	serious ²	no serious imprecision ³	none	708	564	-	not pooled ^{4,5}	⊕⊕⊕○ MODERATE	CRITICAL
Response to treatment (physician evaluation) (follow-up 2 weeks)												
1 ⁶	randomised trial	no serious limitations	no serious inconsistency	serious ⁷	serious ⁸	none	98/201	81/207	RR 1.24 (1 to 1.56)	94 more per 1000 (from 0 more to 219 more)	⊕⊕○○ LOW	IMPORTANT
Quality of life - not measured												
0	-	-	-	-	-	none	0/0	0/0	-	-		
Adverse event leading to discontinuation of treatment (follow-up 2 weeks)												
2	randomised trial	no serious limitations	no serious inconsistency	serious ²	serious ⁹	none	17/331	3/324	RR 5.39 (1.59 to 18.34)	40 more per 1000 (from 5 more to 156 more)	⊕⊕○○ LOW	CRITICAL
Treatment failure leading to discontinuation (follow-up 2 weeks)												
2	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	serious ^{8,9}	none	12/331	23/324	RR 0.52 (0.26 to 1.03)	34 fewer per 1000 (from 2 fewer to 53 more)	⊕⊕⊕○ MODERATE	IMPORTANT
Any adverse event (follow-up 2 weeks)												
2 ¹⁰	randomised trial	no serious limitations	no serious inconsistency	very serious ^{2,11}	no serious imprecision	none	188/139	331/324	RR 1.32 (1.13 to 1.54)	327 more per 1000 (from 133 more to 552 more)	⊕⊕○○ LOW	IMPORTANT
Insomnia (follow-up 2 weeks)												
2	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	serious ⁹	none	38/331	3/324	RR 10.41 (1.8 to 60.3)	85 more per 1000 (from 7 more to 534 more)	⊕⊕⊕○ MODERATE	CRITICAL
Headache (follow-up 2 weeks)												
2	randomised trial	no serious limitations	no serious inconsistency ¹²	no serious indirectness	serious ¹³	none	68/331	81/324	RR 0.75 (0.42 to 1.32)	62 fewer per 1000 (from 80 fewer to 145 more)	⊕⊕⊕○ MODERATE	CRITICAL
Dry mouth (follow-up 2 weeks)												
2	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	serious ⁹	none	29/331	10/324	RR 2.83 (1.4 to 5.72)	57 more per 1000 (from 12 more to 146 more)	⊕⊕⊕○ MODERATE	IMPORTANT

¹ All trials showed more reduction in symptoms with pseudoephedrine compared to placebo, but none provided information, if the difference was statistically significant

² In all trials patients used pseudoephedrine regularly twice (60 or 120 mg per dose) or 4 times (60 mg per dose) daily for 2 weeks

³ we did not downgrade for imprecision because there seemed to be a consistent effect showing small benefit

⁴ No trial provided a measure of variation in symptom scores

⁵ Results were not pooled. Overall effect could not be estimated. Mean symptom scores in pseudoephedrine group were numerically smaller than in placebo group.

⁶ second study reported a mean score in physician evaluation; it was 3.0 in placebo and 2.7 in pseudoephedrine groups (p

⁷ There is uncertainty how physician's global evaluation of treatment response relates to patient importance

⁸ results include no effect or a large effect

⁹ very few events

- ¹⁰ remaining two studies reported adverse events the way it was not possible to estimate the difference between pseudoephedrine and placebo
- ¹¹ there is uncertainty if all adverse event were related to treatment and how important they were to patients
- ¹² one trial showed unusual proportion of patient with headache in placebo group
- ¹³ results do not exclude important benefit or important harm

Question 29 [profile 1]

Date: 2007-08-23

Question: Should combination of oral H1-antihistamine and decongestant vs oral H1-antihistamine alone be used for seasonal allergic rhinitis?

Bibliography: McCrory D.C., Williams J.W., Dolor R.J., Gray R.N., Kolimaga J.T., Reed S., Sundry J., Witsell D.L. Management of allergic rhinitis in the working-age population. Evid Rep Technol Assess (Summ), 2003; 67 :1-4.

Quality assessment							Summary of findings					Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients		Effect		Quality	
							combination of oral H1-antihistamine and decongestant	oral H1-antihistamine alone	Relative (95% CI)	Absolute		
Nasal and non-nasal symptoms (follow-up 2 weeks; Better indicated by more)												
7 ¹	randomised trial	no serious limitations ²	no serious inconsistency	no serious indirectness	no serious imprecision ³	none	1100	1099	-	SMD 0.23 (0.15 to 0.32) ⁴	⊕⊕⊕⊕ HIGH	CRITICAL
Nasal symptoms (follow-up 3 to 15 days; Better indicated by less)												
8	randomised trial	no serious limitations ⁵	no serious inconsistency	no serious indirectness	no serious imprecision ³	none	1115	1114	-	SMD 0.33 (0.24 to 0.41)	⊕⊕⊕⊕ HIGH	CRITICAL
Quality of life - not measured												
0	-	-	-	-	-	none	0	0	-	-		
Adverse effects (follow-up 3 to 14 days)												
12	randomised trial	no serious limitations	serious ⁶	no serious indirectness ⁷	no serious imprecision ⁸	none ⁸	0/0 ⁹	0/0 ⁹	not pooled ⁹	not pooled ⁹	⊕⊕⊕O MODERATE	CRITICAL

¹ There were 11 studies altogether that reported total symptom score, but six studies were excluded from the analysis, because of study duration of less than 2 weeks (2 studies -- showed essentially similar symptom scores in the groups, but no formal statistical tests were reported) or effect size could not be calculated (4 studies -- all showed that an antihistamine-decongestant combination was superior to antihistamine alone for reducing symptoms).

² 6 studies did not describe allocation concealment, and 3 did not describe ITT

³ Consistent small effect

⁴ For 3 studies that used non-sedating H1-antihistamine SMD was 0.16 (95% CI: 0.03 to 0.29)

⁵ 6 trials did not describe concealment, and 5 did not describe ITT

⁶ Reporting was inconsistent, sometimes giving number of total events per group sometimes reporting each type of adverse event in detail with variability between studies.

⁷ In all trials drugs were administered regularly, not "as needed"

⁸ We did not downgrade, since we already downgraded for inconsistency.

⁹ there were altogether over 2700 patients. Adverse events were reported in all studies but one. Reporting was inconsistent, sometimes giving number of all event per group sometimes reporting each type of adverse event in detail. Overall headache seemed the most common adverse event reported in both groups. Commonly reported in H1-antihistamine group was somnolence, and in combination group: dry mouth, insomnia, and also somnolence.

Question 29 [profile 2]

Date: 2007-08-23

Question: Should combination of oral desloratadine and pseudoephedrine vs oral desloratadine alone be used for seasonal allergic rhinitis?

Bibliography: 1. Chervinsky P., Nayak A., Rooklin A., Danzig M. Efficacy and safety of desloratadine/pseudoephedrine tablet, 2.5/120 mg two times a day, versus individual components in the treatment of patients with seasonal allergic rhinitis. Allergy Asthma Proc, 2005;26:391-396. 2. Pleskow W., Grubbe R., Weiss S., Lutsky B. Efficacy and safety of an extended-release formulation of desloratadine and pseudoephedrine vs the individual components in the treatment of seasonal allergic rhinitis. Ann Allergy Asthma Immunol, 2005;94:348-354. 3. Schenkel E., Corren J., Murray J.J. Efficacy of once-daily desloratadine/pseudoephedrine for relief of nasal congestion. Allergy Asthma Proc, 2002;23:325-330.

Quality assessment							Summary of findings					Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients		Effect		Quality	
							combination of oral desloratadine and pseudoephedrine	oral desloratadine alone	Relative (95% CI)	Absolute		
Nasal and non-nasal symptoms (excluding congestion) (follow-up 2 weeks; measured with: 7 symptoms rated on a 4-point scale; range of scores: 0-21; Better indicated by less)												
2	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision ¹	none	586	586	-	WMD -1.15 (-1.57 to -0.72)	⊕⊕⊕⊕ HIGH	CRITICAL
Nasal congestion (follow-up 2 weeks; measured with: 4-point scale; range of scores: 0-3; Better indicated by less)												
3	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision ²	none	922	926	-	not pooled ³	⊕⊕⊕⊕ HIGH	CRITICAL
Quality of life - not measured												
0	-	-	-	-	-	none	0	0	-	-		
Adverse events (follow-up 2 weeks)												
3	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	serious ⁴	none	306/922	222/926	RR 1.45 (0.99 to 2.14)	108 more per 1000 (from 2 fewer to 274 more)	⊕⊕⊕○ MODERATE	IMPORTANT
Dry mouth (follow-up 2 weeks)												
3	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	67/922	22/926	RR 2.97 (1.84 to 4.78)	47 more per 1000 (from 20 more to 91 more)	⊕⊕⊕⊕ HIGH	IMPORTANT
Insomnia (follow-up 2 weeks)												
3	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	serious ⁵	none	54/922	10/926	RR 5.27 (2.7 to 10.3)	47 more per 1000 (from 19 more to 102 more)	⊕⊕⊕○ MODERATE	CRITICAL
Somnolence (follow-up 2 weeks)												
2	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	serious ⁵	none ⁶	24/708	12/712	RR 1.97 (0.99 to 3.95)	16 more per 1000 (from 0 fewer to 50 more)	⊕⊕⊕○ MODERATE	CRITICAL
Headache (follow-up 2 weeks)												
3	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	47/922	44/926	RR 1.06 (0.71 to 1.58)	3 more per 1000 (from 14 fewer to 28 more)	⊕⊕⊕⊕ HIGH	IMPORTANT
Fatigue (follow-up 2 weeks)												
2	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	serious ⁵	none ⁶	15/708	17/712	RR 0.93 (0.34 to 2.51)	2 fewer per 1000 (from 16 fewer to 36 more)	⊕⊕⊕○ MODERATE	IMPORTANT

¹ Results include only small effect.

² Small consistent change.

³ No measure of variation was provided, but mean change from baseline was 0.2 points in all studies.

⁴ results do not exclude no effect or a serious increase in adverse events

⁵ Very few events.

⁶ One study did not report this outcome.

Question 31 [profile 1]

Date: 2007-07-16

Question: Should sodium cromoglycate vs placebo be used for seasonal allergic rhinitis and symptoms of conjunctivitis?

Settings: Canada, Philippines, Northern Ireland, Italy, and the Netherlands

Bibliography: Owen C.G., Shah A., Henshaw K., Smeeth L., Sheikh A. Topical treatments for seasonal allergic conjunctivitis: systematic review and meta-analysis of efficacy and effectiveness. Br J Gen Pract, 2004;54:451-456.

Quality assessment							Summary of findings				Importance	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients		Effect			Quality
							sodium cromoglycate	placebo	Relative (95% CI)	Absolute		
Conjunctivitis symptoms (all trials) (follow-up 1 to 4 weeks; Better indicated by less)												
8	randomised trial	no serious limitations	serious ¹	no serious indirectness	serious ¹	reporting bias ²	0 ³	0 ³	-	not pooled ⁴	⊕○○○ VERY LOW	CRITICAL
Patient perceived benefit (all trials)												
6	randomised trial	no serious limitations	serious ⁵	no serious indirectness	no serious imprecision	reporting bias ²	108/152	42/164	OR 17.2 (3.8 to 78.4)	920 more per 1000 (from 404 more to 1000 more)	⊕⊕○○ LOW	CRITICAL
Patient perceived benefit (seasonal allergic rhinitis only)												
5	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias ²	85/95	32/106	RR 3.4 (1.57 to 7.34) ⁶	725 more per 1000 (from 172 more to 1000 more)	⊕⊕⊕○ MODERATE	CRITICAL
Patient perceived benefit (chronic conjunctivitis) (follow-up 4 weeks)												
1	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	serious ⁷	none	23/57	15/58	RR 1.56 (0.91 to 2.67)	145 more per 1000 (from 23 fewer to 433 more)	⊕⊕⊕○ MODERATE	CRITICAL
Quality of life - not measured⁸												
0	-	-	-	-	-	none	0/0	0/0	-	-		
Adverse effects												
0	no evidence available					none	0/0	0/0	not pooled	not pooled		

¹ It was not possible to assess, because mean scores or measures of accuracy were not reported in the trials.

² Trials reporting marked and statistically significant benefits of active treatment over placebo were mostly small. One of two formal tests for publication bias was statistically significant.

³ Number of patients not reported in the review.

⁴ Not pooled. Five studies reported an improvement in symptoms while using topical sodium cromoglycate preparations whereas the remaining three trials found no difference in symptoms between treatment groups. An additional trial published after the systematic review was done (James 2003) also found important improvement in symptoms compared to placebo. Symptoms were: itching, burning, soreness, and lacrimation.

⁵ Pooled trials were heterogeneous. One trial that showed least effect was performed in patients with chronic conjunctivitis.

⁶ Because event rates were high, presentation of the results as relative risk is more informative than as an odds ratio.

⁷ results include no effect or large effect

⁸ Outcome was not measured in the included studies

Question 31 [profile 2]

Date: 2007-07-23

Question: Should nedocromil sodium vs placebo be used in patients with allergic rhinitis and symptoms of conjunctivitis?

Bibliography: Owen C.G., Shah A., Henshaw K., Smeeth L., Sheikh A. Topical treatments for seasonal allergic conjunctivitis: systematic review and meta-analysis of efficacy and effectiveness. Br J Gen Pract, 2004;54:451-456.

Quality assessment							Summary of findings				Importance	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients		Effect			Quality
							nedocromil sodium	placebo	Relative (95% CI)	Absolute		
Conjunctivitis symptoms (itching, burning, soreness, lacrimation) (follow-up 4 to 9 weeks; Better indicated by less)												
5	randomised trial	no serious limitations	serious ¹	no serious indirectness	serious ¹	none	283	273	-	not pooled ²	⊕⊕○○ LOW	CRITICAL
Patient perceived benefit (all trials) (follow-up 4 to 9 weeks)												
5	randomised trial	no serious limitations	serious ³	no serious indirectness	no serious imprecision	none	175/283	130/273	OR 1.8 (1.3 to 2.6)	241 more per 1000 (from 101 more to 414 more)	⊕⊕⊕○ MODERATE	CRITICAL
Patient perceived benefit (adults) (follow-up 4 to 9 weeks)												
4	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	123/207	81/203	RR 1.49 (1.22 to 1.82)	196 more per 1000 (from 88 more to 327 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Patient perceived benefit (children) (follow-up mean 4 weeks)												
1	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	24/32	19/32	RR 0.98 (0.79 to 1.21)	12 fewer per 1000 (from 125 fewer to 125 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Quality of life - not measured⁴												
0	-	-	-	-	-	none	0	0	-	-		
Adverse effects												
0	no evidence available					none	0/0	0/0	not pooled	not pooled		

¹ It was not possible to assess, because trials were not pooled.

² The differences were statistically significant in three of the studies and of borderline significance in the two studies.

³ There was moderate heterogeneity in the results with one large study conducted in children showing no effect.

⁴ Outcome was not measured in the included studies

Question 31 [profile 3]

Date: 2007-07-24

Question: Should Iodoxamide vs placebo be used in patients with allergic rhinitis and symptoms of conjunctivitis?

Bibliography: Owen C.G., Shah A., Henshaw K., Smeeth L., Sheikh A. Topical treatments for seasonal allergic conjunctivitis: systematic review and meta-analysis of efficacy and effectiveness. Br J Gen Pract, 2004;54:451-456.

Quality assessment							Summary of findings				Importance	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients		Effect			Quality
							Iodoxamide	placebo	Relative (95% CI)	Absolute		
symptoms requiring additional treatment (follow-up 4 weeks)												
1	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	very serious ¹	none	2/14	11/13	RR 0.17 (0.05 to 0.5)	702 fewer per 1000 (from 423 fewer to 804 fewer)	⊕⊕⊕⊕ LOW	CRITICAL
Quality of life - not measured												
0	-	-	-	-	-	none	0	0	-	-		
Adverse effects (follow-up 4 weeks)												
1	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	very serious ¹	none	0/14	0/13	RR 0 (0 to 0) ²		⊕⊕⊕⊕ LOW	

¹ One small trial (n = 27)

² No side effects associated with use of the active treatment were reported.

Question 32

Date: 2007-09-06

Question: Should subcutaneous allergen specific immunotherapy vs placebo be used in adults with allergic rhinitis?

Bibliography: Calderon M., Alves B., Jacobson M., Hurwitz B., Sheikh A., Durham S. Allergen injection immunotherapy for seasonal allergic rhinitis. Cochrane database of systematic reviews (Online), 2007:CD001936.

Quality assessment							Summary of findings					Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients		Effect		Quality	
							subcutaneous allergen specific immunotherapy	placebo	Relative (95% CI)	Absolute		
Symptoms (recorded in diary) (follow-up 3 days to 3 years¹; Better indicated by less)												
15 ²	randomised trial	no serious limitations	no serious inconsistency ³	no serious indirectness	no serious imprecision	none	597	466	-	SMD -0.73 (-0.97 to -0.5)	⊕⊕⊕⊕ HIGH	CRITICAL
Medication score (follow-up 3 days to 3 years¹; Better indicated by less)												
13	randomised trial	no serious limitations	no serious inconsistency ³	serious ⁴	no serious imprecision	none	549	414	-	SMD -0.57 (-0.33 to -0.82)	⊕⊕⊕○ MODERATE	IMPORTANT
symptom and medication score (follow-up 3 days to 3 years¹; Better indicated by less)												
8	randomised trial	no serious limitations	no serious inconsistency	serious ⁴	no serious imprecision	none	320	297	-	SMD -0.48 (-0.29 to -0.67)	⊕⊕⊕○ MODERATE	IMPORTANT
Nasal symptoms (follow-up 3 days to 3 years¹; Better indicated by less)												
9 ⁶	randomised trial	no serious limitations	serious ³	no serious indirectness	no serious imprecision	none	396	276	-	SMD -1.59 (-0.89 to -2.29)	⊕⊕⊕⊕ HIGH	CRITICAL
Bronchial symptoms (follow-up 3 days to 3 years¹; Better indicated by less)												
5 ⁷	randomised trial	no serious limitations	no serious inconsistency ³	no serious indirectness	serious ⁵	none	266	163	-	SMD -0.59 (-0.11 to -1.06)	⊕⊕○○ LOW	IMPORTANT
Ocular symptoms (follow-up 3 days to 3 years¹; Better indicated by less)												
3 ⁸	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	226	119	-	SMD -1.80 (-0.31 to -3.28)	⊕⊕⊕⊕ HIGH	CRITICAL
Global improvement (follow-up 3 days to 3 years¹; Better indicated by less)												
9 ⁹	randomised trial	no serious limitations	- ¹⁰	no serious indirectness	- ¹⁰	none	0	0	-	not pooled ⁹		IMPORTANT
Quality of life (follow-up 3 days to 3 years¹; Better indicated by less)												
5	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	332	239	-	SMD -0.52 (-0.34 to -0.69)	⊕⊕⊕⊕ HIGH	CRITICAL
Adverse events (local reaction not requiring treatment) (follow-up 3 days to 3 years¹)												
24	randomised trial	no serious limitations	- ¹⁰	no serious indirectness	- ¹⁰	none	-/907 ¹¹	-/697 ¹²	not pooled	not pooled		IMPORTANT
Adverse events (local reaction requiring treatment) (follow-up 3 days to 3 years¹)												
7	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	serious ¹³	none	-/208 ¹⁴	-/186 ¹⁵	not pooled	not pooled	⊕⊕⊕○ MODERATE	IMPORTANT
Adverse events (early mild systemic reaction [$<$ 30 minutes]) (follow-up 3 days to 3 years; assessed with: mild systemic reactions¹⁶)												
17	randomised trial	no serious limitations	- ¹⁰	no serious indirectness	- ¹⁰	none	-/706 ¹⁷	-/566 ¹⁸	not pooled	not pooled		CRITICAL
Adverse events (early severe systemic reaction [$<$ 30 minutes]) (follow-up 3 days to 3 years¹; assessed with: non life-threatening systemic reactions¹⁹)												
13	randomised trial	no serious limitations	- ¹⁰	no serious indirectness	- ¹⁰	none	-/615 ²⁰	-/463 ²¹	not pooled	not pooled		CRITICAL

Adverse events (early life-threatening systemic reaction [< 30 minutes]) (follow-up 3 days to 3 years ¹ ; assessed with: anaphylactic shock ²²)												
9	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	serious ¹³	none	-/417 ²³	-/303 ²⁴	not pooled	not pooled	⊕⊕⊕O MODERATE	CRITICAL
Adverse events late systemic reaction [>30 minutes]) (follow-up 3 days to 3 years ¹)												
11	randomised trial	no serious limitations	- ¹⁰	no serious indirectness	- ¹⁰	none	-/514 ²⁵	-/412 ²⁶	not pooled	not pooled		CRITICAL
Adverse events (systemic reaction - severity and time of onset not specified)												
3	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	serious ¹³	none	-/142 ²⁷	-/63 ²⁸	not pooled	not pooled	⊕⊕⊕O MODERATE	CRITICAL
Adverse events (adrenaline use) (follow-up 3 days to 3 years)												
13	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	serious ¹³	none	- ²⁹	- ³⁰	not pooled	not pooled	⊕⊕⊕O MODERATE	CRITICAL
Death - not reported ³¹												
0	-	-	-	-	-	-	-	-	-	-		IMPORTANT

¹ Duration of maintenance treatment and the period of follow-up varied considerably between studies, largely reflecting pre-seasonal, co-seasonal and post-seasonal administration.

² 16 further studies measured symptom scores, but did not provide enough information to allow pooling the results. All 16 favoured the intervention group.

³ There was large heterogeneity in results, but exclusion of an outlying study would not change the conclusion.

⁴ There is uncertainty to what extent use of medications expressed as "medication score" reflects a patient-important outcome.

⁵ Results include large and small effect.

⁶ Seven of the eight studies not included in the meta-analysis, favoured the intervention group.

⁷ Eight of the ten studies not included in the meta-analysis favoured the intervention group.

⁸ Six of the nine studies not included in the meta-analysis favoured the intervention group.

⁹ All nine studies favoured the intervention group.

¹⁰ Not assessed. Without pooled estimate it was not possible to assess the consistency or precision of the results.

¹¹ 834 events

¹² 227 events

¹³ Very few events.

¹⁴ 21 events

¹⁵ 8 events

¹⁶ Mild rhinitis and/or asthma (peak expiratory flow rates over 60% of predicted or of the personal best values) responding adequately to antihistamines or inhaled beta2-agonists.

¹⁷ 154 events

¹⁸ 44 events

¹⁹ Urticaria, angioedema, or severe asthma (PEFR under 60% of predicted or of personal best values) responding well to treatment.

²⁰ 43 events

²¹ 3 events

²² Rapidly evoked reaction of itching, flushing, erythema, bronchial obstruction, etc. requiring intensive treatment.

²³ 3 events

²⁴ one event

²⁵ 458 events

²⁶ 148 events

²⁷ 12 events

²⁸ no events

²⁹ 19 events per 14,085 injections

³⁰ One event per 8278 injections.

³¹ No fatal events were reported in any of the studies included in this systematic review.

Question 33

Date: 2008-12-11

Question: Should subcutaneous immunotherapy be used in children with allergic rhinitis?

Bibliography: Röder E., Berger M.Y., de Groot H., van Wijk R.G. Immunotherapy in children and adolescents with allergic rhinoconjunctivitis: a systematic review. *Pediatr Allergy Immunol*, 2008;19:197-207.

Quality assessment							Summary of findings				Quality	Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients		Effect			
							subcutaneous immunotherapy	control	Relative (95% CI)	Absolute		
Nasal symptoms (follow-up 1 to 36 months; Better indicated by lower values)												
6	randomised trials	serious ¹	serious ²	no serious indirectness	no serious imprecision ³	none	229	230	-	not pooled ^{2,4}	⊕⊕○○ LOW	CRITICAL
Development of asthma (follow-up 5 years)												
1	randomised trials	serious ⁵	no serious inconsistency	no serious indirectness	serious ⁶	none	15/75 (20%)	29/67 (43.3%)	RR 0.46 (0.27 to 0.77)	234 fewer per 1000 (from 100 fewer to 316 fewer)	⊕⊕○○ LOW	CRITICAL
Quality of life - not measured⁷												
0	-	-	-	-	-	none	-	-	-	-	—	CRITICAL
Adverse effects (follow-up 1 to 36 months)												
5	randomised trials	very serious ^{1,8}	no serious inconsistency ⁹	no serious indirectness	no serious imprecision	none	-	-	not pooled	not pooled	⊕⊕○○ LOW	CRITICAL
Non-life threatening systemic adverse events (based on studies in adults)												
13	randomised trials	no serious limitations	no serious inconsistency	serious ¹⁰	no serious imprecision	none	43/615 (7%) ¹¹	3/463 (0.6%) ¹¹	not pooled ¹²	not pooled	⊕⊕⊕○ MODERATE	CRITICAL
Anaphylactic shock (based on studies in adults)												
9	randomised trials	no serious limitations	no serious inconsistency	serious ¹⁰	serious ¹³	none	3/417 (0.7%)	1/303 (0.3%)	not pooled ¹⁴	not pooled	⊕⊕○○ LOW	CRITICAL
Adrenaline use for systemic reaction (based on studies in adults)												
13	randomised trials	no serious limitations	no serious inconsistency	serious ¹⁰	no serious imprecision	none	19/14085 (0.1%) ¹⁵	1/8278 (0%) ¹⁵	RR 11.17 (1.9 to 65.58)	1 more per 1000 (from 0 more to 8 more) ¹⁵	⊕⊕⊕○ MODERATE	CRITICAL

¹ Only 2 trials reported concealment of allocation, groups were not similar at the start of any of the studies, 3 studies attempted to blind at least patients, caregivers or outcome assessors, one reported an intention-to-treat analysis, and 2 lost to follow-up more than 20% of patients. Reporting of the results was poor.

² Two trials "demonstrated efficacy" and four did not.

³ We did not downgrade for imprecision, because it was not possible to assess it without meta-analysis, and we already downgraded for inconsistency.

⁴ Results were not pooled because "description of the various scores was often insufficient as for instance information on the range and composition of the score was lacking. Different point estimates (e.g. mean or ranks) were presented and the measures of variability (e.g. SD or 95% CI) were not always stated"

⁵ Post-hoc subgroup analysis.

⁶ Small trial with small number of events.

⁷ Quality of life was not investigated in any of the included studies.

⁸ Data on adverse events were presented in 5/6 trials. Adverse effects were poorly reported and the definitions of an adverse event were often unclear. Local side-effects were more frequently reported in the intervention groups. Systemic side-effects (e.g. asthma) were rare and mild. Systemic anaphylactic reactions did not occur.

⁹ We did not downgrade for inconsistency or imprecision since they were impossible to assess. We already downgraded the quality of evidence to low because of very serious limitations in design, execution or reporting of outcomes.

¹⁰ Extrapolated from trials in adults (Calderon M. et al. *Cochrane Database Syst Rev*, 2007:CD001936).

¹¹ Most studies reported number of adverse events, rather than the number of participants in which one or more adverse events were observed.

¹² Authors of the systematic review did not combine the results of individual studies. However, under the assumption that all these events were independent (i.e. each event occurred in a different patient) and not taking into consideration the weight of individual studies, the estimated effect would be: RR 10.79 (95% CI: 3.59 to 32.7) and a corresponding absolute difference would be 63 more per 1000 (95% CI: from 17 more to 205 more).

¹³ Very few events.

¹⁴ Authors of the systematic review did not combine the results of individual studies. However, under the assumption that all these events were independent (i.e. each event occurred in a different patient) and not taking into consideration the weight of individual studies, the estimated effect would be: RR 2.18 (95% CI: 0.31 to 15.18) and a corresponding absolute difference would be 4 more per 1000 (95% CI: from 12 less to 18 more).

¹⁵ number of events per number of injections

Question 34 [profile 1]

Date: 2009-01-08

Question: Should sublingual specific immunotherapy be used in adults with seasonal allergic rhinitis?

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Quality assessment							Summary of findings					Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients		Effect		Quality	
							sublingual specific immunotherapy	control	Relative (95% CI)	Absolute		
Nasal symptoms (follow-up median 6 months¹; range of scores: 0-0; Better indicated by lower values)												
22	randomised trials	serious ²	no serious inconsistency ³	no serious indirectness	no serious imprecision	none	1108	1100	-	SMD 0.43 lower (0.28 to 0.58 lower) ⁴	⊕⊕⊕O MODERATE	CRITICAL
Ocular symptoms (follow-up median 7 months⁵; Better indicated by lower values)												
8	randomised trials	serious ⁶	no serious inconsistency ⁷	no serious indirectness	serious ⁸	none	597	616	-	SMD 0.26 lower (0.06 to 0.46 lower)	⊕⊕OO LOW	IMPORTANT
Medication use (follow-up median 7 months⁵; Better indicated by lower values)												
13	randomised trials	serious ^{6,9}	no serious inconsistency	no serious indirectness	no serious imprecision	none	712	704	-	SMD 0.32 lower (0.19 to 0.46 lower)	⊕⊕⊕O MODERATE	IMPORTANT
Symptom-medication score (follow-up 4 to 6 months; Better indicated by lower values)												
3	randomised trials	serious ¹⁰	no serious inconsistency	no serious indirectness	serious ¹¹	none	99	51	-	SMD 0.49 lower (0.14 to 0.84 lower)	⊕⊕OO LOW	IMPORTANT
Quality of life (follow-up median 7 months¹²)												
7	randomised trials	serious ¹³	no serious inconsistency ¹⁴	no serious indirectness	serious ¹⁵	none	445	435	-	not pooled ¹⁵	⊕⊕OO LOW	CRITICAL
Serious adverse effects (follow-up median 7 months¹)												
36	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/2253 (0%)	0/1906 (0%)	not pooled ¹⁶	not pooled	⊕⊕⊕⊕ HIGH	IMPORTANT
Withdrawal due to adverse effect (follow-up median 7 months¹)												
25	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	70/1691 (4.1%)	16/1430 (1.1%)	RR 2.91 (1.72 to 4.92)	21 more per 1000 (from 8 more to 44 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Oral pruritus or burning (follow-up median 7 months¹)												
19	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	strong association ¹⁷	481/1304 (36.9%)	73/1152 (6.3%)	RR 4.92 (3.16 to 7.67)	248 more per 1000 (from 137 more to 423 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Oral oedema (follow-up median 8 months^{1,18})												
7	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious ¹⁹	very strong association ²⁰	113/763 (14.8%)	4/702 (0.6%)	RR 11.47 (4.66 to 28.24)	60 more per 1000 (from 21 more to 155 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Gastrointestinal adverse effects (follow-up median 7 months¹; nausea, vomiting, stomach upset, diarrhoea)												
9	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious ²¹	none	40/482 (8.3%)	10/413 (2.4%)	RR 2.85 (1.44 to 5.65)	45 more per 1000 (from 11 more to 113 more)	⊕⊕⊕O MODERATE	CRITICAL

¹ The duration of maintenance treatment and the period of follow up varied considerably between studies, largely reflecting pre-seasonal, co-seasonal and perennial administration. Range of follow-up was 1 to 48 months.

² Most studies did not report if they followed intention-to-treat principle; no study reported concealment of allocation. In 7 studies 10-20% patients withdrew prematurely and in 3 -- between 20% and 40%.

³ There was some inconsistency in the results, but when one study that included 50% patients with perennial rhinitis was excluded, the results were consistent.

⁴ In the analysis we included 6 studies that did not provide variability in results; we took variability from unpublished data included in a systematic review done by Wilson and colleagues in 2003. Excluding these studies from current analysis would not change the results (SMD: -0.42, 95% CI: -0.25 to -0.59).

⁵ Range: 3.5 to 18 months.

⁶ In all studies but one between 10% and 20% of patients withdrew from the study. Majority of studies did not report following intention-to-treat principle and was analysed per-protocol.

⁷ There was some inconsistency in results, but removing the studies with extreme results did not substantially change the estimate of effect.

⁸ Results do not exclude a moderate effect on no difference.

⁹ In seven studies 10-20% of patients withdrew from the study, and in 2 withdrew more than 20%. Majority of studies did not report following intention-to-treat principle and two were analysed per-protocol.

¹⁰ No study reported intent-to-treat analysis; one study was not blinded, and in one 28% did not complete treatment.

¹¹ Only 150 patients. Results do not exclude a small or a large effect.

¹² Range: 4 to 36.

¹³ Five of seven studies did not report if they followed intention -to-treat principle during the analysis. One study was not blinded and one did not report blinding. In one study 38% of patients did not complete treatment. Outcomes were poorly reported.

¹⁴ Only 2 studies reported variability in results. Other studies described their results as either improved QoL with SLIT or no difference. We did not downgrade for inconsistency, since we already downgraded for limitations in design and execution and for imprecision.

¹⁵ Three of seven studies reported statistically significant improvement in quality of life, however, they reported their results in a way that precluded combining their results. Two studies found an improvement that was statistically not significant, but did not report variability. Two studies found no difference: one did not report what were the results and the other found almost no change in score from baseline in both SLIT and placebo groups.

¹⁶ There were no serious adverse observed in any of the studies.

¹⁷ Lower confidence limit was 3.16.

¹⁸ Range: 4 to 24 months.

¹⁹ Only 117 events.

²⁰ Lower confidence limit was 4.66

²¹ Only 50 events.

Question 34 [profile 2]

Date: 2009-03-21

Question: Should sublingual immunotherapy vs placebo be used in adults with perennial/persistent allergic rhinitis?

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Quality assessment							Summary of findings					Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients		Effect		Quality	
							sublingual immunotherapy	placebo	Relative (95% CI)	Absolute		
Nasal symptoms (house dust mite) (follow-up 12 to 24 months¹; Better indicated by lower values)												
5	randomised trials	serious ²	no serious inconsistency	no serious indirectness	serious ³	none	89	84	-	SMD 0.82 lower (0.24 to 1.4 lower) ⁴	⊕⊕⊕⊕ LOW	CRITICAL
Nasal symptoms (cat) (follow-up 3 to 12 months; Better indicated by lower values)												
3	randomised trials	serious ⁵	no serious inconsistency ⁶	no serious indirectness	serious ⁷	none	53	55	-	SMD 1.68 lower (0.12 to 3.23 lower) ⁸	⊕⊕⊕⊕ LOW	CRITICAL
Quality of life (follow-up 24 months; Better indicated by lower values)												
1	randomised trials	serious ⁹	no serious inconsistency	no serious indirectness	serious ¹⁰	none	28	28	-	not pooled ¹¹	⊕⊕⊕⊕ LOW	CRITICAL
Serious adverse effects (follow-up 3 to 24 months¹)												
6 ¹²	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/171 (0%)	0/169 (0%)	not pooled	not pooled	⊕⊕⊕⊕ HIGH	IMPORTANT
Oral pruritus/burning/oedema												
4 ^{12,13}	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious ¹⁴	none	5/76 (6.6%)	1/74 (1.4%)	RR 2.31 (0.53 to 10.09)	18 more per 1000 (from 6 fewer to 123 more)	⊕⊕⊕⊕ MODERATE	CRITICAL

¹ Four of five studies of SLIT for house dust mites lasted for 24 months, only one followed patients for 12 months. Two studies of SLIT for cat followed patients for 12 months and one for 3 months.

² Only one study reported following intent-to-treat analysis. No study reported concealment of allocation. In one study 44% did not complete treatment.

³ Only 173 patients. Estimate of the effect does not exclude a very large or small effect.

⁴ One study reported implausibly small variability in results; if it were excluded the effect size would be -0.54, 95% CI: -0.09 to -0.99. Another study reported the results as a graph only; using the end-of study results overestimates the effect seen during the study; if this study were also excluded the effect size would be -0.39, 95% CI: -0.79 to 0.01. One study reported its results as change score; mean difference between SLIT and placebo group was -2.17 points (95% CI: -1.14 to -3.20) on a 13-point scale.

⁵ One study reported only the results of per-protocol analysis and other two did not report if they followed the intention-to-treat principle. No study reported concealment of allocation. In one study 34% did not complete treatment.

⁶ One study showed much larger effect than the other two, but it was due to extremely small variability in results caused by all patients in control group been classified in one category.

⁷ Only 108 patients. Results do not exclude a very large or a very small effect.

⁸ If one study with extremely small variability because of too few categories in the scale used to measure the outcome were excluded, the effect size would be -0.74, 95% CI: -0.27 to -1.22.

⁹ method of analysis was not reported and 18% did not complete treatment. Only one study with poor reporting of this outcome.

¹⁰ Only one study with 56 patients. No measure of variability in results.

¹¹ Authors did not report a summary score or any variability in the results. They stated that „there was no statistical change in all the domains of the SF-36 questionnaire at the six time points, and all the scores were quite high“.

¹² Two studies did not mention adverse effects at all.

¹³ Studies in patients allergic to cat dander did not mention adverse effects at all.

¹⁴ Only 6 events. Results do not exclude a very large harm or no effect.

Question 35 [profile 1]

Date: 2009-03-23

Question: Should sublingual immunotherapy vs placebo be used in children with seasonal allergic rhinitis?

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Quality assessment							Summary of findings				Quality	Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients		Effect			
							sublingual immunotherapy	placebo	Relative (95% CI)	Absolute		
Nasal symptoms (follow-up median 21 months¹; Better indicated by lower values)												
12	randomised trials	no serious limitations ²	no serious inconsistency	no serious indirectness	no serious imprecision	none	558	554	-	SMD 0.27 lower (0.15 to 0.37 lower) ³	⊕⊕⊕⊕ HIGH	CRITICAL
Development of asthma (follow-up 3 years)												
1	randomised trials	serious ⁴	no serious inconsistency	no serious indirectness	serious ⁵	none	8/45 (17.8%)	18/44 (40.9%)	RR 0.43 (0.21 to 0.87)	233 fewer per 1000 (from 53 fewer to 323 fewer)	⊕⊕○○ LOW	CRITICAL
Quality of life (children) (follow-up 24 months; measured with: Pediatric Rhinoconjunctivitis Quality of Life Questionnaire; range of scores: 0-6; Better indicated by lower values)												
1	randomised trials	serious ⁶	serious ⁷	no serious indirectness ⁸	serious ⁹	none	30	26	-	MD 0.30 higher (0.14 lower to 0.74 higher)	⊕○○○ VERY LOW	CRITICAL
Quality of life (adolescents) (follow-up 24 months; measured with: Adolescent Rhinoconjunctivitis Quality of Life Questionnaire; range of scores: 0-6; Better indicated by lower values)												
1	randomised trials	serious ⁶	serious ⁷	no serious indirectness ⁸	serious ⁹	none	56	47	-	MD 0.40 lower (0.95 lower to 0.15 higher)	⊕○○○ VERY LOW	CRITICAL
Ocular symptoms (follow-up median 12 months¹⁰; Better indicated by lower values)												
4	randomised trials	no serious limitations	no serious inconsistency ¹¹	no serious indirectness	serious ¹²	none	208	206	-	SMD 0.18 lower (0.44 lower to 0.08 higher)	⊕⊕⊕○ MODERATE	IMPORTANT
Medication use (follow-up median 12 months¹; Better indicated by lower values)												
6	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious ¹³	none	387	390	-	SMD 0.21 lower (0.07 to 0.35 lower) ¹⁴	⊕⊕⊕○ MODERATE	IMPORTANT
Serious adverse effects (follow-up median 24 months¹)												
7	randomised	no serious	no serious	no serious	no serious	none	0/516 (0%)	0/500 (0%)	not pooled ¹⁵	not pooled ¹⁵	⊕⊕⊕⊕	IMPORTANT

	trials	limitations	inconsistency	indirectness	imprecision						HIGH	
Withdrawal due to adverse effects (follow-up median 24 months)¹⁶												
8	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious ¹⁷	none	19/620 (3.1%)	8/543 (1.5%)	RR 2.07 (0.89 to 4.84)	16 more per 1000 (from 2 fewer to 57 more)	⊕⊕⊕○ MODERATE	CRITICAL
Oral pruritus/oedema (follow-up median 18 months)¹⁶												
5	randomised trials	serious ¹⁸	no serious inconsistency	no serious indirectness	no serious imprecision	strong association ¹⁹	157/446 (35.2%)	38/438 (8.7%) 2% ²⁰	RR 4.03 (1.64 to 9.93)	263 more per 1000 (from 56 more to 775 more) 61 more per 1000 (from 13 more to 179 more)	⊕⊕⊕⊕ HIGH	CRITICAL

¹ Range: 3 to 36 months.

² Only 4 of 12 studies reported following intention-to-treat principle; none reported concealment of allocation, and on average 12% of children withdrew prematurely from these studies.

³ The results did not change substantially if we included two studies that enrolled children with asthma (and/or allergic rhinitis) that also measured nasal symptoms (SMD: -0.26, 95% CI: -0.14 to -0.38). Three studies did not report variability in their results, but we obtained it from unpublished data included in the systematic review by M. Penagos and colleagues (2006); when we excluded these studies the results also did not change substantially (SMD: -0.23, 95% CI: -0.09 to -0.37).

⁴ Randomisation, concealment of allocation, and type of analysis (intention-to-treat or per protocol) were not described, no blinding, 21% lost to follow-up.

⁵ One small study. Very few events.

⁶ Subgroup analysis.

⁷ Results pointed opposite directions in children and in adolescents.

⁸ Some experts consider the dosing of SLIT in this study inadequate, however, the authors do not share this view.

⁹ Few patients. Results do not exclude important benefit or harm.

¹⁰ Range: 3 to 32 months.

¹¹ There was inconsistency with results, but could be explained by one study (Caffarelli 2000) explicitly including patients with allergic conjunctivitis. This study showed a larger effect (ES: -0.68, 95% CI: -0.07 to -1.29) than the other three studies together (SMD: -0.11, 95% CI: -0.32 to 0.09). Inclusion of one additional study that enrolled children with asthma some of whom had also rhinitis did not substantially change the results (SMD: -0.18, 95% CI: -0.39 to 0.03).

¹² Results do not exclude a moderate benefit with SLIT or no difference.

¹³ Results do not exclude small benefit with SLIT or no effect.

¹⁴ Including two additional studies that enrolled children with asthma, of whom some also had rhinitis, did not change the results (SMD: -0.23, 95% CI: -0.06 to -0.39).

¹⁵ There were no serious adverse events related to the treatment in these studies.

¹⁶ Range: 5 to 36 months.

¹⁷ Results do not exclude appreciable harm with SLIT or no difference.

¹⁸ Most studies poorly reported this and other adverse effects (e.g. stating the total number of events in the study but not reporting in which group they occurred).

¹⁹ Lower confidence limit is 1.64 and all plausible biases as well as the results from studies in adults suggest that the effect is larger than estimated.

²⁰ A low (2%) assumed baseline risk was estimated based on 2 most recent studies included in the analysis.

Question 35 [profile 2]

Date: 2009-03-23

Question: Should sublingual immunotherapy vs placebo be used in children with perennial/persistent allergic rhinitis?

Bibliography: 1. Hirsch T., Sahn M., Leupold W. Double-blind placebo-controlled study of sublingual immunotherapy with house dust mite extract (D.pt.) in children. *Pediatr Allergy Immunol*, 1997;8:21-27. 2. Marcucci F., Sensi L., Di Cara G., Salvatori S., Bernini M., Pecora S., Burastero S.E. Three-year follow-up of clinical and inflammation parameters in children monosensitized to mites undergoing sub-lingual immunotherapy. *Pediatr Allergy Immunol*, 2005;16:519-526. 3. Tari M.G., Mancino M., Monti G. Efficacy of sublingual immunotherapy in patients with rhinitis and asthma due to house dust mite. A double-blind study. *Allergologia et immunopathologia*, 1990;18:277-284. 4. Tseng S.H., Fu L.S., Nong B.R., Weng J.D., Shyur S.D. Changes in serum specific IgG4 and IgG4/ IgE ratio in mite-sensitized Taiwanese children with allergic rhinitis receiving short-term sublingual-swallow immunotherapy: a multicenter, randomized, placebo-controlled trial. *Asian Pac J Allergy Immunol*, 2008;26:105-112.

Quality assessment							Summary of findings				Importance	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients		Effect			Quality
							sublingual immunotherapy	placebo	Relative (95% CI)	Absolute		
Nasal symptoms (follow-up 6 to 12 months; Better indicated by lower values)												
4 ¹	randomised trials	serious ²	no serious inconsistency	no serious indirectness	serious ³	none	54	54	-	SMD 0.02 higher (0.36 lower to 0.4 higher) ⁴	⊕⊕⊕⊕ LOW	CRITICAL
Ocular symptoms (follow-up 18 months; Better indicated by lower values)												
1	randomised trials	serious ⁵	no serious inconsistency	no serious indirectness	serious ⁶	none	30	28	-	not pooled ⁷	⊕⊕⊕⊕ LOW	IMPORTANT
Medication use - not measured												
0	-	-	-	-	-	none	0	0	-	-		IMPORTANT
Serious adverse effects (follow-up 6 to 18 months)												
2	randomised trials	serious ⁸	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/64 (0%)	0/65 (0%)	not pooled ⁹	not pooled	⊕⊕⊕⊕ MODERATE	IMPORTANT
Withdrawal due to adverse effects (follow-up 12 months)												
1	randomised trials	serious ¹⁰	no serious inconsistency	no serious indirectness	very serious ¹¹	none	1/15 (6.7%)	0/15 (0%) 1% ¹²	RR 3.0 (0.13 to 68.26)	0 more per 1000 (from 0 fewer to 0 more) 20 more per 1000 (from 9 fewer to 673 more)	⊕⊕⊕⊕ VERY LOW	CRITICAL
Oral pruritus/oedema (follow-up 12 months)												
1	randomised trials	serious ¹⁰	no serious inconsistency	no serious indirectness	very serious ¹³	none	5/15 (33.3%)	1/15 (6.7%) 2% ¹⁴	RR 5.0 (0.66 to 37.87)	267 more per 1000 (from 23 fewer to 2458 more) 80 more per 1000 (from 7 fewer to 737 more)	⊕⊕⊕⊕ VERY LOW	CRITICAL

¹ All trials included children allergic to house dust mite.

² Only one study properly reported results. One study did not report variability; one reported large baseline imbalance in symptoms, despite randomisation, that overestimated the treatment effect; one had serious errors in labelling the results on the graphs that involve making critical assumptions in order to interpret the results.

³ Results do not exclude a small benefit or no effect.

⁴ One additional study (Tari 1990) including 58 patients (SLIT= 30, placebo = 28) reported results in a way that their interpretation involves many assumptions. It reported the results on a graph with variability labelled as standard deviation (SD). However, SD of this little magnitude is very implausible (compared to variability in other similar studies) and there were errors in labelling the graphs. Assuming the measure of variability was really a SD (very implausible, showing an effect size an order of magnitude larger than any other study) the pooled estimate across all 4 studies would be SMD: -0.43 (95% CI: -1.50 to 0.63). Assuming an error in labelling and the reported measure of variability was actually a standard error (SE) the pooled estimate would be SMD: -0.12 (95% CI: -0.42 to 0.19) and the results would be consistent across all 4 studies.

⁵ One small study that did not report concealment of allocation or intent-to-treat analysis. reporting of outcomes was ambiguous.

⁶ One small study. Results do not exclude a plausible benefit or no effect.

⁷ The only study that reported ocular symptoms had important flaws in reporting that require critical assumptions in order to interpret its results. The difference between the groups was 0.74 point on a 22-point scale, which shows a small difference likely not important to patients (assuming a difference of 1.5 on a 22-point scale would be a minimal important difference). Point estimate favoured SLIT. The precision of this estimate is uncertain, but irrespective of the assumptions it was not statistically significant.

⁸ Only two of four studies reported measuring serious adverse effects.

⁹ There were no serious adverse effects in two studies that reported measuring them.

¹⁰ Only one study reported measuring this outcome.

¹¹ One very small study, only one event, but results do not exclude an important harm.

¹² Assumed risk based on the event rate among children receiving placebo in studies of seasonal allergens.

¹³ One small study. Very few events, but results do not exclude important harm.

¹⁴ A low (2%) assumed baseline risk was estimated based on 2 most recent studies of SLIT in children allergic to seasonal allergens.

Question 36 [profile 1]

Date: 2009-02-24

Question: Should local nasal immunotherapy (LNIT) vs placebo or usual care be used in adults with allergic rhinitis?

Bibliography: 1. Andri L., Senna G., Andri G., Dama A., Givanni S., Betteli C., Dimitri G., Falagiani P., Mezzelani P. Local nasal immunotherapy for birch allergic rhinitis with extract in powder form. Clin Exp Allergy, 1995;25:1092-1099. 2. Andri L., Senna G., Betteli C., Givanni S., Andri G., Dimitri G., Falagiani P., Mezzelani P. Local nasal immunotherapy with extract in powder form is effective and safe in grass pollen rhinitis: a double-blind study. The Journal of allergy and clinical immunology, 1996;97:34-41. 3. Andri L., Senna G., Betteli C., Givanni S., Andri G., Falagiani P. Local nasal immunotherapy for Dermatophagoides-induced rhinitis: efficacy of a powder extract. The Journal of allergy and clinical immunology, 1993;91:987-996. 4. Andri L., Senna G.E., Betteli C., Givanni S., Andri G., Falagiani P., Lugo G. Local nasal immunotherapy in allergic rhinitis to Parietaria. A double-blind controlled study. Allergy, 1992;47:318-323. 5. Ariano R., Panzani R.C., Chiapella M., Augeri G., Falagiani P. Local intranasal immunotherapy with allergen in powder in atopic patients sensitive to Parietaria officinalis pollen. J Investig Allergol Clin Immunol, 1995;5:126-132. 6. Ascione E., De Lucia A., Imperiali M., Varicchio A., Motta G. Nasal application of immunotherapy. Chem Immunol Allergy, 2003;82:89-98. 7. Bertoni M., Cosmi F., Bianchi I., Di Berardino L. Clinical efficacy and tolerability of a steady dosage schedule of local nasal immunotherapy. Results of preseasonal treatment in grass pollen rhinitis. Ann Allergy Asthma Immunol, 1999;82:47-51. 8. Ciria A.M., Sforza N., Roffi G.P., Alessandrini A., Stanizzi R., Dorigo N., Sala E., Della Torre F. Preseasonal intranasal immunotherapy in birch-alder allergic rhinitis. A double-blind study. Allergy, 1996;51:299-305. 9. D'Amato G., Lobefalo G., Liccardi G., Cazzola M. A double-blind, placebo-controlled trial of local nasal immunotherapy in allergic rhinitis to Parietaria pollen. Clin Exp Allergy, 1995;25:141-148. 10. Fanales-Belasio E., Ciofalo A., Zambetti G., Anotegui I.J., Scala E., Paganelli R., Filiaci F. Intranasal immunotherapy with Dermatophagoides extract: in vivo and in vitro results of a double-blind placebo-controlled trial. Rhinology, 1995;33:126-131. 11. Gaglani B., Borish L., Bartelson B.L., Buchmeier A., Keller L., Nelson H.S. Nasal immunotherapy in weed-induced allergic rhinitis. Ann Allergy Asthma Immunol, 1997;79:259-265. 12. Johansson S.G., Deuschl H., Zetterstrom O. Use of glutaraldehyde-modified timothy grass pollen extract in nasal hyposensitisation treatment of hay fever. Int Arch Allergy Appl Immunol, 1979;60:447-460. 13. Motta G., Passali D., De Vincentiis I., Ottaviani A., Maurizi M., Sartoris A., Pallestrini E., Motta S., Salzano F.A. A multicenter trial of specific local nasal immunotherapy. Laryngoscope, 2000;110:132-139. 14. Nickelsen J.A., Goldstein S., Mueller U., Wypych J., Reisman R.E., Arbesman C.E. Local intranasal immunotherapy for ragweed allergic rhinitis. I. Clinical response. The Journal of allergy and clinical immunology, 1981;68:33-40. 15. Passalacqua G., Albano M., Ruffoni S., Pronzato C., Riccio A.M., Di Berardino L., Scordamaglia A., Canonica G.W. Nasal immunotherapy to Parietaria: evidence of reduction of local allergic inflammation. American journal of respiratory and critical care medicine, 1995;152:461-466. 16. Schumacher M.J., Pain M.C. Intranasal immunotherapy and polymerized grass pollen allergens. Allergy, 1982;37:241-248. 17. Taylor G., Shivalkar P.R. Local nasal desensitization in allergic rhinitis. Clin Allergy, 1972;2:125-136.

Quality assessment							Summary of findings				Importance	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients		Effect			Quality
							local nasal immunotherapy (LNIT)	placebo or usual care	Relative (95% CI)	Absolute		
Nasal symptoms (seasonal rhinitis) (follow-up median 4 months¹; Better indicated by lower values)												
7	randomised trials	no serious limitations ²	no serious inconsistency ³	no serious indirectness	serious ⁴	none	72	72	-	SMD 1.33 lower (0.38 to 2.28 lower) ⁵	⊕⊕⊕○ MODERATE	CRITICAL
Nasal symptoms (perennial rhinitis due to house dust mite) (follow-up 3 and 12 months; Better indicated by lower values)												
2	randomised trials	no serious limitations ²	no serious inconsistency ⁶	no serious indirectness	very serious ⁷	none	21	20	-	SMD 0.95 lower (2.98 lower to 1.08 higher)	⊕⊕○○ LOW	CRITICAL
Patient rating as improved (seasonal rhinitis) (follow-up 4 months¹)												
7	randomised trials	no serious limitations ²	no serious inconsistency	no serious indirectness	serious ⁸	none	88/114 (77.2%)	43/104 (41.3%)	RR 1.79 (1.21 to 2.65)	327 more per 1000 (from 87 more to 682 more)	⊕⊕⊕○ MODERATE	CRITICAL
Patient rating as improved (perennial rhinitis due to house dust mite) (follow-up 8 to 12 months)												
3	randomised trials	no serious limitations ²	serious ⁹	no serious indirectness	serious ¹⁰	none	61/68 (89.7%)	14/61 (23%)	RR 3.73 (0.78 to 17.8)	627 more per 1000 (from 50 fewer to 3856 more)	⊕⊕○○ LOW	CRITICAL
Ocular symptoms (seasonal rhinitis) (follow-up median 3.5 months¹¹; Better indicated by lower values)												
5	randomised trials	no serious limitations ²	no serious inconsistency ¹²	no serious indirectness	serious ¹³	none	57	54	-	SMD 0.64 lower (1.31 lower to 0.02 higher)	⊕⊕⊕○ MODERATE	IMPORTANT
Quality of life - not measured												
0	-	-	-	-	-	none	0	0	-	-		CRITICAL

Medication use (seasonal rhinitis) (follow-up median 3 months; Better indicated by lower values)												
4	randomised trials	no serious limitations ²	no serious inconsistency	no serious indirectness	serious ¹⁴	none	43	41	-	SMD 0.72 lower (0.27 to 1.16 lower)	⊕⊕⊕O MODERATE	IMPORTANT
Serious adverse effects (follow-up median 4 months ¹)												
9	randomised trials	no serious limitations ¹⁵	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/143 (0%)	0/137 (0%)	not pooled ¹⁶	not pooled ¹⁶	⊕⊕⊕⊕ HIGH	IMPORTANT
Withdrawal due to adverse effect (follow-up median 5 months)												
12	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious ¹⁷	none	5/193 (2.6%)	3/179 (1.7%)	RR 1.23 (0.38 to 4.00)	4 more per 1000 (from 10 fewer to 50 more)	⊕⊕⊕O MODERATE	CRITICAL
Local adverse effects (follow-up median 5 months)												
6	randomised trials	serious ¹⁸	no serious inconsistency	no serious indirectness	serious ¹⁹	none	28/64 (43.8%)	6/67 (9%)	RR 3.29 (1.45 to 7.47)	205 more per 1000 (from 40 more to 579 more)	⊕⊕OO LOW	CRITICAL

¹ Range: 1.5 to 8 months.

² No study reported allocation concealment or following intention-to-treat principle, however, most studies were done before year 2000 when reporting of methods was less rigorous.

³ There was serious inconsistency in the results, but it could be explained by very large effect of one study that reported its results on a graph and end-of-study values clearly overestimated the treatment effect. Another study reported its results as a composite of nasal and ocular symptoms. If these two studies were excluded from analysis the results did not change substantially (SMD: -1.21, 95% CI: -0.78 to -1.64).

⁴ Only 144 patients.

⁵ However, studies reported that symptoms were higher in LNIT group during the treatment phase.

⁶ We did not downgrade for inconsistency since there were only two studies that differed by length of follow-up and we already downgraded for imprecision.

⁷ Only 41 patients and results do not exclude a large benefit or no effect.

⁸ Only 218 patients; results do not exclude a very small effect and improvement was observed in 40% of patients receiving placebo.

⁹ One study showed no difference and two studies showed large improvement.

¹⁰ Results do not exclude a very large benefit or no difference.

¹¹ Range: 1.5 to 5 months.

¹² There was serious inconsistency in the results, but it could be explained by very large effect of one study that reported its results on a graph and end-of-study values overestimated the treatment effect. If this study was excluded from analysis the results would be SMD: -0.37 (95% CI: -0.85 to 0.11).

¹³ Only 111 patients and results do not exclude a large effect or no difference.

¹⁴ Only 84 patients.

¹⁵ Only 50% of studies reported measuring this outcome, but we assumed that if serious adverse effects occurred they would be reported.

¹⁶ There were no serious adverse effects in these studies.

¹⁷ Very few events, but results do not exclude a 5% absolute increase in risk.

¹⁸ Only 35% of studies reported measuring this outcome.

¹⁹ Only 34 events.

Question 36 [profile 2]

Date: 2009-02-24

Question: Should local nasal immunotherapy (LNIT) vs placebo (or usual treatment) be used in children with allergic rhinitis?

Bibliography: Röder E, Berger MY, de Groot H, Gert van Wijk R. Immunotherapy in children and adolescents with allergic rhinoconjunctivitis: a systematic review. *Pediatr Allergy Immunol* 2008;19(3):197-207.

Quality assessment							Summary of findings				Quality	Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients		Effect			
							local nasal immunotherapy (LNIT)	placebo (or usual treatment)	Relative (95% CI)	Absolute		
Nasal symptoms (follow-up 3 to 18 months; Better indicated by lower values)												
4	randomised trials	very serious ¹	no serious inconsistency ²	no serious indirectness	serious ³	none	82	71	-	not pooled ⁴	⊕○○○ VERY LOW	CRITICAL
Ocular symptoms (Better indicated by lower values)												
3	randomised trials	very serious ⁵	serious ⁶	no serious indirectness	serious ³	none	0	0	-	not pooled	⊕○○○ VERY LOW	IMPORTANT
Quality of life - not measured												
0	-	-	-	-	-	none	0/0 (0%)	0/0 (0%)	-	-		CRITICAL
Adverse effects (Better indicated by lower values)												
4	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	serious ³	none	82 ⁷	71 ⁷	-	not pooled	⊕○○○ VERY LOW	CRITICAL

¹ Allocation was not concealed and ITT analysis not mentioned in any study. Baseline imbalance in prognostic factors was noted in 3 of 4 studies. Primary outcome was not stated in 3/4 studies. Outcomes were poorly reported.

² We did not downgrade for inconsistency, because we already downgraded for limitations in design and for imprecision and no meta-analysis was possible (3/4 studies did not report variability in results). However, all studies found "positive effect on symptoms".

³ We downgraded for imprecision, because of few participants (154) and no information on variability in results in 3/4 studies.

⁴ No meta-analysis was possible (3/4 studies did not report variability in results). However, all studies found "positive effect on symptoms". One study that reported variability in results did not clearly specify the measurement scale so it was possible to calculate effect size only (ES: -3.10, 95% CI: -1.90 to -4.30; n=26). Another study reported that patients rated their symptoms as "benefit from treatment" and those receiving LNIT were 3 times more likely to benefit (RB: 3.00, 95% CI: 1.33 to 6.75).

⁵ Allocation was not concealed and ITT analysis not mentioned in any study. Baseline imbalance in prognostic factors was noted in 2 of 3 studies. Primary outcome was not stated in any study. Outcomes were poorly reported.

⁶ We downgraded for inconsistency, because one study showed a decrease in symptoms, one did not, and the results of the third were discordant between two groups that received different allergens.

⁷ Adverse effects were reported inconsistently and qualitatively. The definition of an adverse event was often unclear (e.g. one trial stated that no side-effects occurred, but some patients suffered from nasal complaints after the LNIT application). Two studies reported that there were no serious adverse effects.

Question 42 [profile 1]

Date: 2007-08-27

Question: Should oral H1-antihistamines be used for symptoms of asthma in adults with concomitant allergic rhinitis?

Bibliography: 1. Aaronson D.W. Evaluation of cetirizine in patients with allergic rhinitis and perennial asthma. *Ann Allergy Asthma Immunol*, 1996;76:440-446. 2. Baena-Cagnani C.E., Berger W.E., DuBuske L.M., Gurne S.E., Stryszak P., Lorber R., Danzig M. Comparative effects of desloratadine versus montelukast on asthma symptoms and use of beta 2-agonists in patients with seasonal allergic rhinitis and asthma. *Int Arch Allergy Immunol*, 2003;130:307-313. 3. Grant J.A., Nicodemus C.F., Findlay S.R., Glovsky M.M., Grossman J., Kaiser H., Meltzer E.O., Mitchell D.Q., Pearlman D., Selner J., et al. Cetirizine in patients with seasonal rhinitis and concomitant asthma: prospective, randomized, placebo-controlled trial. *The Journal of allergy and clinical immunology*, 1995;95:923-932. 4. Pasquali M., Baiardini I., Rogkakou A., Riccio A.M., Gamalero C., Descalzi D., Folli C., Passalacqua G., Canonica G.W. Levocetirizine in persistent allergic rhinitis and asthma: effects on symptoms, quality of life and inflammatory parameters. *Clin Exp Allergy*, 2006;36:1161-1167.

Quality assessment							Summary of findings				Importance	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients		Effect			Quality
							oral H1-antihistamines	control	Relative (95% CI)	Absolute		
Asthma symptoms (follow-up 4 weeks¹; measured with: Sum of 3 individual symptoms rated on 4-point scale each¹; range of scores: 0-9; Better indicated by less)												
4	randomised trial	serious ²	serious ³	no serious indirectness ⁴	serious ⁵	reporting bias ⁶	311 ¹	302 ¹	-	WMD -0.32 (-0.04 to -0.6) ^{1,4}	⊕○○○ VERY LOW	CRITICAL
Quality of life (follow-up 8 weeks; measured with: Rhinasthma lower airways scale⁷; range of scores: 0-100; Better indicated by less)												
1	randomised trial	no serious limitations	no serious inconsistency	serious ⁸	very serious ^{9,10}	none ¹¹	20 ¹²	20 ¹²	-	WMD -5.7 (0 to 0) ⁹	⊕○○○ VERY LOW	CRITICAL
Adverse effects												
3	randomised trial	serious ²	no serious inconsistency	no serious indirectness	no serious imprecision ¹³	reporting bias ¹⁴	0/0	0/0	not pooled	not pooled	⊕⊕○○ LOW	IMPORTANT

¹ From one trial that was high quality and provided numerical data.

² No study reported concealment of allocation; only one reported intention-to-treat analysis; and percentage of patients that dropped out from the studies was 12% to 36%. Randomisation and blinding were adequate in 2 studies and unclear in the other two.

³ One trial showed a small, borderline statistically significant effect, the other suggested important difference, and in the other it was not possible to interpret the magnitude of effect.

⁴ One study did not report a separate score for asthma symptoms, just a combined asthma and rhinitis score. This was only presented on a graph, but a visual inspection of the graphs for combined score and rhinitis score suggests that all differences were due to the difference in rhinitis score.

⁵ We did not downgrade for imprecision, since we already downgraded for inconsistency.

⁶ Reporting of this outcome was very poor, in most cases not possible to interpret. One large and methodologically sound trial showed borderline statistically significant small effect.

⁷ Authors also measured quality of life using SF-36 questionnaire, but did not report data, except the statement that the results were statistically significant for some of the domains at different time-points.

⁸ Only 40% of patients had current asthma. 60% had no current symptoms and only past history of asthma.

⁹ Measure of variation for a change score could not be extracted from data.

¹⁰ One very small study.

¹¹ We did not downgrade for reporting bias since we already downgraded for very serious imprecision.

¹² 5 patients in each group dropped out.

¹³ We did not downgrade for imprecision, since we already downgraded for reporting bias.

¹⁴ Adverse events were reported, but inconsistently and it was not possible to calculate any overall effect without making several assumptions. Overall number of all adverse events in both groups seemed to be the same; one study reported 17 vs 4 events of fatigue or somnolence among cetirizine 10 mg and placebo; other reported adverse events occurred equally frequently.

Question 42 [profile 2]

Date: 2007-08-27

Question: Should ketotifen be used for long-term control of asthma and wheeze in children?

Bibliography: 1. Bassler D., Mitra A., Ducharme F.M., Forster J., Schwarzer G. Ketotifen alone or as additional medication for long-term control of asthma and wheeze in children. Cochrane database of systematic reviews (Online), 2004:CD001384.

Quality assessment							Summary of findings					Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients		Effect		Quality	
							ketotifen	control	Relative (95% CI)	Absolute		
Asthma symptoms (follow-up 10 to 12 weeks; Better indicated by less)												
4	randomised trial	no serious limitations ¹	no serious inconsistency	serious ²	very serious ^{3,4}	none ^{5,6}	72	76	-	SMD -0.49 (-0.16 to -0.82)	⊕⊕⊕⊕ VERY LOW	CRITICAL
Asthma exacerbations (follow-up 12 weeks)												
2	randomised trial	no serious limitations ¹	no serious inconsistency	serious ^{2,7}	serious ⁴	none ⁵	10/105	32/104	RR 0.31 (0.19 to 0.59)	213 fewer per 1000 (from 126 fewer to 249 fewer)	⊕⊕⊕⊕ LOW	CRITICAL
Use of oral glucocorticosteroid (follow-up 10 to 20 weeks)												
4	randomised trial	no serious limitations ¹	no serious inconsistency	serious ²	serious ⁴	none ^{5,6}	21/156	73/150	RR 0.28 (0.13 to 0.58)	351 fewer per 1000 (from 205 fewer to 424 fewer)	⊕⊕⊕⊕ LOW	CRITICAL
Efficacy assessed either by participants or parents (follow-up 12 to 26 weeks)												
7	randomised trial	no serious limitations ¹	no serious inconsistency	serious ²	serious ⁸	none ⁶	101/301	143/298	RR 0.71 (0.52 to 0.96)	139 fewer per 1000 (from 19 fewer to 230 fewer)	⊕⊕⊕⊕ LOW	CRITICAL
Efficacy evaluated by physicians (follow-up 10 to 26 weeks)												
10	randomised trial	serious ⁹	serious ¹⁰	very serious ^{2,11}	no serious imprecision	reporting bias ¹²	113/310	188/315	RR 0.6 (0.46 to 0.79)	239 fewer per 1000 (from 125 fewer to 322 fewer)	⊕⊕⊕⊕ VERY LOW	IMPORTANT
Reduction in the use of bronchodilators (follow-up 12 to 16 weeks)												
12	randomised trial	no serious limitations ¹	no serious inconsistency	serious ²	serious ⁴	none ⁶	56/76	21/73	RR 2.39 (1.64 to 3.48)	400 more per 1000 (from 184 more to 714 more)	⊕⊕⊕⊕ LOW	IMPORTANT
Sedation (follow-up 10 to 26 weeks)												
7	randomised trial	no serious limitations ¹	no serious inconsistency	no serious indirectness	very serious ^{4,13}	none ⁶	45/218	26/221	RR 1.69 (1.11 to 2.59) ¹⁴	81 more per 1000 (from 13 more to 188 more)	⊕⊕⊕⊕ LOW	CRITICAL
Weight gain (follow-up 10 to 26 weeks)												
5	randomised trial	no serious limitations ¹	no serious inconsistency	no serious indirectness	very serious ^{13,15}	none ^{6,16}	38/142	24/141	RR 1.42 (1.02 to 1.99)	71 more per 1000 (from 3 more to 168 more)	⊕⊕⊕⊕ LOW	IMPORTANT
Withdrawal from study due to side effects (follow-up 10 to 16 weeks)												
3	randomised trial	no serious limitations ¹	no serious inconsistency	serious ²	very serious ^{4,17}	none ^{6,16}	5/129	3/109	RR 1.22 (0.3 to 4.92)	6 more per 1000 (from 20 fewer to 110 more)	⊕⊕⊕⊕ VERY LOW	CRITICAL

¹ Most trials have been published before 1990, when reporting of methods were not as stringent as they are now, which may lead to inadequate reporting of good methods rather than bad methods per se.

² Inhaled corticosteroids were allowed as additional intervention in eight trials. There was not enough information in the studies to assess the effect of ketotifen as an add-on therapy to inhaled corticosteroids that are the mainstay of therapy of asthma today.

³ Results include small or large effect.

⁴ Very small trials with few events.

⁵ Only four trials reported that outcome, but we did not downgrade since we already downgraded for very serious imprecision.

⁶ Minority of all 25 trials reported each outcome that might suggest reporting bias. However, we did not automatically downgrade for reporting bias because most trials were done before 1990 when less emphasis was placed on patient-important outcomes and more on measurement of physiological parameters.

⁷ There is less uncertainty about directness since both trials included 70% children with nasal symptoms. Children had also eczema (31%) and a family history of asthma (55%) that might suggest a high risk population.

⁸ Results do not exclude negligible or large effect.

⁹ Seven of 10 studies had unclear blinding and these trials showed larger benefit. In three studies with adequate blinding the RR was 0.75 (95% CI: 0.52-1.09)

¹⁰ There was heterogeneity between trials which could not be explained by differences between age groups and appropriateness of blinding.

¹¹ There is serious uncertainty to what extent efficacy assessed by a physician reflects a patient important benefit.

¹² Funnel plot suggested bias.

¹³ Results do not exclude negligible or large increase in the risk of sedation.

¹⁴ No information was available on the time lag between onset of treatment with ketotifen and sedation to confirm resolution of sedation with use.

¹⁵ The magnitude of weight gain could not be determined because of reporting issues.

¹⁶ We did not downgrade since we already downgraded for very serious imprecision.

¹⁷ Results do not exclude large benefit or large harm.

Question 43

Date: 2007-08-28

Question: Should combination of oral H1-antihistamine and decongestant vs placebo be used for treatment of asthma in patients with concomitant allergic rhinitis?

Bibliography: 1. Corren J., Harris A.G., Aaronson D., Beaucher W., Berkowitz R., Bronsky E., Chen R., Chervinsky P., Cohen R., Foure J., Grossman J., Meltzer E., Pedinoff A., Stricker W., Wanderer A. Efficacy and safety of loratadine plus pseudoephedrine in patients with seasonal allergic rhinitis and mild asthma. The Journal of allergy and clinical immunology, 1997;100:781-788. 2. Nathan R.A., Finn A.F., Jr., LaForce C., Ratner P., Chapman D., de Guia E.C., Hewlett D., Kramer B. Comparison of cetirizine-pseudoephedrine and placebo in patients with seasonal allergic rhinitis and concomitant mild-to-moderate asthma: randomized, double-blind study. Ann Allergy Asthma Immunol, 2006;97:389-396.

Quality assessment							Summary of findings					Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients		Effect		Quality	
							combination of oral H1-antihistamine and decongestant	placebo	Relative (95% CI)	Absolute		
Asthma symptoms (follow-up 4 weeks; measured with: 4-point scale (0 - none; 3 - severe); range of scores: 0-12; Better indicated by less)												
2	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	serious ¹	none ²	225	226	-	not pooled ³	⊕⊕⊕○ MODERATE	CRITICAL
Asthma exacerbation (follow-up 4 weeks)												
1	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	very serious ⁴	none	20/139	14/135	RR 1.39 (0.74 to 2.61)	41 more per 1000 (from 27 fewer to 167 more)	⊕⊕○○ LOW	CRITICAL
Quality of life (follow-up 4 to 6 weeks; Better indicated by less)												
2	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	serious ⁵	reporting bias ⁶	225	226	-	not pooled ⁶	⊕⊕○○ LOW	CRITICAL
Headache (follow-up 4 to 6 weeks)												
2	randomised trial	no serious limitations	no serious inconsistency ⁷	no serious indirectness	serious ⁸	none	33/236	34/231	RR 0.97 (0.65 to 1.44)	4 fewer per 1000 (from 51 fewer to 65 more)	⊕⊕⊕○ MODERATE	IMPORTANT
Insomnia (follow-up 4 to 6 weeks)												
2	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	very serious ⁹	none	14/236	1/231	RR 9.50 (1.79 to 50.41)	34 more per 1000 (from 3 more to 198 more)	⊕⊕○○ LOW	CRITICAL

¹ One study reported symptom scores without measure of variation and the other one presented results on a graph without any numerical results.

² We did not downgrade for reporting bias since we already downgraded for imprecision.

³ In one study mean difference in change from baseline was 0.6 point for daytime symptoms and 0.4 point for nighttime symptoms; no measure of variation was provided, but authors stated the change was statistically significant for daytime symptoms. In the other study change from baseline was 0.86 point in the morning and 0.79 in the evening, and both were reported as statistically significant. All in favour of combination treatment compared to placebo.

⁴ Results do not exclude important benefit or harm. One trial with few events.

⁵ In both studies quality of life improved by 0.5-0.55 point in placebo group and by 0.77-0.9 point in the combined treatment group. No measure of variation was provided. These results suggest that both groups reached minimal important improvement in quality of life with small difference between the groups.

⁶ In one study quality of life improved by 0.5 point in placebo group and by 0.9 point in the combined treatment group. No measure of variation was provided. These results suggest that both groups reached minimal important improvement in quality of life with small difference between the groups. In the second study three different quality of life questionnaires were used, and not all data were reported. Authors did not provide information on what scales were used in these questionnaires and it was not possible to determine the results for which of the questionnaires were actually reported.

⁷ We did not downgrade for inconsistency, since we already downgraded for imprecision.

⁸ Few events. Very large difference in risk (2% to 32%)

⁹ Very few events.

Question 45 [profile 1]

Date: 2007-08-26

Question: Should licensed dose of anti-leukotrienes plus inhaled glucocorticosteroids vs same dose of inhaled glucocorticosteroids be used for chronic asthma?

Bibliography: F Ducharme, Z Schwartz, R Kakuma. Addition of anti-leukotriene agents to inhaled corticosteroids for chronic asthma. Cochrane Database of Systematic Reviews 2004, Issue 1.

Quality assessment							Summary of findings				Quality	Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients		Effect			
							licensed dose of anti-leukotrienes plus inhaled glucocorticosteroids	same dose of inhaled glucocorticosteroids	Relative (95% CI)	Absolute		
Asthma symptoms (follow-up 4 to 16 weeks; measured with: Daytime asthma symptom score; range of scores: 0-6; Better indicated by less)												
2	randomised trial	no serious limitations	no serious inconsistency	serious ¹	serious ²	reporting bias ³	510	508	-	MD -0.10 (-0.24 to 0.03)	⊕○○○ VERY LOW	CRITICAL
Night-time awakenings (measured with: episodes/week; Better indicated by less)												
1	randomised trial	serious ⁴	no serious inconsistency	serious ¹	serious ⁵	none	193	200	-	MD -0.59 (-1.68 to 0.5)	⊕○○○ VERY LOW	CRITICAL
Exacerbations requiring systemic steroids (follow-up 4 to 16 weeks)												
4	randomised trial	no serious limitations	no serious inconsistency	serious ⁶	serious ²	reporting bias ³	22/493	35/495	RR 0.64 (0.38 to 1.07)	14 fewer per 1,000	⊕○○○ VERY LOW	CRITICAL
								11%		39 fewer per 1,000		
Quality of life (follow-up 4 to 16 weeks; measured with: Asthma Quality of Life Questionnaire; range of scores: 0-7; Better indicated by more)												
2	randomised trial	no serious limitations	no serious inconsistency	serious ⁶	serious ²	reporting bias ³	465	456	-	MD 0.08 (-0.03 to 0.2)	⊕○○○ VERY LOW	CRITICAL
Overall adverse effects (follow-up 4 to 16 weeks)												
2	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias ³	255/594	246/578	RR 1.01 (0.88 to 1.15)	4 more per 1000 (from 51 fewer to 64 more)	⊕⊕⊕○ MODERATE	IMPORTANT

¹ There was no effect in trials that reported including patients with both allergic rhinitis and asthma. Therefore, there is serious uncertainty if the results obtained in studied populations apply equally to patients who have both asthma and allergic rhinitis.

² The confidence interval crosses no difference and does not rule out worse outcome.

³ Few studies that measured this outcome were pooled.

⁴ Only one of 16 trials reported that outcome.

⁵ results include big benefit and small harm

⁶ This outcome was not reported in trials that reported including patients with both allergic rhinitis and asthma. Therefore, there is serious uncertainty if the results obtained in studied populations apply equally to patients who have both asthma and allergic rhinitis.

Question 45 [profile 2]

Date: 2007-12-02

Question: Should leukotriene receptor antagonists vs inhaled glucocorticosteroids be used for asthma?

Bibliography: Ducharme FM, Di Salvio F. Anti-leukotriene agents compared to inhaled corticosteroids in the management of recurrent and/or chronic asthma in adults and children. Cochrane Database of Systematic Reviews 2004, Issue 1. Art. No.: CD002314. DOI: 10.1002/14651858.CD002314.pub2.

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	leukotriene receptor antagonists	inhaled glucocorticosteroids	Relative (95% CI)	Absolute		
At least one exacerbation requiring systemic steroids (follow-up 6 to 40 weeks)												
18	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	254/2529	128/2436	RR 1.56 (1.36 to 2.00)	30 more per 1000 (from 19 more to 53 more)	⊕⊕⊕⊕ HIGH	CRITICAL
At least one exacerbation requiring hospital admission (follow-up 6 to 40 weeks)												
13	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	serious ¹	none	10/1641	5/1548	RR 1.62 (0.64 to 4.15)	2 more per 1000 (from 1 fewer to 9 more)	⊕⊕⊕○ MODERATE	CRITICAL
Quality of life (change from baseline) (follow-up 8 to 16 weeks; measured with: Asthma Quality of Life Questionnaire; Better indicated by more)												
2	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias ²	575	452	-	MD -0.30 (-0.43 to -0.17)	⊕⊕⊕○ MODERATE	CRITICAL
Daytime symptoms (change from baseline) (follow-up 8 to 16 weeks³; Better indicated by less)												
6	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	1376	1167	-	SMD 0.29 (0.21 to 0.37)	⊕⊕⊕⊕ HIGH	CRITICAL
Night-time awakenings (change from baseline) (follow-up 8 to 16 weeks³; Better indicated by less)												
6	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	1089	906	-	SMD 0.21 (0.13 to 0.30)	⊕⊕⊕⊕ HIGH	CRITICAL
Symptom-free days (change from baseline) (follow-up 8 to 16 weeks³; measured with: percentage; Better indicated by more)												
5	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	652	676	-	MD -11.47 (-15.72 to -7.23)	⊕⊕⊕⊕ HIGH	CRITICAL
Withdrawal due to adverse effects (follow-up 6 to 40 weeks)												
16	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	serious ⁴	none	96/3257	77/3020	RR 1.15 (0.86 to 1.54)	4 more per 1000 (from 3 fewer to 13 more)	⊕⊕⊕○ MODERATE	CRITICAL
Adverse effects (overall) (follow-up 6 to 40 weeks)												
15	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	serious ⁵	none	1284/2942	1120/2706	RR 0.99 (0.93 to 1.04)	4 fewer per 1000 (from 29 fewer to 17 more)	⊕⊕⊕○ MODERATE	IMPORTANT
Rescue-free days (change from baseline) (follow-up 8 to 16 weeks; measured with: percentage; Better indicated by more)												
3	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	545	565	-	MD -13.92 (-18.32 to -9.51)	⊕⊕⊕⊕ HIGH	IMPORTANT
Daily use of beta2-agonists (change from baseline) (follow-up 8 to 16 weeks³; Better indicated by less)												
8	randomised trial	no serious limitations	no serious inconsistency	serious ⁶	no serious imprecision	none	1467	1266	-	SMD 0.28 (0.20 to 0.36)	⊕⊕⊕○ MODERATE	IMPORTANT
Days off work or school (follow-up 8 to 16 weeks; measured with: number of days; Better indicated by less)												

2	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	298	312	-	MD 0.06 (-0.03 to 0.15)	⊕⊕⊕⊕ HIGH	IMPORTANT
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¹ Results include no effect or 1% more patients requiring hospitalization in absolute terms.

² Only two trials reported this outcome

³ We chose a follow-up of 12 ±4 weeks, because it was the longest follow-up with the most studies providing the results. However, results were consistently similar during shorter and longer observation.

⁴ Possible harm or no effect.

⁵ From 3% fewer to 2% more in absolute terms.

⁶ There is serious uncertainty if the number of puffs of reliever medication per day is critical to patients.

Question 47 [profile 1]

Date: 2009-03-25

Question: Should sublingual immunotherapy vs placebo be used in adults with asthma?

Bibliography: 1. Dahl R., Stender A., Rak S. Specific immunotherapy with SQ standardized grass allergen tablets in asthmatics with rhinoconjunctivitis. *Allergy*, 2006;61:185-190. 2. Alvarez-Cuesta E., Berges-Gimeno P., Gonzalez-Mancebo E., Fernandez-Caldas E., Cuesta-Herranz J., Casanovas M. Sublingual immunotherapy with a standardized cat dander extract: evaluation of efficacy in a double blind placebo controlled study. *Allergy*, 2007;62:810-817.

Quality assessment							Summary of findings				Importance	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients		Effect			Quality
							sublingual immunotherapy	placebo	Relative (95% CI)	Absolute		
Asthma symptoms (follow-up 5 and 12 months; Better indicated by lower values)												
2	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ²	none	85	55	-	SMD 0.38 lower (0.04 to 0.73 lower)	⊕⊕⊕⊕ LOW	CRITICAL
Medication use (follow-up 5 months; measured with: daily asthma medication score; range of scores: 0-32; Better indicated by lower values)												
1	randomised trials	serious ³	no serious inconsistency	no serious indirectness	serious ⁴	none	68	39	-	mean 0.05 higher (0.41 lower to 0.51 higher)	⊕⊕⊕⊕ LOW	IMPORTANT
Quality of life - not measured												
0	-	-	-	-	-	none	0/0 (0%)	0/0 (0%)	-	-		CRITICAL
Serious adverse effects												
2	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious ⁵	none	0/85 (0%)	0/55 (0%)	not pooled ⁶	not pooled	⊕⊕⊕⊕ MODERATE	IMPORTANT
Oral pruritus (follow-up 5 months)												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious ⁵	strong association ⁷	32/61 (52.5%)	1/32 (3.1%)	RR 16.79 (2.40 to 117.26)	493 more per 1000 (from 44 more to 3633 more)	⊕⊕⊕⊕ HIGH	CRITICAL

¹ Both studies reported the results of per-protocol analysis only. In one study 18% did not complete treatment and in the other -- 36%.

² Few patients. Results do not exclude large effect or no difference.

³ Study reported the results of per-protocol analysis only and 18% did not complete treatment.

⁴ Few patients.

⁵ Few patients.

⁶ There were no serious adverse effects.

⁷ Lower confidence limit is 2.4.

Question 47 [profile 2]

Date: 2009-03-25

Question: Should sublingual immunotherapy vs placebo be used in children with asthma?

Bibliography: 1. Caffarelli C., Sensi L.G., Marcucci F., Cavagni G. Preseasonal local allergoid immunotherapy to grass pollen in children: a double-blind, placebo-controlled, randomized trial. *Allergy*, 2000;55:1142-1147. 2. Ippoliti F., De Santis W., Volterrani A., Lenti L., Canitano N., Lucarelli S., Frediani T. Immunomodulation during sublingual therapy in allergic children. *Pediatr Allergy Immunol*, 2003;14:216-221. 3. Lue K.H., Lin Y.H., Sun H.L., Lu K.H., Hsieh J.C., Chou M.C. Clinical and immunologic effects of sublingual immunotherapy in asthmatic children sensitized to mites: a double-blind, randomized, placebo-controlled study. *Pediatr Allergy Immunol*, 2006;17:408-415. 4. Niu C.K., Chen W.Y., Huang J.L., Lue K.H., Wang J.Y. Efficacy of sublingual immunotherapy with high-dose mite extracts in asthma: a multi-center, double-blind, randomized, and placebo-controlled study in Taiwan. *Respir Med*, 2006;100:1374-1383. 5. Pajno G.B., Morabito L., Barberio G., Parmiani S. Clinical and immunologic effects of long-term sublingual immunotherapy in asthmatic children sensitized to mites: a double-blind, placebo-controlled study. *Allergy*, 2000;55:842-849. 6. Pajno G.B., Vita D., Parmiani S., Caminiti L., La Grutta S., Barberio G. Impact of sublingual immunotherapy on seasonal asthma and skin reactivity in children allergic to Parietaria pollen treated with inhaled fluticasone propionate. *Clin Exp Allergy*, 2003;33:1641-1647. 7. Pham-Thi N., Scheinmann P., Fadel R., Combebias A., Andre C. Assessment of sublingual immunotherapy efficacy in children with house dust mite-induced allergic asthma optimally controlled by pharmacologic treatment and mite-avoidance measures. *Pediatr Allergy Immunol*, 2007;18:47-57. 8. Stelmach I., Kaczmarek-Wozniak J., Majak P., Olszowiec-Chlebna M., Jerzynska J. Efficacy and safety of high-doses sublingual immunotherapy in ultra-rush scheme in children allergic to grass pollen. *Clin Exp Allergy*, 2008.

Quality assessment							Summary of findings				Quality	Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients		Effect			
							sublingual immunotherapy	placebo	Relative (95% CI)	Absolute		
Asthma symptoms (seasonal allergen) (follow-up 3 to 24 months; Better indicated by lower values)												
3 ¹	randomised trials	no serious limitations ²	no serious inconsistency	no serious indirectness	serious ³	none	59	50	-	SMD 0.53 lower (0.08 to 0.98 lower) ¹	⊕⊕⊕○ MODERATE	CRITICAL
Asthma symptoms (children allergic to house dust mite) (follow-up median 6 months⁴; Better indicated by lower values)												
5 ⁵	randomised trials	no serious limitations ⁶	serious ⁷	no serious indirectness	serious ⁸	none	172	161	-	SMD 1.17 lower (0.05 to 2.28 lower) ⁵	⊕⊕○○ LOW	CRITICAL
Quality of life - not reported⁹												
0	-	-	-	-	-	none	0	0	-	-		CRITICAL
Serious adverse effects (follow-up 3 to 24 months)												
8	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/237 (0%)	0/225 (0%)	not pooled ¹⁰	not pooled	⊕⊕⊕⊕ HIGH	IMPORTANT
Withdrawal due to adverse effects (follow-up 6 to 24 months)												
5	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious ¹¹	none	2/152 (1.3%)	2/145 (1.4%)	RR 0.97 (0.15 to 6.44)	0 fewer per 1000 (from 12 fewer to 75 more)	⊕⊕⊕○ MODERATE	CRITICAL
Local adverse effects (follow-up 24 months; oral burning, pruritus or oedema)												
2	randomised trials	serious ¹²	no serious inconsistency	no serious indirectness	serious ¹³	none	14/37 (37.8%)	3/37 (8.1%)	RR 4.12 (1.43 to 11.89)	253 more per 1000 (from 35 more to 883 more)	⊕⊕○○ LOW	CRITICAL

¹ Four additional studies investigated SLIT in children with allergic rhinitis due to seasonal allergen and measured asthma symptoms. Some of them were also included in systematic reviews of Calamita 2007, Olaguibel 2005 or Penagos 2008. However, these trials included less than 50% children with asthma. One of them could not be used (see text of guideline for details). If we included the results of other three studies the effect would be smaller (for all 6 studies: n = 266; SMD: -0.32, 95% CI: -0.67 to 0.03).

² In one study 30% did not complete treatment.

³ Few patients. Results do not exclude a large effect or no difference.

⁴ Range: 6 to 24 months.

⁵ Three additional studies investigated SLIT in children with allergic rhinitis due to house dust mite and measured asthma symptoms. Two of them was also included in systematic reviews of Calamita 2007, Olaguibel 2005 or Penagos 2008. Two of these trials (Hirsh 1997 and Marcucci 2001) included 74% and 83% children with asthma. If we included the results of these two studies the effect would be smaller (for

all 6 studies: $n = 378$; SMD: -0.93 , 95% CI: -0.08 to -1.79). One additional study that included unreported proportion of children with asthma was included in two systematic reviews. This study poorly reported this outcome and its inclusion would not change the conclusions (see text of guideline for details).

⁶ Four of six studies did not report following intention-to-treat principle.

⁷ There was serious inconsistency in the results that could not be explained neither by study methodology, year of publication or manufacturer of allergen extract.

⁸ Results do not exclude a large effect or no difference.

⁹ One study measured quality of life, but found no difference between the SLIT and placebo groups and did not report any numerical values.

¹⁰ There were no serious adverse effects in these studies.

¹¹ Very few events, but results do not exclude an important increase in risk.

¹² Only 2 of 8 studies reported these obvious adverse effects.

¹³ Few events.

Question 48 [profile 1]

Date: 2007-08-27

Question: Should subcutaneous anti-IgE vs placebo be used for chronic asthma in patients receiving stable dose of inhaled corticosteroids?

Settings: stable steroid phase

Bibliography: S Walker, M Monteil, K Phelan, TJ Lasserson, EH Walters. Anti-IgE for chronic asthma in adults and children. Cochrane Database of Systematic Reviews 2006, Issue 2.

Quality assessment							Summary of findings				Quality	Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients		Effect			
							subcutaneous anti-IgE	placebo	Relative (95% CI)	Absolute		
Asthma symptoms (follow-up 16 to 28 weeks; measured with: Asthma score at end of treatment; range of scores: 0-4; Better indicated by less)												
3	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none ¹	668	649	-	MD -0.46 (-0.63 to -0.29)	⊕⊕⊕⊕ HIGH	CRITICAL
Asthma exacerbation (follow-up 12 to 28 weeks)												
6	randomised trial	no serious limitations	no serious inconsistency ²	no serious indirectness	no serious imprecision	none ¹	181/1152	252/999	RR 0.64 (0.47 to 0.88) ³	9 fewer per 100 (from 3 fewer to 13 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
Asthma exacerbations per patient (follow-up 16 to 28 weeks; measured with: exacerbations per patient; Better indicated by less)												
4	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none ¹	893	758	-	MD -0.19 (-0.29 to -0.09)	⊕⊕⊕⊕ HIGH	CRITICAL
Change in Quality of Life (follow-up 16 to 28 weeks; measured with: Asthma Quality of Life Questionnaire; range of scores: 0-6; Better indicated by more)												
5	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness ⁴	no serious imprecision	none ¹	1081	1050	-	MD 0.32 (0.22 to 0.43) ⁵	⊕⊕⊕⊕ HIGH	CRITICAL
Global evaluation (rated good or excellent) (follow-up 16 to 28 weeks)												
2	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none ¹	240/418	141/406	RR 1.95 (1.63 to 2.29)	0 more per 1,000	⊕⊕⊕⊕ HIGH	IMPORTANT

¹ Authors of the review did not assess publication bias,

² One small trial in patients with more severe asthma receiving oral corticosteroids showed OR: 1.65 (95% CI: 0.66 to 4.13)

³ Based on the results assuming random effects.

⁴ The end of trial data on quality of life suggested an important placebo effect. The improvements in global treatment efficacy and overall quality of life noted in control subjects suggest that the basic trial design which included close medical monitoring, might have contributed to a large placebo effect.

⁵ Effect size did not reach clinical relevance of 0.5.

Question 48 [profile 2]

Date: 2007-08-27

Question: Should subcutaneous anti-IgE vs placebo be used for chronic asthma in patients receiving tapered doses of inhaled corticosteroids?

Settings: steroid reduction phase

Bibliography: S Walker, M Monteil, K Phelan, TJ Lasserson, EH Walters. Anti-IgE for chronic asthma in adults and children. Cochrane Database of Systematic Reviews 2006, Issue 2.

Quality assessment							Summary of findings				Quality	Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients subcutaneous anti-IgE	placebo	Effect Relative (95% CI)	Absolute		
Asthma symptoms - not measured¹												
0	-	-	-	-	-	none	0/0	0/0	-	-		CRITICAL
Asthma exacerbation (follow-up 12 to 16 weeks)												
5	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none ²	179/934	250/792	RR 0.54 (0.44 to 0.67)	15 fewer per 100 (from 10 fewer to 18 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
Asthma exacerbations per patient (follow-up 16 to 28 weeks; measured with: exacerbations per patient; Better indicated by less)												
5	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	934	795	-	MD -0.27 (-0.37 to -0.16)	⊕⊕⊕⊕ HIGH	CRITICAL
Change in Quality of life (follow-up 16 weeks; measured with: Asthma Quality of Life Questionnaire; range of scores: 0-6; Better indicated by less)												
1	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none ²	126	120	-	MD 0.42 (0.17 to 0.67) ³	⊕⊕⊕⊕ HIGH	CRITICAL
Complete inhaled corticosteroid withdrawal (follow-up 12 to 16 weeks)												
4	randomised trial	no serious limitations	no serious inconsistency	serious	no serious imprecision	none ²	370/884	159/750	RR 2.04 (1.74 to 2.38)	220 more per 1000 (from 157 more to 293 more)	⊕⊕⊕○ MODERATE	IMPORTANT
More than 50% reduction in inhaled corticosteroid usage (follow-up 12 to 16 weeks)												
4	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none ²	678/884	420/750	RR 1.79 (1.59 to 1.99)	44 more per 100 (from 33 more to 55 more)	⊕⊕⊕⊕ HIGH	IMPORTANT
Change in steroid consumption (follow-up 12 to 16 weeks; measured with: micro gram of budesonide equivalent; Better indicated by more)												
3	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	618	570	-	MD -118.76 (-83.14 to -154.38)	⊕⊕⊕⊕ HIGH	IMPORTANT
Oral steroid withdrawal (follow-up 16 weeks)												
1	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	very serious ⁴	none	21/50	19/45	RR 0.99 (0.50 to 1.74)	4 fewer per 1000 (from 211 fewer to 312 more)	⊕⊕○○ LOW	CRITICAL

¹ Outcome was not measured in the included studies

² Reporting bias not assessed.

³ Effect size did not reach clinical relevance.

⁴ One small trial

Question 48 [profile 3]

Date: 2007-08-31

Question: What are the adverse effects of subcutaneous anti-IgE used for chronic asthma in adults and children?

Settings: all phases

Bibliography: S Walker, M Monteil, K Phelan, TJ Lasserson, EH Walters. Anti-IgE for chronic asthma in adults and children. Cochrane Database of Systematic Reviews 2006, Issue 2.

Quality assessment							Summary of findings				Importance	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients		Effect			Quality
							subcutaneous anti-IgE	control	Relative (95% CI)	Absolute		
Withdrawal due to adverse event (follow-up 28 to 30 weeks)												
4	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	serious ¹	none	7/893	10/759	RR 0.53 (0.21 to 1.31)	6 fewer per 1000 (from 10 fewer to 4 more)	⊕⊕⊕○ MODERATE	CRITICAL
Injection site reaction (follow-up 24 to 32 weeks)												
4	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	87/854	45/825	RR 1.91 (1.35 to 2.67)	50 more per 1000 (from 19 more to 92 more)	⊕⊕⊕⊕ HIGH	IMPORTANT
Urticaria (follow-up 24 to 32 weeks)												
4	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	serious ¹	none	10/834	9/697	RR 0.93 (0.38 to 2.27)	1 fewer per 1000 (from 8 fewer to 17 more)	⊕⊕⊕○ MODERATE	IMPORTANT
Malignancy												
14 ²	randomised trial	no serious limitations	no serious inconsistency ³	no serious indirectness	serious ⁴	none	20/4127	5/2236	RR 1.9 (0.7 to 6.5)	2 more per 1000 (from 1 fewer to 11 more)	⊕⊕⊕○ MODERATE	CRITICAL
Malignancy (excluding non-melanoma skin cancer)												
14 ²	randomised trial	no serious limitations	no serious inconsistency ³	no serious indirectness	serious ⁴	none	16/4127	2/2236	RR 3.8 (0.9 to 34.3)	3 more per 1000 (from 0 fewer to 33 more)	⊕⊕⊕○ MODERATE	CRITICAL

¹ Results do not exclude important benefit or important harm.

² All completed trials reported by the manufacturer to Food and Drug Administration. Department of Health & Human Services Public Health Service. Food and Drug Administration. Omalizumab (recombinant humanized monoclonal antibody to IgE) for treatment of allergic asthma (Briefing document on safety BLA STN 103976/0). Rockville, MD, 2003

³ We did not downgrade for inconsistency, since we already downgraded for imprecision.

⁴ Results do not exclude no effect or a serious harm.