National Asthma Council Australia

AUSTRALIAN ASTHMA HANDBOOK

VERSION 2.0

CLINICAL ISSUES

Thunderstorm asthma

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ABBREVIATIONS

CFC	chlorofluorocarbon
COPD	chronic obstructive pulmonary disease
COX	cyclo-oxygenase
DXA	dual-energy X-ray absorptiometry
ED	emergency department
EIB	exercise-induced bronchoconstriction
FEV_1	forced expiratory volume over one second
FEV_6	forced expiratory volume over six seconds
FSANZ	Food Standards Australia and New Zealand
FVC	forced vital capacity
GORD	gastro-oesophageal reflux disease
HFA	formulated with hydrofluroalkane propellant
ICS	inhaled corticosteroid
ICU	intensive care unit
IgE	Immunoglobulin E
IL	interleukin
IU	international units
IV	intravenous
LABA	long-acting beta$_2$-adrenergic receptor agonist
LAMA	long-acting muscarinic antagonist
LTRA	leukotriene receptor antagonist
MBS	Medical Benefits Scheme
NHMRC	National Health and Medical Research Council
NIPPV	non-invasive positive pressure ventilation
NSAIDs	nonsteroidal anti-inflammatory drugs
OCS	oral corticosteroids
OSA	obstructive sleep apnoea
PaCO	carbon dioxide partial pressure on blood gas analysis
PaO	oxygen partial pressure on blood gas analysis
PBS	Pharmaceutical Benefits Scheme
PEF	peak expiratory flow
pMDI	pressurised metered-dose inhaler or 'puffer'
PPE	personal protective equipment
SABA	short-acting beta$_2$ -adrenergic receptor agonist
SAMA	short-acting muscarinic antagonist
SaO_2	oxygen saturation
SpO_2	peripheral capillary oxygen saturation measured by pulse oximetry
TGA	Therapeutic Goods Administration

RECOMMENDED CITATION

National Asthma Council Australia. *Australian Asthma Handbook*, Version 2.0. National Asthma Council Australia, Melbourne, 2019.

Available from: http://www.asthmahandbook.org.au

ISSN 2203-4722

SPONSORS

National Asthma Council Australia would like to acknowledge the support of the sponsors of Version 2.0 of the *Australian Asthma Handbook*:

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DISCLAIMER

Preventing thunderstorm asthma

Overview

Certain types of thunderstorms in spring or early summer in regions with high ryegrass pollen concentrations in the air can cause life-threatening allergic asthma flare-ups in individuals sensitised to ryegrass pollen (i.e. anyone with seasonal allergic rhinitis), even if they have not had asthma before.[1-3]

People with allergic rhinitis and allergy to ryegrass pollen (i.e. most people with springtime allergic rhinitis symptoms) are at risk of thunderstorm asthma if they live in, or are travelling to, a region with seasonal high grass pollen levels – even if they have never had asthma symptoms before. This includes people with undiagnosed asthma, no previous asthma, known asthma.[3] Lack of inhaled corticosteroid preventer treatment has been identified as a risk factor.[3]

Prevention of thunderstorm asthma in individuals is based on:

- year-round asthma control
- preventive inhaled corticosteroid treatment
- avoiding exposure to thunderstorms on days with high ryegrass pollen levels
- ensuring appropriate access to relievers during grass pollen season.

▶ See: *Managing allergic rhinitis in adults and adolescents*
See: *Managing allergies as part of asthma management*
See: *Managing avoidable triggers*

▶ Go to: National Asthma Council Australia's *Epidemic thunderstorm asthma* information paper
Go to: ASCIA's *Pollen calendar*

In this section

Preventing thunderstorm asthma

Preventing thunderstorm asthma in individuals

http://www.asthmahandbook.org.au/clinical-issues/thunderstorm-asthma/thunderstorm-triggered-asthma

Preventing thunderstorm asthma in individuals

Recommendations

Warn people with allergic rhinitis and allergy to ryegrass pollen (i.e. most people with springtime allergic rhinitis symptoms) that they may be at risk of thunderstorm asthma if they live in, or are travelling to, a region with seasonal high grass pollen levels – even if they have never had asthma symptoms before.

How this recommendation was developed

Consensus

Based on clinical experience and expert opinion (informed by evidence, where available), with particular reference to named source(s):

- Thien et al. 2018[1]
- O'Hehir et al. 2018[2]
- Lee et al. 2017[3]
- Davies. 2017[4]
- Girgis *et al.* 2000[5]
- Marks *et al.* 2001[6]

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For people with asthma who are at risk of thunderstorm asthma:

- **prescribe regular inhaled corticosteroids for continuous use if indicated (most adults and older adolescents with asthma)**
- **for patients for whom preventer therapy is not otherwise indicated, prescribe regular inhaled corticosteroids for at least 2 weeks before and throughout the pollen season (e.g. in Victoria, ideally 1 September–31 December)**
- **provide training in correct inhaler technique, and check technique and adherence regularly**
- **advise patients to carry a reliever inhaler and replace it before the expiry date**
- **provide an up-to-date written asthma action plan that includes thunderstorm advice and instructs the person to increase doses of both inhaled preventer and reliever (as well as starting oral corticosteroids, if indicated) in response to flare-ups.**

Notes: Most adults and older adolescents with asthma should be using a regular inhaled corticosteroid long term.

People with asthma are particularly at risk of thunderstorm asthma if they have seasonal (springtime) allergic rhinitis (i.e. allergic to ryegrass pollen), and live in or are travelling to an area with high grass pollen levels. People with allergy to ryegrass pollen without known asthma are also at risk of thunderstorm asthma.

For people with seasonal allergic rhinitis who do not use intranasal corticosteroid treatment all year, advise intranasal corticosteroid starting 6 weeks before the pollen season (or exposure) and continuing until pollen levels abate (e.g. in Victoria, ideally 1 September–31 December).

Refer to ASCIA's *Pollen calendar* for information on local high-risk periods.

How this recommendation was developed

Adapted from existing guidance

Based on reliable clinical practice guideline(s) or position statement(s):

- NACA, 2017[7]

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Advise patients who are at risk of thunderstorm asthma to:

- **check grass pollen counts for their region during spring and early summer (if available)**
- **on high grass pollen days, avoid exposure to outdoor air when a thunderstorm is approaching, especially during wind gusts just**

before the rain front hits (e.g. by going indoors with windows closed and air conditioner off or on recirculation mode, or shutting car windows and recirculating air).

Pollen counts are available during spring and summer (dates vary) for Melbourne, Sydney, Brisbane, Canberra, Adelaide and Tasmania. Phone apps are available for some areas.

▶ **Go to:** *pollenforecast.com.au*

How this recommendation was developed

Adapted from existing guidance

Based on reliable clinical practice guideline(s) or position statement(s):

- NACA, 2017[7]

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More information

Thunderstorm asthma

Certain types of thunderstorms in spring or early summer in regions with high grass pollen concentrations in the air can cause life-threatening allergic asthma flare-ups in individuals sensitised to rye grass, even if they have not had asthma before.[3,5,6,8,9]

Sensitisation to rye grass allergen is almost universal in patients who have reported flare-ups consistent with thunderstorm asthma in Australia.

People with allergic rhinitis and allergy to ryegrass pollen (i.e. most people with springtime allergic rhinitis symptoms) are at risk of thunderstorm asthma if they live in, or are travelling to, a region with seasonal high grass pollen levels – even if they have never had asthma symptoms before. This includes people with undiagnosed asthma, no previous asthma, known asthma.[3, 5] Lack of inhaled corticosteroid preventer treatment has been identified as a risk factor.[3]

Epidemics of thunderstorm asthma can occur when such a storm travels across a region and triggers asthma in many susceptible individuals. Epidemic thunderstorm asthma events are uncommon, but when they occur can they make a high demand on ambulance and health services.[1, 9, 10]

Data from thunderstorm asthma epidemics suggest that the risk of asthma flare-ups being triggered by a thunderstorm is highest in adults who are sensitised to grass pollen and have seasonal allergic rhinitis (with or without known asthma).[3]

The worst outcomes are seen in people with poorly controlled asthma.[1] Treatment with an inhaled corticosteroid asthma preventer was significantly protective in a well-conducted Australian case-control study.[5]

There is insufficient evidence to determine whether intranasal corticosteroids help protect against thunderstorm asthma. Intranasal corticosteroids reduce symptoms of allergic rhinitis and limited indirect evidence suggests they may protect against asthma flare-ups in people not taking inhaled corticosteroids.[11]

The effectiveness of specific allergen immunotherapy in protecting against thunderstorm asthma has not been evaluated in randomised clinical trials, but data from a small Australian open-label study suggest that short-term treatment with five-grass sublingual immunotherapy may have been protective in individuals.[4]

▶ Go to: National Asthma Council Australia's *Epidemic thunderstorm asthma* information paper
Go to: ASCIA's *Pollen calendar*
Go to: *Vic Emergency's Thunderstorm asthma forecast (Victoria only)*

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Treatment of allergic rhinitis in adults and adolescents

Table. Overview of efficacy of allergic rhinitis medicines for specific symptoms

Please view and print this figure separately: http://www.asthmahandbook.org.au/table/show/102

Intranasal corticosteroids

If continuous treatment is required, an intranasal corticosteroid is the first-choice treatment unless contraindicated. Intranasal corticosteroids are more effective in the treatment of allergic rhinitis than other drug classes including oral H_1-antihistamines, intranasal H_1-antihistamines and montelukast.[8, 9, 10] Intranasal corticosteroid are most effective when taken continuously.[8]

Intranasal corticosteroids are effective in reducing congestion, rhinorrhoea, sneezing and itching in adults and adolescents with allergic rhinitis.[8, 9] They are also effective for ocular symptoms.[11]

All available intranasal corticosteroids appear to be equally effective.[8]

The onset of action is between 3 and 36 hours after first dose and, in practice, the full therapeutic effect takes a few days.[12]

The addition of an oral H_1-antihistamine or leukotriene receptor antagonist to an intranasal corticosteroid is generally no more effective than intranasal corticosteroid monotherapy.[10]

Intranasal corticosteroids are well tolerated. Common (>1%) adverse effects include nasal stinging, itching, nosebleed, sneezing, sore throat, dry mouth, cough.[13] Nose bleeds are usually due to poor spray technique or crusting. Evidence from studies mainly in adults suggests that intranasal corticosteroids do not cause atrophy of nasal epithelium.[14]

Intranasal corticosteroids are not generally associated with clinically significant systemic adverse effects when given in recommended doses.[8, 15] Studies in adults evaluating effects on the hypothalamic-pituitary axis using morning cortisol concentrations, cosyntropin stimulation, and 24-hour urinary free cortisol excretion show no adverse effects with beclomethasone dipropionate, budesonide, ciclesonide, fluticasone propionate, fluticasone furoate, or triamcinolone acetonide.[8]

In patients with asthma already taking inhaled corticosteroids, both the intranasal corticosteroid dose and the inhaled corticosteroid dose should be taken into account when calculating the total daily corticosteroid dose. Drug–drug interactions (e.g. with CYP3A4 inhibitors such as such as erythromycin, clarithromycin, ritonavir and itraconazole) may change the metabolism or increase absorption of corticosteroids administered by any route, increasing the risk of adrenal suppression.[13]

Combination intranasal corticosteroid plus intranasal antihistamines

Combined intranasal fluticasone propionate and azelastine hydrochloride in a single device is more effective than fluticasone propionate alone for a range of nasal and ocular symptoms.[8, 10, 16]

The onset of therapeutic action is approximately 30 minutes after dosing.[16]

Oral antihistamines

Second-generation (less sedating) antihistamines (e.g. cetirizine, desloratadine, fexofenadine or loratadine) should be used in preference to older, more sedating antihistamines. Cetirizine is the most likely of the less sedating antihistamines to cause sedation, while fexofenadine and loratadine appear to be the least sedating.[17]

Less sedating oral H_1-antihistamines are effective in managing allergic rhinitis symptoms of rhinorrhoea, sneezing, nasal itching and ocular symptoms.[10, 18] They can provide adequate relief for some individuals when taken continuously or intermittently.[8] Available agents appear to be equally effective.[15]

However, oral antihistamines are less effective than continuous intranasal corticosteroids, especially for nasal congestion.[8, 19] In adults with allergic rhinitis, oral antihistamines usually produce no further improvement when added to intranasal corticosteroid treatment.[8]

Common (>1%) adverse effects include drowsiness, fatigue, headache, nausea and dry mouth.[13] Oral antihistamines can also cause ocular dryness.[20]

Intranasal antihistamines

Intranasal antihistamines are at least equally effective as second-generation, less sedating oral H_1-antihistamines for the treatment of allergic rhinitis, but are generally less effective than intranasal corticosteroids.[9]

Intranasal antihistamines are more effective than oral antihistamines for reducing nasal congestion.[8] They have a rapid onset of action (15–30 minutes).[8]

The most common (>1%) adverse effect is local irritation.[13] Bitter taste is more common intranasal antihistamines than with intranasal corticosteroids.[8]

Montelukast

Leukotriene receptor antagonists are no more effective than oral H_1-antihistamines.[9, 10] Montelukast is less effective than intranasal corticosteroid in the treatment of allergic rhinitis.[8, 9] In most studies, adding montelukast to an intranasal corticosteroid was not more effective than intranasal corticosteroid alone.[10]

Montelukast is approved by TGA for treatment of in adults with asthma or seasonal allergic rhinitis.

It is generally very well tolerated, but has been infrequently associated with neuropsychiatric adverse effects, including suicidal ideation, in children and young people.[21, 22, 23, 24, 25] A recent analysis of databases of adults and children taking montelukast suggests

it is associated with nightmares, depression, and aggression.[25] Allergic granulomatous angiitis has also been reported, but a causal relationship has not been established.[25]

Other nasal sprays

Ipratropium bromide spray is effective in managing persistent rhinorrhoea in patients with allergic rhinitis, but not blockage or itch.[9] It is indicated for use in adults and adolescents over 12 years old.

Intranasal sodium cromoglycate is less effective than intranasal corticosteroids, but is effective in some patients for prevention and treatment of allergic rhinitis and is associated with minimal adverse effects.[15]

Specific allergen immunotherapy

Specific allergen immunotherapy (desensitisation) is effective in reducing allergic rhinitis symptoms (see separate topic).

▶ Go to: National Asthma Council Australia's *Allergic rhinitis and asthma* information paper
Go to: National Asthma Council Australia's information on intranasal delivery technique, including *How-to videos*
Go to: National Asthma Council Australia's *Allergic rhinitis treatments chart*

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Treatment of allergic rhinitis in children

Table. Overview of efficacy of allergic rhinitis medicines for specific symptoms

Please view and print this figure separately: http://www.asthmahandbook.org.au/table/show/102

Intranasal corticosteroids

Intranasal corticosteroids are effective in reducing congestion, rhinorrhoea, sneezing and itching in school-aged children with allergic rhinitis.[8, 9] However, there is weaker evidence to support their efficacy in children than in adults.[9] There is limited evidence to guide the treatment of allergic rhinitis in preschool children.[10]

The addition of an oral H_1-antihistamine or leukotriene receptor antagonist to an intranasal corticosteroid is generally no more effective than intranasal corticosteroid monotherapy.[10]

TGA-approved indications vary between age groups. Intranasal corticosteroids indicated for children aged under 12 years include fluticasone furoate (age 2 years and over), mometasone furoate (age 3 years and over), and budesonide (age 6 years and over).

Intranasal corticosteroids are well tolerated. Evidence from studies mainly in adults suggests that they do not cause atrophy of nasal epithelium.[26] Intranasal corticosteroids are not generally associated with clinically significant systemic adverse effects in children when given in recommended doses.[8][15] Studies in children evaluating effects on the hypothalamic-pituitary axis using morning cortisol concentrations, cosyntropin stimulation, and 24-hour urinary free cortisol excretion showed no adverse effects with ciclesonide, fluticasone propionate, fluticasone furoate, mometasone furoate, or triamcinolone acetonide.[8] One knemometry study showed reduced lower leg growth rate in children using intranasal budesonide.[8] In studies using stadiometry over 12 months, higher-than-recommended doses of intranasal beclomethasone dipropionate were associated with growth suppression, but fluticasone propionate and mometasone furoate showed no effects on growth compared with placebo.[8]

In children already taking inhaled corticosteroids, both the intranasal corticosteroid dose and the inhaled corticosteroid dose should be taken into account when calculating the total daily corticosteroid dose.

Oral antihistamines

Second-generation (less sedating) antihistamines (e.g. cetirizine, desloratadine, fexofenadine or loratadine) should be used in preference to older, more sedating antihistamines. Cetirizine is the most likely of the less sedating antihistamines to cause sedation, while fexofenadine and loratadine appear to be the least sedating.[17]

These antihistamines can be taken long term by children. Eighteen months of treatment with cetirizine was well tolerated in a large, prospective, multi-country, randomised controlled trial in infants with atopic dermatitis aged 12–24 months.[8]

Less sedating oral H_1-antihistamines are effective in managing allergic rhinitis symptoms of rhinorrhoea, sneezing, nasal itching and ocular symptoms,[10, 18] including in preschool children. [10] They can provide adequate relief for some individuals when taken continuously or intermittently.[8] Available agents appear to be equally effective.[15]

However, oral antihistamines are less effective than continuous intranasal corticosteroids, especially for nasal congestion.[8, 19] The addition of oral antihistamines to intranasal corticosteroids has not been demonstrated to be an effective strategy in children.[27]

TGA-approved indications vary between age groups. Less sedating oral antihistamines indicated for children under 12 years include cetirizine (1 year and over), loratatidine (1 year and over), desloratadine (6 months and over), and fexofenadine (6 months and over).

Intranasal antihistamines

Intranasal antihistamines are at least equally effective as second-generation, less sedating oral H_1-antihistamines for the treatment of allergic rhinitis, but are generally less effective than intranasal corticosteroids.[9]

Intranasal antihistamines are more effective than oral antihistamines for reducing nasal congestion.[8] They have a rapid onset of action (15–30 minutes).[8]

Montelukast

Leukotriene receptor antagonists are no more effective than oral H_1-antihistamines.[9, 10] Montelukast is less effective than intranasal corticosteroid in the treatment of allergic rhinitis.[8, 9] In most studies, adding montelukast to an intranasal corticosteroid was not more effective than intranasal corticosteroid alone.[10]

Montelukast is approved by TGA for the treatment of asthma in children over 2 years, and for the treatment of seasonal allergic rhinitis.

It is generally very well tolerated, but has been infrequently associated with neuropsychiatric adverse effects, including suicidal ideation, in children and young people.[21, 22, 23, 24] A recent analysis of databases of adults and children taking montelukast suggests it is associated with nightmares (especially in children), depression, and aggression (especially in children).[25] Allergic granulomatous angiitis has also been reported, but a causal relationship has not been established.[25]

The potential association of montelukast with behaviour-related adverse events should be mentioned to parents when commencing treatment, and treatment should be stopped if such adverse events are suspected.

Specific allergen immunotherapy

Specific allergen immunotherapy (desensitisation) is effective in reducing allergic rhinitis symptoms (see separate topic).

▶ Go to: National Asthma Council Australia's *Allergic rhinitis and asthma* information paper
Go to: National Asthma Council Australia's information on intranasal delivery technique, including *How-to videos*
Go to: National Asthma Council Australia's *Allergic rhinitis treatments chart*

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References

1. Thien F, Beggs PJ, Csutoros D et al. The Melbourne epidemic thunderstorm asthma event 2016: an investigation of environmental triggers, effect on health services, and patient risk factors. *Lancet Planet Health* 2018; 2: e255-e63. Available from: https://www.ncbi.nlm.nih.gov/pubmed/29880157/
2. O'Hehir RE, Varese NP, Deckert K et al. Epidemic thunderstorm asthma protection with five-grass pollen tablet sublingual immunotherapy: a clinical trial. *Am J Respir Crit Care Med* 2018; 198: 126-8. Available from: https://www.ncbi.nlm.nih.gov/pubmed/29461859/
3. Lee J, Kronborg C, O'Hehir RE, Hew M. Who's at risk of thunderstorm asthma? The ryegrass pollen trifecta and lessons learnt from the Melbourne thunderstorm epidemic. *Respir Med* 2017; 132: 146-8. Available from: https://www.ncbi.nlm.nih.gov/pubmed/29229087/
4. Davies J, Queensland University of Technology. Literature review on thunderstorm asthma and its implications for public health advice. Final report. Melbourne: *Victorian State Government Department of Health and Human Services*; 2017. Available from: https://www2.health.vic.gov.au/about/publications/researchandreports/thunderstorm-asthma-literature-review-may-2107/
5. Girgis ST, Marks GB, Downs SH et al. Thunderstorm-associated asthma in an inland town in south-eastern Australia. Who is at risk? *Eur Respir J* 2000; 16: 3-8.
6. Marks GB, Colquhoun JR, Girgis ST, *et al*. Thunderstorm outflows preceding epidemics of asthma during spring and summer. *Thorax*. 2001; 56: 468-71.
7. National Asthma Council Australia. Thunderstorm asthma. Melbourne *NACA*.2017. Available from: https://www.nationalasthma.org.au/living-with-asthma/resources/health-professionals/information-paper/thunderstorm-asthma/
8. Szefler, SJ, Phillips, BR, Martinez, FD, *et al*. Characterization of within-subject responses to fluticasone and montelukast in childhood asthma. *J Allergy Clin Immunol*. 2005; 115: 233-242. Available from: https://www.ncbi.nlm.nih.gov/pubmed/15696076
9. Brożek JL, Bousquet J, Baena-Cagnani CE, *et al*. Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines: 2010 Revision. *J Allergy Clin Immunol*. 2010; 126: 466-476. Available from: http://www.jacionline.org/article/S0091-6749(10)01057-2/fulltext
10. Basheti, IA; Obeidat, NM; Reddel, HK;. Effect of novel inhaler technique reminder labels on the retention of inhaler technique skills in asthma: a single-blind randomized controlled trial.. *NPJ Prim Care Respir Med*. 2017; 27: 9. Available from: https://www.ncbi.nlm.nih.gov/pubmed/28184045
11. Hong J, Bielory B, Rosenberg JL, Bielory L. Efficacy of intranasal corticosteroids for the ocular symptoms of allergic rhinitis: A systematic review. *Allergy Asthma Proc*. 2011; 32: 22-35. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21262095
12. Aldea Perona, A., Garcia-Saiz, M., Sanz Alvarez, E.. Psychiatric disorders and montelukast in children: a disproportionality analysis of the VigiBase®. *Drug Saf*. 2016; 39: 69-78. Available from: https://www.ncbi.nlm.nih.gov/pubmed/26620206

13. Valovirta, E., Boza, M. L., Robertson, C. F., *et al*. Intermittent or daily montelukast versus placebo for episodic asthma in children. *Ann Allergy Asthma Immunol*. 2011; 106: 518-26. Available from: https://www.ncbi.nlm.nih.gov/pubmed/21624752
14. Harmanci, K, Bakirtas, A, Turktas, I, Degim, T. Oral montelukast treatment of preschool-aged children with acute asthma. *Ann Allergy Asthma Immunol*. 2006; 96: 731-735. Available from: https://www.ncbi.nlm.nih.gov/pubmed/16729788
15. Wallace DV, Dykewicz MS, Bernstein DI, *et al*. The diagnosis and management of rhinitis: An updated practice parameter. *J Allergy Clin Immunol*. 2008; 122: S1-S84. Available from: http://www.jacionline.org/article/S0091-6749(08)01123-8/fulltext
16. National Asthma Council Australia,. *Monoclonal antibody therapy for severe asthma. An information paper for health professionals.*. NACA, Melbourne, 2018.
17. Kooi, EM, Schokker, S, Marike Boezen, H, *et al*. Fluticasone or montelukast for preschool children with asthma-like symptoms: randomized controlled trial. *Pulm Pharmacol Ther*. 2008; 21: 798-804. Available from: https://www.ncbi.nlm.nih.gov/pubmed/18647656
18. Bachert C, Maspero J. Efficacy of second-generation antihistamines in patients with allergic rhinitis and comorbid asthma. *J Asthma*. 2011; 48: 965-73. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21970671
19. Bousquet J, Khaltaev N, Cruz AA, *et al*. Allergic Rhinitis and its Impact on Asthma (ARIA) 2008. *Allergy*. 2008; 63: 8-160. Available from: http://onlinelibrary.wiley.com/doi/10.1111/j.1398-9995.2007.01620.x/full
20. Bacharier LB, Phillips BR, Zeiger RS, *et al*. Episodic use of an inhaled corticosteroid or leukotriene receptor antagonist in preschool children with moderate-to-severe intermittent wheezing. *J Allergy Clin Immunol*. 2008; 122: 1127-1135. Available from: https://www.ncbi.nlm.nih.gov/pubmed/18973936
21. Schumock GT, Stayner LT, Valuck RJ, *et al*. Risk of suicide attempt in asthmatic children and young adults prescribed leukotriene-modifying agents: a nested case-control study. *J Allergy Clin Immunol*. 2012; 130: 368-75. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22698520
22. Wallerstedt SM, Brunlöf G, Sundström A, Eriksson AL. Montelukast and psychiatric disorders in children. *Pharmacoepidemiol Drug Saf*. 2009; 18: 858-864. Available from: http://www.ncbi.nlm.nih.gov/pubmed/19551697
23. Philip G, Hustad C, Noonan G, *et al*. Reports of suicidality in clinical trials of montelukast. *J Allergy Clin Immunol*. 2009; 124: 691-6.e6. Available from: http://www.jacionline.org/article/S0091-6749(09)01247-0/fulltext
24. Philip G, Hustad CM, Malice MP, *et al*. Analysis of behavior-related adverse experiences in clinical trials of montelukast. *J Allergy Clin Immunol*. 2009; 124: 699-706.e8. Available from: http://www.jacionline.org/article/S0091-6749(09)01248-2/fulltext
25. Szefler, S. J., Carlsson, L. G., Uryniak, T., Baker, J. W.. Budesonide inhalation suspension versus montelukast in children aged 2 to 4 years with mild persistent asthma. *J Allergy Clin Immunol Pract*. 2013; 1: 58-64. Available from: https://www.ncbi.nlm.nih.gov/pubmed/24229823
26. Knorr, B, Franchi, LM, Bisgaard, H, *et al*. Montelukast, a leukotriene receptor antagonist, for the treatment of persistent asthma in children aged 2 to 5 years. *Pedriatrics*. 2001; 108: E48. Available from: https://www.ncbi.nlm.nih.gov/pubmed/11533366
27. Brodlie M, Gupta A, Rodriguez-Martinez CE, *et al*. Leukotriene receptor antagonists as maintenance and intermittent therapy for episodic viral wheeze in children. *Cochrane Database Syst Rev*. 2015; Issue 10: CD008202. Available from: https://www.ncbi.nlm.nih.gov/pubmed/26482324