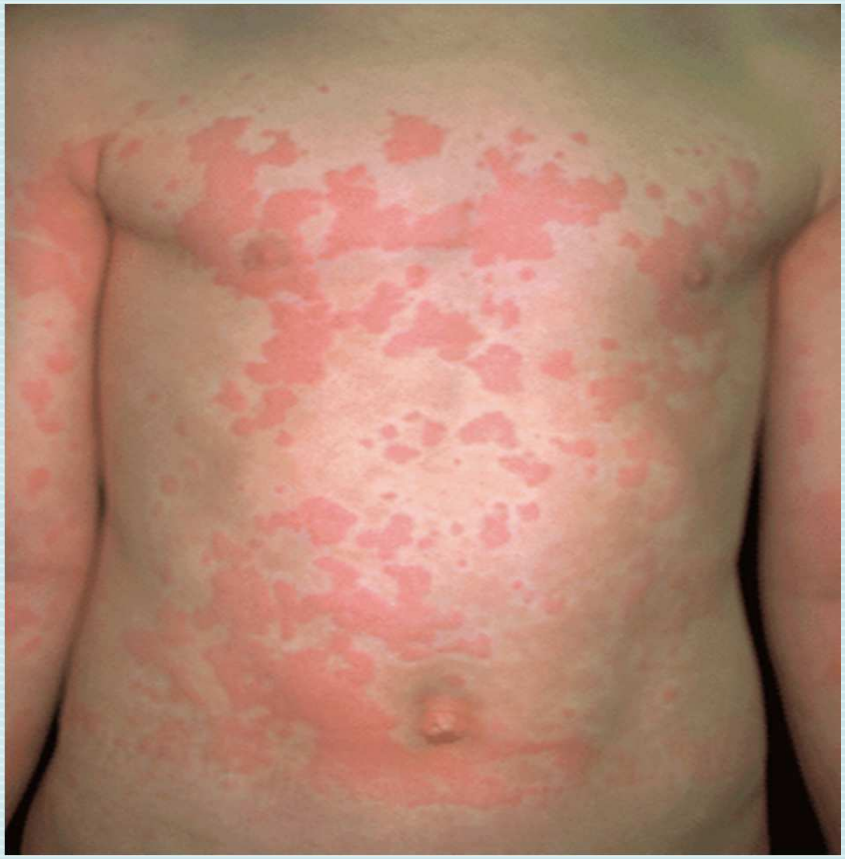
H1- Antihistamines for Chronic Spontaneous Urticaria

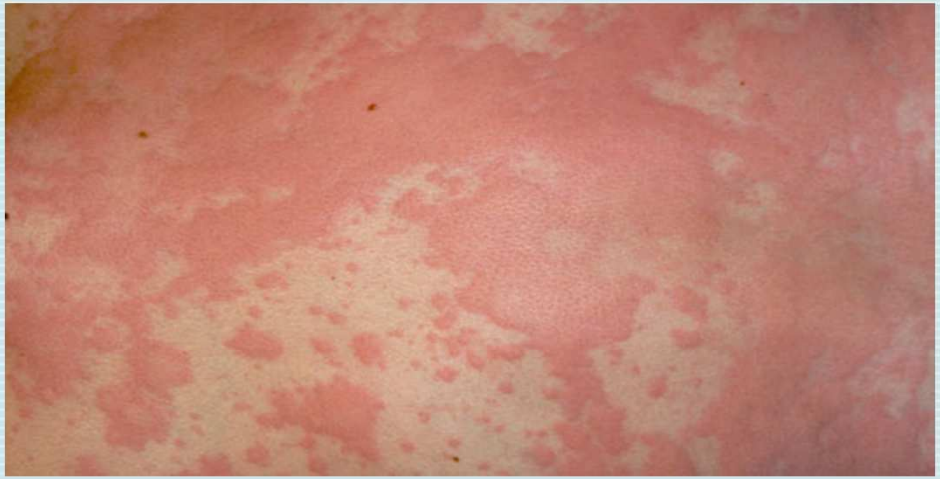
Dr Maulina Sharma
Consultant Dermatologist
Derby Hospitals NHS Foundation Trust

Chronic Spontaneous/ Idiopathic Urticaria

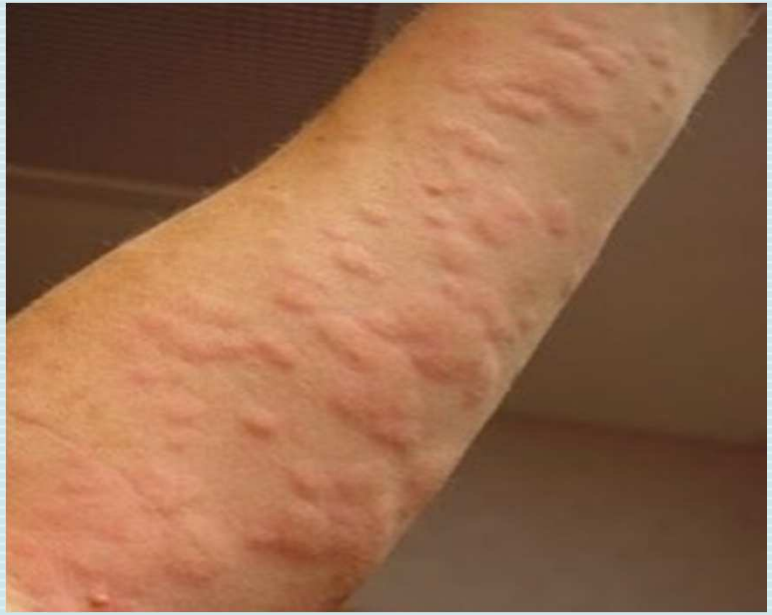


- Recurrent itchy weals, up to 24 hr
- More than 6 weeks' duration
- Associated angio-oedema
- No obvious identifiable cause

Chronic Spontaneous Urticaria



- Unpredictable
- Disabling
- 20% still suffer after 10 years



Impact of CSU

Impact of CSU

To assess the effects of H1-antihistamines for CSU

- Whether one antihistamine superior to another
- Combination better than monotherapy?
- High doses superior to standard?
- Duration of benefit from H1-antihistamines
- Risks and side effects
- Quality of life

Criteria for studies

RCTs only including cross over designs and quasi RCTs
All other designs excluded

- **Participants**

  Any age with clinical diagnosis of CSU/CIU

- **Exclusions**

  Urticaria of less than 6 weeks
  Other types of urticaria including immune complex, papular, contact, physical, cholinergic or auto-inflammatory

Interventions

Any H1-antihistamine, first or second generation, any dose, any route of administration

With or without concomitant medications

Duration:

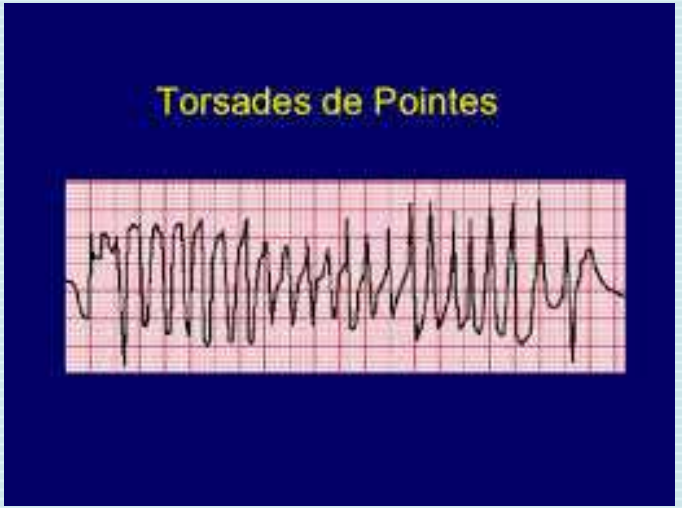
Short (up to 2 weeks)
Intermediate (2 weeks up to 3 months)
Long term (more than 3 months)

Comparators

- No treatment (placebo) or any active pharmacological compound
- Included head-to-head comparisons

- Excluded terfenadine, astemizole (withdrawn)

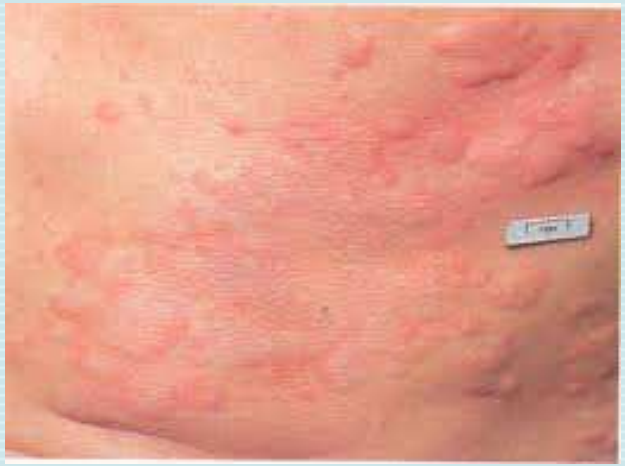
e.g. acupuncture, psychological interventions



Outcomes

Primary

- Proportion with complete suppression of urticaria
- With good or excellent response
- Participants with 50% QoL



Secondary

- Adverse events (serious requiring withdrawal)
- Minor adverse events
- Relapse with one month of stopping H1-antihistamines

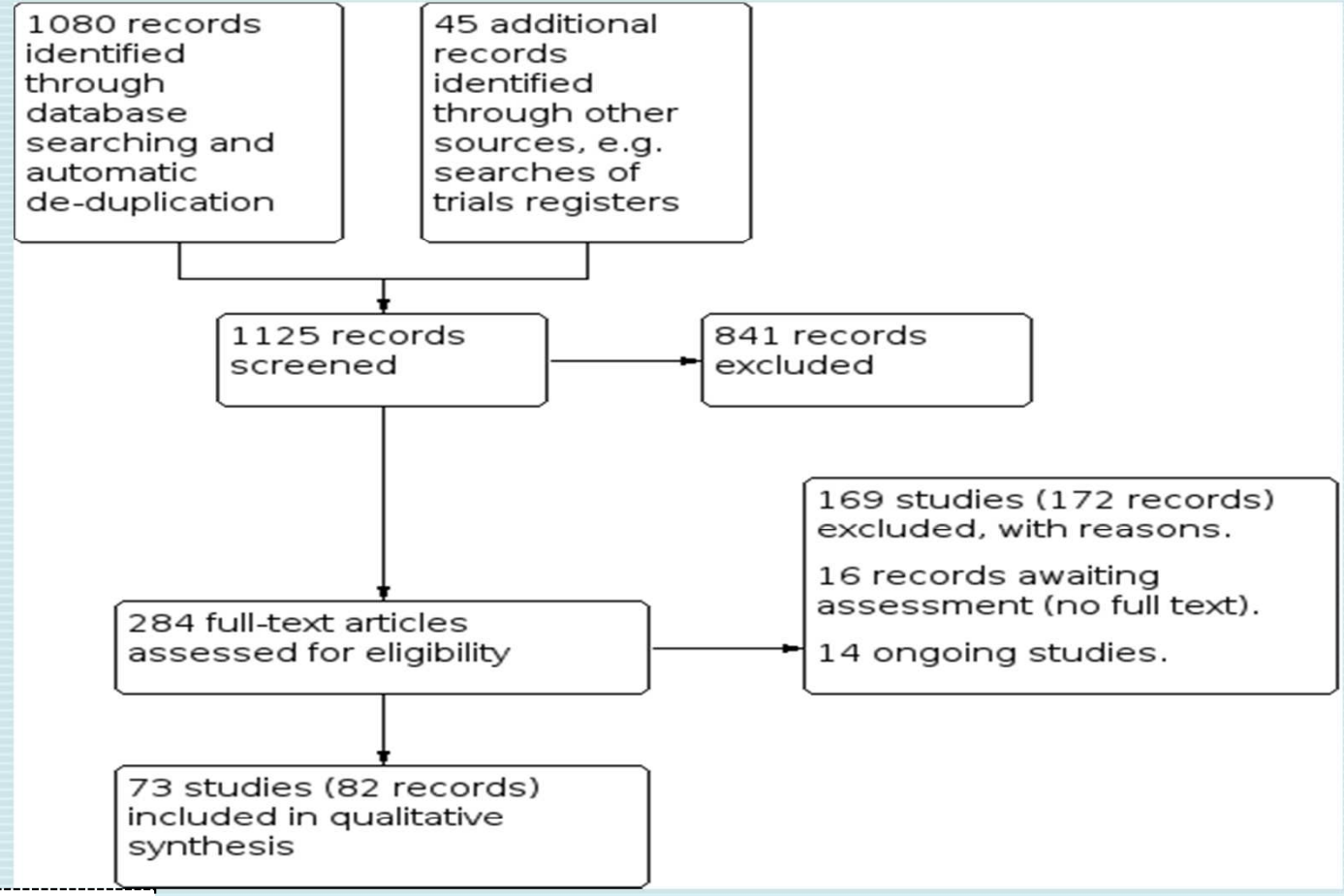
Searches (up to June 2014)

- Exhaustive searches of all bibliographic data bases
  - *Cochrane skin group specialised register*
  - *Cochrane central register of Controlled Trials (Cochrane library)*
  - *MEDLINE(from 1946)*
  - *EMBASE(from 1974)*
  - *PsycINFO(from 1806)*

- Trials registers
  - *The meta Register of Controlled Trials*
  - *The US National Institutes of Health Ongoing Trials Register*
  - *The Australian New Zealand Clinical Trials Registry*
  - *The WHO International Clinical Trials Registry platform*
  - *The EU Clinical Trials Register*

- Reference lists

Results



9759 participants
34 trials reported outcome data for
23 comparisons


Greenland
Iceland
Finland
Russia
Canada
United States
Mexico
United Kingdom
Spain
France
Italy
Ukraine
Turkey
Kazakhstan
Mongolia
China
Japan
South Korea
Afghanistan
Iran
Iraq
Pakistan
India
Saudi Arabia
Algeria
Libya
Egypt
Mali
Niger
Chad
Sudan
Nigeria
Ethiopia
Kenya
DR Congo
Tanzania
Angola
Namibia
Madagascar
South Africa
Indonesia
Papua New Guinea
Australia
New Zealand
Venezuela
Colombia
Brazil
Peru
Bolivia
Chile
Argentina
North Pacific Ocean
North Atlantic Ocean
South Pacific Ocean
South Atlantic Ocean
Indian Ocean

Included studies

First generation antihistamines

Hydroxyzine
Pheniramine

Second generation antihistamines

Cetirizine
Desloratadine
Ebastine
Emedastine
Fexofenadine
Levocetirizine
Loratadine
Ketotifen
Mizolastine
Rupatadine

Other comparators

Montelukast
Doxepin

Design and Duration

Some unusual designs:

Garavaglia 1995 (drop-outs replaced by new recruits)

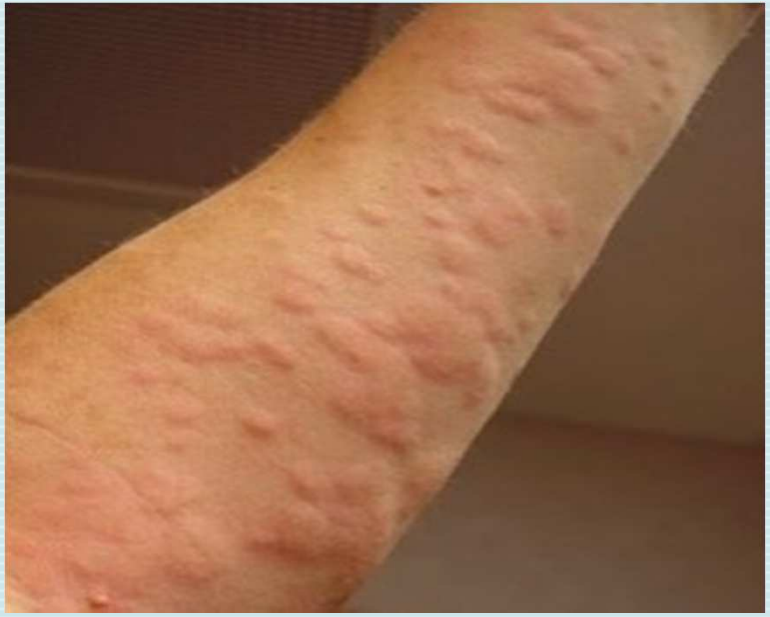
Wang 2012 (dose reduction study)

Weller 2013 (single body part)

Staevska 2014

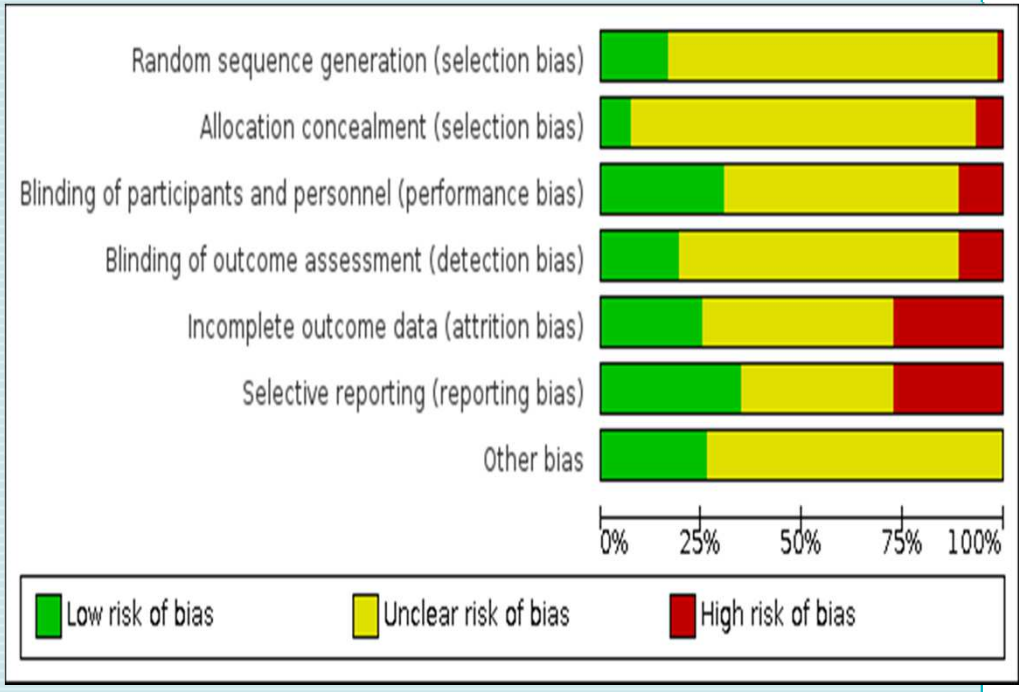
(cross-over after randomisation and in-hospital stay; levo vs hydroxy; after 5 days crossed without wash-out)

- 17 short term
- 55 intermediate
- None long term



Risk of Bias

- Randomisation:12 out of 73 described adequately
- Allocation: 4 studies used coded sealed envelopes; 5 studies at high risk, 3 were open label
- Blinding: 20 studies adequate; 8 not blinded to participants or personnel
- Blinding of outcome assessment: 14 adequate; 8 did not attempt it



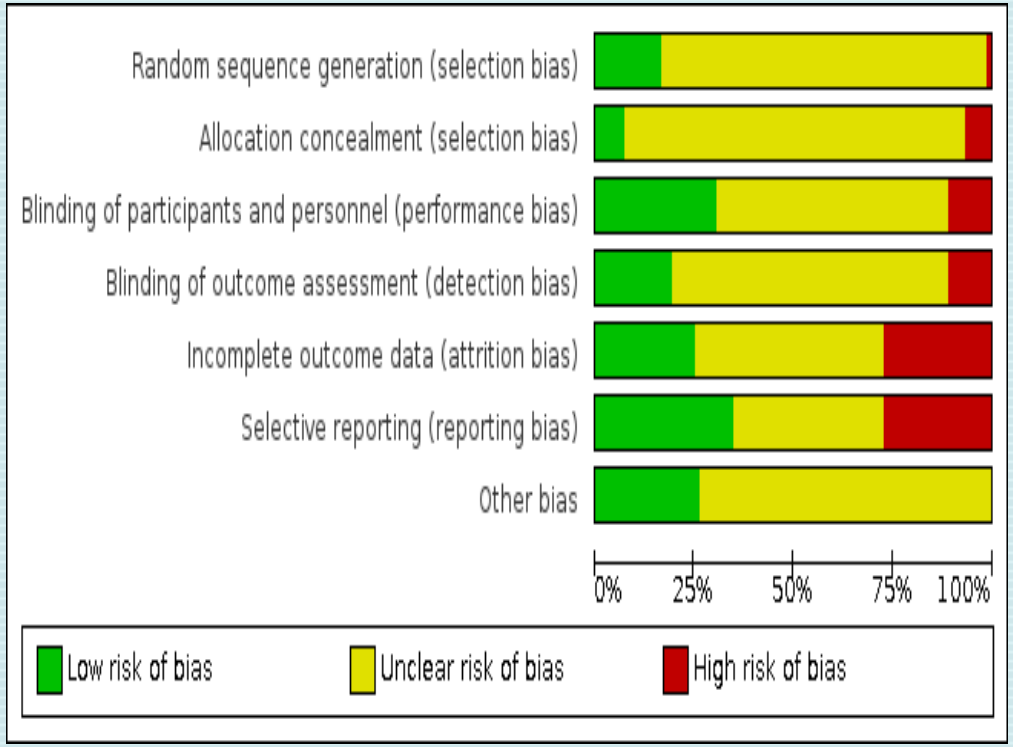
Risk of Bias

Selective reporting:
24 studies low risk

20 studies risk associated:

- no. of participants not reported
- mean scores and graphs only
- no adverse events reported
- whether concomitant meds allowed

- lab results done but not reported
- duration of follow up not reported
- results in placebo arm not reported



Quality of Evidence

GRADE
Of 73 studies: 31 industry sponsored, 6 through research grants and non-profit organisations

Notable methodological limitations

- Only 12 adequately randomised
- Only 4 adequate concealment
- Only 20 adequately blinded (participants and personnel)
- Only 14 adequately blinded for outcome assessors
- 20 studies incomplete reporting of outcome date (attrition bias)
- 20 studies high risk of selective reporting bias

Key Findings

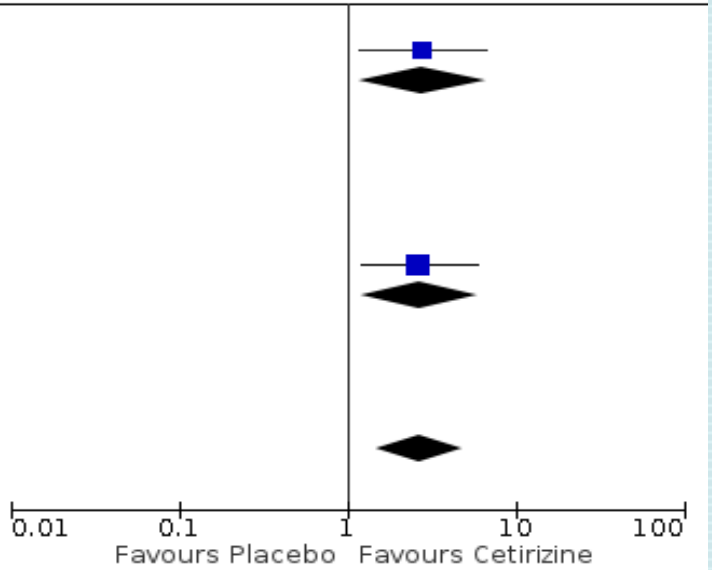
Limitations:

- Considerable variation in interventions and comparators
- Outcomes reported were not comparable
- Of the 23 comparisons, 10 provided outcome data for meta-analysis

- H1 antihistamines at standard doses are better than placebo, though no clear winner!
- Limited evidence to support increased doses

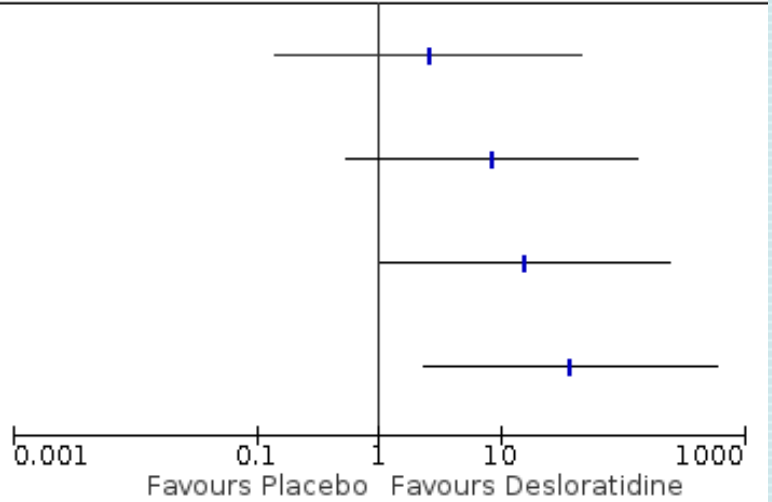
Cetirizine 10 to 20 mg versus placebo:
Proportion of participants with complete suppression of urticaria

Study or Subgroup	Cetirizine Events	Cetirizine Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
7.1.1 Short-term duration of intervention (cetirizine 10 mg)						
Go 1989	14	28	5	28	45.3%	2.80 [1.17, 6.73]
Subtotal (95% CI)		**28**		**28**	**45.3%**	**2.80 [1.17, 6.73]**
Total events	14		5			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.30 (P = 0.02)						
7.1.2 Intermediate-term duration of intervention (cetirizine 10 mg)						
Breneman 1995	18	60	7	62	54.7%	2.66 [1.20, 5.90]
Subtotal (95% CI)		**60**		**62**	**54.7%**	**2.66 [1.20, 5.90]**
Total events	18		7			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.40 (P = 0.02)						
Total (95% CI)		**88**		**90**	**100.0%**	**2.72 [1.51, 4.91]**
Total events	32		12			
Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 1 (P = 0.93); I² = 0%						
Test for overall effect: Z = 3.33 (P = 0.0009)						
Test for subgroup differences: Chi² = 0.01, df = 1 (P = 0.93), I² = 0%						



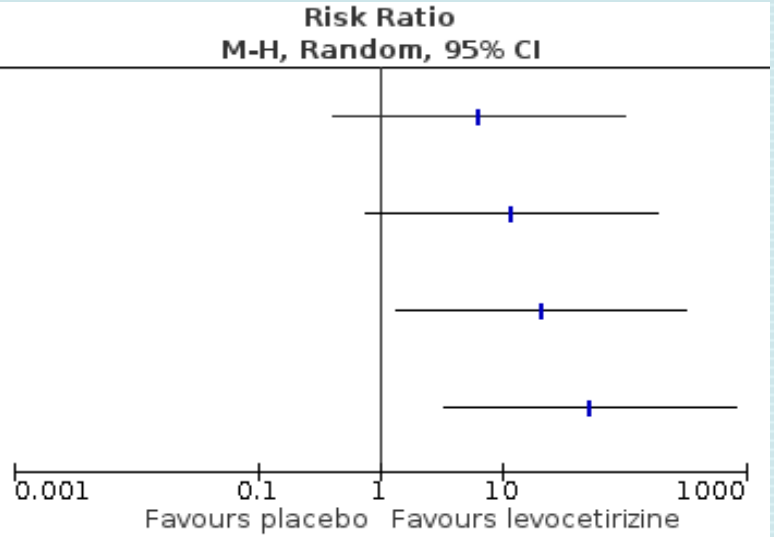
Desloratadine 5 to 20mg versus placebo: Proportion of participants with complete suppression of urticaria

Study or Subgroup	Desloratidine Events	Total	Placebo Events	Total	Risk Ratio M-H, Random, 95% CI
9.1.1 Short-term duration of intervention (desloratadine 5 mg)					
Hoxha 2011	3	34	0	12	2.60 [0.14, 46.97]
9.1.2 Short-term duration of intervention (desloratadine 10 mg)					
Hoxha 2011	11	34	0	12	8.54 [0.54, 134.83]
9.1.3 Short-term duration of intervention (desloratadine 20 mg)					
Hoxha 2011	21	34	0	12	15.97 [1.04, 245.04]
9.1.4 Intermediate-term duration of intervention (desloratadine 5 mg)					
Di Lorenzo 2004	18	40	0	40	37.00 [2.31, 593.70]



Levocetirizine 5 to 20 mg versus placebo: Proportion of participants with complete suppression of urticaria

Study or Subgroup	Levocetirizine Events	Total	Placebo Events	Total	Risk Ratio M-H, Random, 95% CI
11.1.1 Short-term duration of intervention (levocetirizine 5 mg)					
Hoxha 2011	9	37	0	12	6.50 [0.41, 104.06]
11.1.2 Short-term duration of intervention (levocetirizine 10 mg)					
Hoxha 2011	17	37	0	12	11.97 [0.77, 185.38]
11.1.3 Short-term duration of intervention (levocetirizine 20 mg)					
Hoxha 2011	30	37	0	12	20.87 [1.37, 317.60]
11.1.4 Intermediate-term duration of intervention (levocetirizine 5 mg)					
Nettis 2006	27	51	0	49	52.88 [3.31, 843.81]



Key findings

- Cetirizine 10 mg OD short-term and intermediate-term duration was effective in completely suppressing urticaria
- Desloratadine 5 mg OD for at least an intermediate term and at 20 mg in the short term in completely suppressing urticaria
- Levocetirizine 5 mg effective for complete suppression in the intermediate term but not in the short term
- Levocetirizine 20 mg effective in the short term for complete supression but 10 mg was not
- Rupatadine showed good/ excellent response at either 10mg or 20mg (RR 1.35, 95% CI 1.03 to 1.77; 1 study; n=245).

Key Findings

- Adverse events e.g. headache, dry mouth and somnolence tolerable with most antihistamines

- Evidence is less clear for improvement QoL
  (e.g. reduction in sleep disturbance from itching, less distress from appearance of hives) many studies did not address this

Implications for research

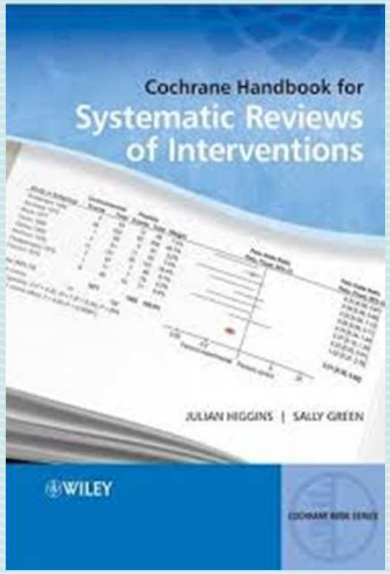
- Use of higher doses of H1-antihistamines
- Studies to be conducted over a longer duration period
- Assessment of response after stopping treatment
- Trials with two or more active arms rather than placebo
- Standardised outcome scores (e.g. UAS/ UAS7)
- Clearer outcome scores (e.g. no. of participants with complete suppression of urticaria or 75% reduction in itch severity)
- Wider use of standardised and validated quality of life (QoL) scores

Challenges and experience of doing the review

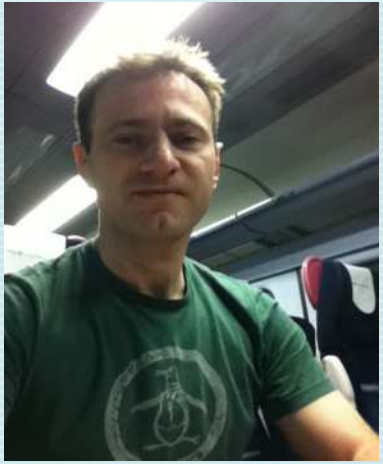
- Large review
- Consistency within the review
- Consistency within studies

Large review

- Labour intensive
- Steep learning curve >>>>
- 4 authors
- CSG support, searches
- Cochrane copy edit
- Cochrane Editorial Unit
- Translation of foreign papers
- Information from investigators



H1 team



Challenges and experience of doing the review

- Large review
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Consistency within review

- Protocol updated
- Changes to author team
- Cochrane Reviews changed in format plus methodological issues (RoB), quality of evidence, conduct and reporting expectations
- Data extraction of foreign language studies
- Location of studies (ILLs)
- Several studies part of wider multicentre trials-some published some not
- Nomenclature of CIU/CSU changed over time

Challenges and experience of doing the review

- Large review
- Consistency within the review
- Consistency within studies

Consistency within studies

- ‘Chronic urticaria’, refractory to antihistamines
- Interventions H1 large and disparate class
- Comparators were very wide changed original protocol
- Outcomes strictly defined led to studies not being included in analyses e.g. scales of QoL, harmonised between studies
- Clinical heterogeneity

What helps

- Experienced systematic reviewer (CB) and a good team
- Data management systems (spreadsheets and Endnote to keep track of everything), templates
- CSG guidance and patience
- Substantial commitment of time

Updates

- Larger team - to extract further data
- ? Recruit Chinese co-author
- Time and resources - financial, library access interlibrary loans, translations
- Defined team roles
- Deadlines
- Centralised data management e.g. data extraction
- Software that simplifies processes
- Widen to include more outcome measures e.g. continuous measures QoL (departure from protocol)

Update - Split?

For

- Split intervention vs. placebo and head to head
- H1 vs. Biologics
- Smaller job for each review

Against

- No good clinical reason to split first and second generation or other interventions
- QoL can be included as not very many
- Biologics-Omalizumab should be separate

Summary of review

- Considerable variation in interventions and comparators
- Outcomes reported were difficult to compare

- H1 antihistamines at standard doses are better than placebo
- Limited evidence to support increased doses

- Cetirizine 10 mg OD effective in short duration
- Desloratadine 5 mg OD effective at intermediate term and at 20 mg in the short
- Levocetirizine 5 mg at intermediate but not short term
- Levocetirizine 20 mg effective in the short term for complete supression but 10 mg was not

- Side effects of H1 antihistamines tolerable
- QoL measures not well reported

Summary of experience doing the review

- Invaluable experience in acquiring knowledge and skills to perform systematic reviews
- Akin to climbing Mt Everest!
- Huge sense of relief and achievement to see it published!