



Department of Vermont Health Access

Therapeutic Class Review

Leukotriene Modifiers

Overview/Summary

The leukotriene modifiers (LTMs) are a class of medications used for long-term symptom control in patients with asthma as well as allergic rhinitis. The LTMs can be divided into two pharmacologic categories: leukotriene receptor antagonists (LTRAs) and 5-lipoxygenase inhibitors. The LTRAs, which include montelukast and zafirlukast, exert their pharmacologic action by blocking the leukotriene receptor, thereby inhibiting the action of cysteinyl leukotrienes.^{1,2} Cysteinyl leukotrienes play an important role in the pathophysiology of asthma and contribute to bronchoconstriction, increased airway responsiveness, mucous secretion and recruitment of inflammatory cells.³ Blocking the action of cysteinyl leukotrienes has been shown to reduce or prevent airway obstruction and decrease the activation of inflammatory cells.³ The only 5-lipoxygenase inhibitor currently available is zileuton. This agent inhibits the actions of the 5-lipoxygenase enzyme thereby preventing the formation of leukotrienes.^{4,5} LTRAs and 5-lipoxygenase inhibitors elicit similar biologic responses in asthmatic patients, but differ in dosing requirements, adverse reactions, drug interactions and pharmacokinetic parameters.^{1,2,4,5} The LTMs are Food and Drug Administration (FDA)-approved for prophylaxis and chronic treatment of asthma.^{1,2,4,5} One of the LTMs, montelukast, carries additional indications for the treatment of symptoms of seasonal and perennial allergic rhinitis and for the prevention of exercise-induced bronchoconstriction.¹ Montelukast has been used for the treatment of atopic dermatitis and aspirin-induced asthma and zafirlukast has been used for the treatment of exercise-induced asthma, though neither agent is FDA-approved for those indications.⁶⁻⁹ Currently, zafirlukast is available generically. Zileuton is available in both immediate- and controlled-release preparations.

Treatment guidelines published by the National, Heart, Lung, Blood Institute recommend the use of inhaled corticosteroids (ICS) as first-line therapy for long-term control of persistent asthma symptoms in children and adults. In individuals over the age of 12, a long-acting β_2 -agonist (LABA) used concurrently with either a low- or medium-dose ICS is preferred for the treatment of moderate persistent asthma. All three LTMs can be used as alternative adjunctive agents to low- and medium-dose ICS; however they are not recommended as preferred agents. Zileuton has not been studied in patients less than 12 years of age and either LTRA agent is preferred compared to zileuton due to its limited efficacy data and the need for liver function monitoring. In children 5 to 11 years of age, a LTRA is an alternative to low-dose ICS monotherapy. Additionally, a low-dose ICS concurrently with a LABA or LTRA or medium-dose ICS monotherapy are all considered preferred options. LTRAs are also considered alternative agents in pediatric patients with severe asthma.¹⁰ In children ages 0 to 4 years, montelukast is recommended as an alternative to a low-dose ICS and as an adjunctive option alongside the LABA agents with a medium and high-dose ICS in the more severe asthma stages.¹⁰

The Global Initiative for Asthma guidelines recommend that LTMs be used as alternative agents to low-dose ICSs. The LTMs are particularly appropriate in patients who are unable or unwilling to use ICSs, or in those who experience intolerable adverse events on ICS therapy. The LTM agents are also recommended as add-on treatment to medium- or high-dose ICS agents; however, the benefit reported with this treatment combination has been shown to be less than that of a combination ICS and LABA.¹¹

The Joint Task Force on Practice Parameters for Allergy and Immunology recommend intranasal corticosteroids as the most effective medication class for controlling symptoms of allergic rhinitis and all are considered equally efficacious. It is also suggested that intranasal antihistamines be considered as first-line treatment for both allergic and nonallergic rhinitis. The LTRAs alone or in combination with antihistamines are effective in the treatment of allergic rhinitis.¹²

The Institute for Clinical Systems Improvement guidelines notes that intranasal corticosteroids are the most effective single agents for controlling the spectrum of allergic rhinitis symptoms and should be

considered first-line therapy in patients with moderate to severe symptoms. Antihistamines and cromolyn can be considered alternatives in patients who prefer not to use intranasal corticosteroids. Antihistamines are somewhat less effective than intranasal corticosteroids; however, oral antihistamines are an effective alternative in patients who cannot use or prefer not to use intranasal corticosteroids. LTMs are as effective as second-generation antihistamines for the treatment of allergic rhinitis; however, they are not as effective as intranasal corticosteroids.¹³

Medications

Table 1. Medications Included Within Class Review

Generic Name (Trade name)	Medication Class	Generic Availability
Montelukast (Singulair [®])	Leukotriene receptor antagonist	-
Zafirlukast (Accolate ^{®*})	Leukotriene receptor antagonist	✓
Zileuton (Zyflo [®] , Zyflo [®] CR)	5-lipoxygenase inhibitor	-

*Generic is available in at least one dosage form or strength.
CR=controlled release.

Indications

Table 2. Food and Drug Administration-Approved Indications^{1,2,4-9}

Indication	Montelukast	Zafirlukast	Zileuton
Prophylaxis and chronic treatment of asthma	✓	✓	✓
Prophylaxis of exercise-induced bronchoconstriction	✓		
Symptoms of seasonal allergic rhinitis	✓		
Symptoms of perennial allergic rhinitis	✓		

Although not Food and Drug Administration-approved, montelukast has been used for the treatment of atopic dermatitis and aspirin-induced asthma and zafirlukast has been used for the treatment of exercise-induced asthma.⁶⁻⁹

Pharmacokinetics

Table 3. Pharmacokinetics^{1,2,4-9,14}

Generic Name	Duration (hours)	Renal Excretion (%)	Active Metabolites	Serum Half-Life (hours)
Montelukast	>24	<0.2	Unspecified	2.7 to 5.0
Zafirlukast	Unspecified	10	No	8 to 16
Zileuton	Unspecified	94.5	Yes	2.5 to 3.2

Clinical Trials

There are numerous placebo controlled trials examining the efficacy of the leukotriene modifiers for asthma as well as allergic rhinitis. There is also a large body of clinical data comparing the leukotriene modifiers to inhaled corticosteroids and long-acting β_2 -agonists. However the availability of head-to-head trials specifically comparing the leukotriene modifiers is lacking.

When compared to placebo, leukotriene modifiers demonstrated efficacy in most aspects of asthma control, including pulmonary function, asthma symptoms, β_2 -agonist use, asthma exacerbations, and nighttime symptom control.¹⁵⁻²³ When compared to other long-term controller medications, such as inhaled corticosteroids and long-acting β_2 -agonists, the leukotriene modifiers have not demonstrated equivalence or significant advantages in clinical outcomes.²⁴⁻³⁹

With regards to allergic rhinitis, montelukast has been shown to be more effective than placebo, and has demonstrated comparable efficacy to second-generation antihistamines; however it has not been shown to be as effective as intranasal corticosteroids.⁴⁰⁻⁴⁷

Table 4. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Asthma				
Virchow et al ¹⁵ (MONICA) Montelukast 10 mg Daily Therapy added to current therapy with ICS or ICS and LABA.	OL, OS, PRO Patients 18 years of age or older with mild or moderate persistent asthma insufficiently controlled with ICS or ICS and LABA	N=1,681 6 months	Primary: ACT scores Secondary: Mini-AQLQ	Primary: Mean ACT score significantly improved compared to baseline ($P<0.0001$). The percentage of patients with uncontrolled or poorly controlled asthma at baseline decreased. The percentage of patients with well-controlled or completely controlled asthma increased. Secondary: Significant improvement in the Mini-AQLQ was observed from baseline ($P<0.0001$). Significant improvements in FEV ₁ were observed from baseline ($P<0.0001$).
Virchow et al ¹⁶ (MONICA follow-up and sub-group analysis) Montelukast 10 mg Daily Therapy added to current therapy with ICS or ICS and LABA.	OL, OS, PRO Patients 18 years of age or older with mild or moderate persistent asthma insufficiently controlled with ICS or ICS and LABA	N=1,681 12 months (additional 6 month follow-up after original MONICA)	Primary: ACT scores Secondary: Mini-AQLQ	Primary: Mean ACT score significantly improved at month 12 compared to baseline ($P<0.0001$). Secondary: Mean total Mini-AQLQ score increased significantly at month 12 compared to baseline ($P<0.0001$). Asthma control improved in all patient subgroups (gender, age [<30 , 30 to 50 , >50], duration of asthma [<5 years, ≥ 5 years], presence of allergic rhinitis, prior therapy with ICS or LABA and ICS). Comorbid allergic rhinitis, younger age, shorter duration of asthma and prior treatment with only ICS were indicators of better control with add-on montelukast.
Knorr et al ¹⁷ Montelukast 5 mg Daily at bedtime	DB, MC, PC, RCT Children 6 to 14 years of age with an FEV ₁ between 50 to 85% of	N=336 8 weeks	Primary: Improvements in morning FEV ₁ from baseline	Primary: A significant improvement in percent change from baseline in FEV ₁ was reported in patients in the montelukast group compared to the placebo group ($P<0.001$).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo	expected value, 15% or better reversibility after inhaled β_2 -agonist therapy, daytime asthma symptoms that met a minimal value, and reported daily β_2 -agonist use		Secondary: Daytime asthma symptoms, morning and evening PEF, daily use of inhaled SABAs, nocturnal awakenings, pediatric asthma-specific quality of life questionnaire, global evaluations, changes in blood eosinophil count, school absences, asthma exacerbations, use of oral corticosteroids, discontinuations due to worsening of asthma, asthma control days	<p>Secondary: A significant improvement in daily use of β_2-agonists was observed in the montelukast group ($P=0.01$).</p> <p>Significant improvements in percentage of days and percentage of patients experiencing asthma exacerbations were reported in the montelukast group ($P=0.049$).</p> <p>A significant improvement in the pediatric asthma-specific quality of life questionnaire was noted in the montelukast group (symptoms; $P=0.007$, activity; $P=0.001$, emotions; $P=0.002$).</p> <p>A significant improvement in parental ($P=0.049$) and combined ($P=0.04$) global evaluations were observed in the montelukast group.</p> <p>A significant improvement in morning clinic-measured PEF was reported in the montelukast group ($P=0.03$).</p> <p>A significant decrease in blood eosinophil levels over eight weeks was observed in the montelukast group ($P=0.02$).</p> <p>Other secondary endpoints did not reach statistical significance because the study was not powered appropriately to detect a difference.</p>
Reiss et al ¹⁸ Montelukast 10 mg Daily in the evening vs placebo The use of ICSs during study was permitted.	DB, MC, PC, PG, RCT Patients 15 to 79 years with chronic stable asthma, FEV ₁ 50 to 85% predicted value, 15% or better improvement of FEV ₁ after β_2 -agonist, minimum level of daytime asthma symptoms, and use of an inhaled β_2 -agonist	N=681 12 weeks	Primary: FEV ₁ percent change from baseline and daytime asthma symptom score Secondary: Morning and evening PEF, daily use of inhaled SABAs, number of nocturnal	<p>Primary: A significant improvement in percent change from baseline in FEV₁ was reported in patients in the montelukast group ($P<0.001$).</p> <p>Secondary: A significant improvement in morning and evening PEF was reported in the montelukast group ($P<0.001$).</p> <p>A significant improvement in daytime asthma symptoms and β_2-agonist use was observed in the montelukast group ($P<0.001$).</p> <p>Improvement in nocturnal awakenings was observed in the montelukast group (P value not reported).</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			<p>awakenings/week, asthma- specific quality of life, global assessment, blood eosinophil count, percentage of days with asthma exacerbation, use of oral corticosteroids, discontinuation due to worsening of asthma, and asthma control days</p>	<p>A significant improvement in asthma specific quality of life questionnaire was reported in the montelukast group ($P \leq 0.001$).</p> <p>A significant improvement in global assessments was observed in the montelukast group ($P < 0.001$).</p> <p>A significant improvement in days without asthma exacerbations and days with asthma control was reported in the montelukast group ($P < 0.001$).</p> <p>A significant improvement in blood eosinophil count was observed in the montelukast group ($P < 0.001$).</p> <p>Remainder of secondary endpoints (use of oral corticosteroids and discontinuation due to worsening of asthma) were not significantly different between the montelukast group and the placebo group.</p>
<p>Suissa et al¹⁹</p> <p>Zafirlukast 20 mg BID</p> <p>vs</p> <p>placebo</p>	<p>DB, MC, PC, RCT</p> <p>Patients 12 years or older, non-smokers in the last 6 months, smoking history of less than 10 pack-years, FEV₁ at least 55% of predicted value, with bronchial hyperresponsiveness and who were symptomatic during the 7 day run-in period of the study</p>	<p>N=146</p> <p>13 weeks</p>	<p>Primary:</p> <p>Days without limitation of activity, days without use of β_2-agonists, days without episodes of asthma, days without sleep disturbance</p> <p>Secondary:</p> <p>Unscheduled health care visits and contacts, total number of β_2-agonist inhalers used, number of prescriptions for non-asthma medications</p>	<p>Primary:</p> <p>Significantly more days without asthma symptoms was observed in the zafirlukast group ($P=0.03$).</p> <p>Significantly more days without β_2-agonist use were observed in the zafirlukast group ($P=0.001$).</p> <p>Significantly more days without episodes of asthma were reported in the zafirlukast group ($P=0.003$).</p> <p>More days without sleep disturbances were reported in the zafirlukast group ($P>0.2$).</p> <p>Secondary:</p> <p>A significant decrease in health care contacts was reported in the zafirlukast group ($P=0.007$).</p> <p>A significant decrease in asthma-related absenteeism was reported in zafirlukast group ($P=0.04$).</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			consumed, number of days absent from work or school	<p>A decrease in canisters of β_2-agonists used was observed in the zafirlukast group ($P=0.17$).</p> <p>A decrease in the use of non-asthma medications was observed in the zafirlukast group ($P>0.2$).</p>
<p>Israel et al²⁰</p> <p>Zileuton 600 mg QID</p> <p>vs</p> <p>zileuton 800 mg BID</p> <p>vs</p> <p>placebo</p>	<p>DB, PC, RCT</p> <p>Patients 18 to 65 years with FEV₁ 40 to 75% of predicted value, a 15% or greater increase in FEV₁ 30 minutes after inhalation of albuterol, and who were not being treated with inhaled or oral corticosteroids</p>	<p>N=139</p> <p>4 weeks</p>	<p>Primary: FEV₁, asthma symptoms, and frequency of β_2-agonist use</p> <p>Secondary: Not reported</p>	<p>Primary: There was a significant (14.6%) increase in FEV₁ within one hour in both zileuton groups compared to baseline ($P<0.001$).</p> <p>There was a significant change in FEV₁ in the zileuton 600 mg group after four weeks compared to placebo ($P=0.02$).</p> <p>There was a significant decrease in asthma symptoms in all three groups ($P<0.01$), but the change was the greatest in the zileuton 600 mg group compared to placebo ($P=0.02$).</p> <p>There was a significant decrease in β_2-agonist use in the zileuton 600 and 800 mg group ($P<0.001$ and $P=0.005$ respectively) from baseline. Compared to placebo, the change was only significant in the 600 mg group ($P=0.03$).</p> <p>Secondary: Not reported</p>
<p>Israel et al²¹</p> <p>Zileuton 600 mg QID</p> <p>vs</p> <p>zileuton 400 mg QID</p> <p>vs</p> <p>placebo</p>	<p>DB, PG, RCT</p> <p>Patients with mild to moderate asthma, FEV₁ 40 to 80% of predicted value, only being treated with inhaled β_2-agonists</p>	<p>N=401</p> <p>13 weeks</p>	<p>Primary: Frequency of asthma exacerbations requiring corticosteroid treatment, use of inhaled β_2-agonists, FEV₁, asthma symptoms, and quality of life evaluations</p>	<p>Primary: There was a significantly lower percentage of patients requiring corticosteroid treatment in the zileuton 600 mg group compared to placebo ($P=0.02$).</p> <p>There was a significant increase in FEV₁ in the zileuton 600 mg group compared to placebo ($P=0.006$).</p> <p>There was a significant improvement in quality of life assessments in the zileuton group compared to the placebo group ($P=0.007$).</p> <p>Secondary: Not reported</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>Nelson et al²²</p> <p>Zileuton CR 1,200 mg BID</p> <p>vs</p> <p>zileuton IR 600 mg QID</p> <p>vs</p> <p>placebo CR</p> <p>or</p> <p>placebo IR</p>	<p>AC, DB, MC, PC, RCT</p> <p>Patients ≥12 years with moderate persistent asthma with an FEV₁ of 40 to 75% of predicted when taken ≥48 hours after the last theophylline use and at least 6 hours after SABA use or 24 hours after LABA use who had not been hospitalized for asthma within 6 months</p>	<p>N=591</p> <p>16 weeks</p>	<p>Secondary: Not reported</p> <p>Primary: Change from baseline in morning trough FEV₁</p> <p>Secondary: Percentage of patients with clinically significant improvement in lung function (≥12% in FEV₁), change from baseline in morning PEFr, reduction in the number of daily puffs of SABA, safety</p>	<p>Primary: At week 12 compared with the placebo CR group the zileuton CR group demonstrated a significant mean improvement in FEV₁ (0.39 L [20.8%] vs 0.27 L [12.7%]; <i>P</i>=0.02). Compared to the placebo IR group the zileuton IR group reported a non significant improvement (0.38 L [19.3%] vs 0.28 L [14.1%]; <i>P</i>=0.19).</p> <p>Secondary: At week 12, 63.2% of the zileuton CR patients showed a 12.0% or greater improvement in FEV₁, compared to 50.0% in the placebo CR group. In the zileuton IR group 45.5% of patients had a 12.0% or great FEV₁ improvement, compared with 27.8% in the placebo IR group (<i>P</i>=0.02). However this was only seen in the IR group at week four.</p> <p>The zileuton CR group reported an increasing mean improvement from baseline morning PEFr from 19.42 L/minute for days two to 22 to 58.45 L/minute for days 72 to 92. The difference between the zileuton CR group and the placebo CR group were not significant (<i>P</i> value not reported). Similar improvements were reported in the zileuton IR treatment group however the values were also not statistically significant.</p> <p>There was a 15.14% reduction from baseline of SABA use in the zileuton CR treatment grouped compared to a 2.29% reduction in the zileuton IR treatment group. The difference between the two groups was significant (<i>P</i>=0.009).</p> <p>The overall incidence of adverse events in the study was similar between all treatment groups (78.4% with zileuton CR, 76.8% with zileuton IR, and 77.3% with placebo IR).</p> <p>The most common adverse events in the zileuton CR group were: exacerbation of asthma, headache, sinusitis, nausea, nasopharyngitis, and pharyngolaryngeal pain. Eight percent more patients in the placebo CR treatment group experienced asthma exacerbation that the zileuton CR</p>

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				<p>group.</p> <p>Five out of 199 patients (2.5%) in the zileuton CR group and one out of 198 patients (0.5%) in the placebo CR group developed ALT level elevations of three times the ULN or greater. The investigators did not attribute the adverse events to the treatment medication.</p> <p>Two of the 97 patients (2.1%) in the zileuton IR group and one of the 97 patients (1.0%) in the placebo IR group developed ALT levels of three times the ULN or greater.</p>
<p>Wenzel et al²³</p> <p>Zileuton 1,200 mg BID plus usual care</p> <p>vs</p> <p>placebo plus usual care</p>	<p>MC, PC, RCT</p> <p>Patients ≥12 years of age, with moderate persistent asthma, with an FEV₁ of ≥40% of predicted when taken at least 48 hours after the last theophylline use, at least 12 hours after the last salmeterol use, and had a ≥15% increase in FEV₁ at least 15 minutes after inhaled albuterol</p>	<p>N=926</p> <p>6 months</p>	<p>Primary: Proportion of patients who experienced an ALT elevation of three times the ULN or greater</p> <p>Secondary: FEV₁, morning and evening PEF, albuterol utilization, hospitalizations, change in quality of life test</p>	<p>Primary: A total of 13 patients in the study experienced an ALT elevation of three times the ULN or greater. Of these patients 11 were in the zileuton CR group and two in the placebo group. Ten of the 11 cases were characteristic of pure hepatocellular injury.</p> <p>Secondary: Mean changes in FEV₁ were 0.17 L for zileuton CR and 0.13 L for placebo (<i>P</i>=0.260).</p> <p>Mean increase in morning PEF was 55.41 L/minute in the zileuton CR treatment group, compared to 30.38 L/minute in the placebo group (<i>P</i>=0.002). The mean increase in evening PEF was 38.98 L/minute in the zileuton CR group, compared to 21.83 L/minute in the placebo group (<i>P</i>=0.031).</p> <p>The number of albuterol puffs/day and occasions for use, was slightly reduced in both treatment groups, however the results were not significant (<i>P</i> values not reported).</p> <p>Sixteen patients in the zileuton group and 10 in the placebo group required an emergency room visit (<i>P</i>=0.408).</p> <p>The overall asthma quality of life score improved by 0.71 in the zileuton group and by 0.57 in the placebo group (<i>P</i>=0.083).</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>Szeffler et al²⁴</p> <p>Montelukast 5 to 10 mg Daily</p> <p>vs</p> <p>fluticasone 100 µg BID</p>	<p>MC, RCT, XO</p> <p>Children 6 to 17 years of age with mild to moderate persistent asthma, asthma symptoms or rescue bronchodilator use on average ≥ 3 days/week for past 4 weeks, reversibility defined as $\geq 12\%$ improvement in FEV₁ after maximum bronchodilation or 20% improvement in FEV₁ after methacholine dose of ≤ 12.5 mg/mL, and FEV₁ 70% of predicted value or greater</p>	<p>N=144</p> <p>16 weeks</p>	<p>Primary: Percent change in pre-bronchodilator FEV₁ from baseline</p> <p>Secondary: Not reported</p>	<p>Primary: A significantly greater percent change in FEV₁ from baseline in the fluticasone group was reported compared to the montelukast group ($P < 0.001$).</p> <p>Seventeen percent of patients responded to both treatments, 23% responded to fluticasone alone, 5% responded to montelukast alone, and 55% responded to neither medication. Children with low pulmonary function or high levels of markers associated with allergic inflammation responded better to the ICS than to montelukast.</p> <p>Secondary: Not reported</p>
<p>Zeiger et al²⁵</p> <p>Montelukast 5 to 10 mg Daily</p> <p>vs</p> <p>fluticasone 100 µg BID</p> <p>This is additional data from the previous study by Szeffler et al¹⁹.</p>	<p>MC, RCT, XO</p> <p>See Szeffler et al¹⁹</p>	<p>N=144</p> <p>16 weeks</p>	<p>Primary: Asthma control days</p> <p>Secondary: Pulmonary function as measured by eNO, FEV₁ and FEV₁/FVC, resistance of the respiratory system at 5 Hz, and area of reactance</p>	<p>Primary: Significant improvements in asthma control days were reported compared to baseline in both groups ($P < 0.001$).</p> <p>A significant improvement in asthma control days in the fluticasone group was reported compared to the montelukast group ($P < 0.001$).</p> <p>Secondary: A significant decrease in eNO in both groups was reported compared to baseline ($P < 0.001$), and the difference between groups was significant, favoring fluticasone ($P = 0.028$).</p> <p>Significant improvements were noted in both groups in FEV₁, FEV₁/FVC, resistance of the respiratory system at 5 Hz, and area of reactance compared to baseline.</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>Garcia et al²⁶</p> <p>Montelukast 5 mg Daily vs fluticasone 100 µg BID</p>	<p>DB, NI, RCT</p> <p>Children 6 to 14 years of age with mild persistent asthma, FEV₁ ≥80% predicted value with β₂-agonist withheld ≥6 hours at least twice in run in period, and FEV₁ or PEF ≥70% predicted value at visit 3</p>	<p>N=994</p> <p>12 months</p>	<p>Primary: Percent of asthma rescue-free days measured as change from baseline</p> <p>Secondary: Percentage change from baseline in predicted FEV₁, percentage of patients requiring anti-asthma medications other than β₂-agonists, percentage of patients with an asthma attack, average percentage of days with β₂-agonist use, change in blood eosinophil count, patient reports of asthma control, patient lost school days, and parental lost work days</p>	<p>Primary: Montelukast was shown to be equivalent to fluticasone in percentage of asthma rescue-free days.</p> <p>Secondary: A significant difference in change from baseline in percentage of predicted FEV₁ favoring fluticasone was observed (<i>P</i>=0.04).</p> <p>No significant difference in change from baseline in FEV₁ between the fluticasone group and montelukast group was observed.</p> <p>There was a significant difference in percentage of β₂-agonist use from baseline in both groups (<i>P</i>≤0.001).</p> <p>A significant decrease in percentage of β₂-agonist use in the fluticasone group was reported compared to the montelukast group (<i>P</i>=0.003). Significantly fewer patients in the fluticasone group used rescue asthma medications, other than β₂-agonists, compared to the montelukast group (<i>P</i> value not reported).</p> <p>Significantly fewer patients in the fluticasone group experienced an asthma attack compared to the montelukast group (<i>P</i> value not reported).</p> <p>There was no significant difference in the proportion of patients experiencing an asthma attack between the fluticasone group and montelukast group when analyzing only the patients who received no systemic corticosteroids during the previous year (<i>P</i> value not reported).</p> <p>A significant improvement in overall quality of life from baseline in both fluticasone and montelukast groups was reported (<i>P</i>≤0.001).</p> <p>A significant decrease in blood eosinophil count was reported in both fluticasone and montelukast groups from baseline (<i>P</i>≤0.001).</p> <p>There was a significant improvement in patient asthma control from baseline in both the fluticasone and montelukast groups (<i>P</i>≤0.001) though</p>

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				<p>between-group comparison favored fluticasone (<i>P</i> value not reported).</p> <p>The proportion of patients with ≥ 1 lost school day during the four weeks preceding the 12 month visit was 8.8% in the montelukast group and 6.2% in the fluticasone group. The percentage of patients who lost >3 school days was 1.9% in the montelukast group and 2.1% in the fluticasone group. A ≥ 1 lost work day was reported in parents of 2.9% of montelukast patients and 2.0% of fluticasone patients during the four weeks prior to the 12 month visit, and the percentage whose parents lost >3 work days were reported as 0.4% in the montelukast group and 0.2% in the fluticasone group. The significance of these differences was not reported.</p>
<p>Busse et al²⁷</p> <p>Montelukast 10 mg Daily</p> <p>vs</p> <p>fluticasone 44 μg BID</p>	<p>DB, DD, PG, RCT</p> <p>Patients 15 to 83 years diagnosed with asthma for at least 6 months, pre-bronchodilator FEV₁ between 50 to 80% of predicted value, increase in FEV₁ of 15% or greater after β_2-agonist use, regular or as-needed use of inhaled or oral β_2-agonist in the 3 months prior to screening</p>	<p>N=533</p> <p>24 weeks</p>	<p>Primary: Mean percentage change from baseline in morning pre-medication FEV₁</p> <p>Secondary: Mean change in FVC, FEF_{25%-75%}, morning and evening PEF, percentage of symptom-free days, asthma symptom scores, nighttime awakenings, daily rescue albuterol use, percentage of rescue-free days, physicians' global assessment of effectiveness, asthma quality of life questionnaire, patient-rated</p>	<p>Primary: A significantly greater improvement in FEV₁ in the fluticasone group was reported compared to the montelukast group (<i>P</i>\leq0.002).</p> <p>Secondary: A significantly greater improvement in all spirometric values in the fluticasone group was reported compared to the montelukast group (<i>P</i>\leq0.002).</p> <p>A significant improvement in asthma symptom-free days in the fluticasone group was reported compared to the montelukast group (<i>P</i><0.001).</p> <p>A significant improvement in asthma symptom scores in the fluticasone group was observed compared to the montelukast group (<i>P</i><0.001).</p> <p>A significant improvement in nighttime awakenings in the fluticasone group was observed compared to the montelukast group (<i>P</i>=0.023).</p> <p>A significant improvement in rescue albuterol use in the fluticasone group was observed compared to the montelukast group (<i>P</i><0.001).</p> <p>The physician's global assessment significantly favored fluticasone compared to montelukast (<i>P</i><0.001).</p> <p>Significantly greater improvements noted on the asthma quality of life</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			satisfaction with treatment	questionnaire in the fluticasone group compared to the montelukast group ($P \leq 0.001$). Patient-rated satisfaction with treatment significantly favored the fluticasone group compared to the montelukast group ($P < 0.001$).
<p>Yildirim et al²⁸</p> <p>Montelukast 10 mg Daily and budesonide 400 µg daily</p> <p>vs</p> <p>budesonide 800 µg daily</p>	<p>PG, RCT</p> <p>Patients with moderate persistent asthma for minimum of 6 months admitted into the Department of Chest Diseases in Trabzon, Turkey</p>	<p>N=30</p> <p>6 weeks</p>	<p>Primary: Morning, daytime, and evening asthma symptoms, morning and evening PEF, FEV₁, blood eosinophil counts, frequency of SABA use, frequency of asthma exacerbations</p> <p>Secondary: Not reported</p>	<p>Primary: A significant decrease in morning and daytime symptom scores was reported in both groups compared to baseline scores ($P < 0.05$), but no significant differences between the two groups were noted.</p> <p>No significant difference in evening symptom scores was reported in either group compared to baseline.</p> <p>No significant differences in FEV₁ or PEF values from baseline or between groups were reported.</p> <p>A significant decrease in blood eosinophil counts in both groups when compared to baseline ($P < 0.05$) was reported but there was no significant difference between the two groups.</p> <p>There was a significant decrease in beta-agonist use in the budesonide plus montelukast group compared to baseline ($P < 0.05$), but there was no significant difference in β_2-agonist use in the budesonide group compared to baseline.</p> <p>No patients in either group experienced an asthma exacerbation during the study period.</p> <p>Secondary: Not reported</p>
<p>Price et al²⁹</p> <p>Montelukast 10 mg Daily and budesonide 800 µg daily</p>	<p>DB, NI, PG, RCT</p> <p>Patients 15 to 75 years of age diagnosed with asthma not optimally controlled on regular</p>	<p>N=889</p> <p>12 weeks</p>	<p>Primary: Morning PEF values</p> <p>Secondary: Initial treatment effect on PEF (days</p>	<p>Primary: A significant improvement in morning PEF compared to baseline for both groups was reported ($P < 0.001$) but differences between groups were insignificant at the end of the study.</p> <p>Secondary:</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs budesonide 1,600 µg daily	ICS		one to three), daily self-reported β ₂ -agonist use, daytime symptoms, nocturnal awakenings, asthma exacerbations, asthma-free days, blood eosinophil counts, asthma specific quality of life	The change from baseline in PEF during the first three days of treatment was significantly more rapid in the montelukast plus budesonide group compared to the budesonide group alone (<i>P</i> <0.001). All other secondary endpoints were not significantly different from baseline or between groups.
Fish et al ³⁰ Montelukast 10 mg Daily vs salmeterol 50 µg BID	DB, DD, MC, PG, RCT Patients ≥15 years of age diagnosed with asthma remaining symptomatic despite therapy with a stable dose of ICS for the previous 30 days	N=948 12 weeks	Primary: Morning PEF values Secondary: Evening PEF, daytime asthma symptom score, supplemental albuterol use, nighttime awakenings	Primary: Significant increases in morning PEF in the salmeterol group were observed compared to the montelukast group (<i>P</i> <0.001). Secondary: A significant decrease in symptom scores in the salmeterol group was reported compared to the montelukast group (<i>P</i> =0.039). A significant decrease in supplemental albuterol use in the salmeterol group was reported compared to the montelukast group (<i>P</i> ≤0.012). Significantly greater reductions in nighttime awakenings in the salmeterol group were reported compared to the montelukast group (<i>P</i> =0.015).
Bjermer et al ³¹ Montelukast 10 mg Daily and fluticasone 100 µg BID vs fluticasone propionate 100 µg BID and salmeterol 50 µg BID	DB, DD, MC, PG, RCT Patients 15 to 72 years of age with chronic asthma ≥1 year, baseline FEV ₁ 50 to 90% predicted value, improvement of 12% or more in FEV ₁ or in morning PEF after β ₂ -agonist use, regular use of ICS for at least 8	N=1,490 52 weeks	Primary: Percentage of patients with at least one asthma exacerbation Secondary: Asthma specific quality of life, nocturnal awakenings, mean FEV ₁ before and	Primary: No significant difference between the two groups in percentage of patients with at least one asthma attack was reported. Secondary: A significant improvement in asthma specific quality of life compared to baseline in both groups was reported (<i>P</i> ≤0.001), though there was no significant difference between the two groups. A significant decrease in nocturnal awakenings from baseline in both groups was reported (<i>P</i> ≤0.001), though there was no significant difference between the two groups.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	weeks prior to study, average β_2 -agonist use of at least 1 puff/day		after β_2 -agonist use, mean morning PEF, time to first asthma exacerbation, blood eosinophil counts	<p>A significant improvement in FEV₁ before β_2-agonist use in the salmeterol and fluticasone group was observed compared to the montelukast and fluticasone group ($P \leq 0.001$), though the improvement in FEV₁ after β_2-agonist use was similar between the two groups.</p> <p>A significantly larger increase in morning PEF in the salmeterol and fluticasone group was reported compared to the montelukast and fluticasone group ($P \leq 0.001$), though both groups significantly improved morning PEF values from baseline ($P \leq 0.001$).</p> <p>No significant differences between the groups regarding time to first asthma exacerbation were observed.</p> <p>A significant decrease in blood eosinophils in the montelukast and fluticasone group was reported compared to the salmeterol and fluticasone group ($P = 0.011$).</p>
<p>Calhoun et al³²</p> <p>Montelukast 10 mg Daily</p> <p>vs</p> <p>fluticasone/salmeterol 100/50 μg BID</p>	<p>DB, DD, MC, RCT</p> <p>Patients 15 to 72 years diagnosed with asthma for at least 6 months and had been treated with oral or inhaled β_2-agonists for at least 6 weeks prior to study, FEV₁ values of between 50 to 80% of predicted value, and an increase in FEV₁ of at least 12% within 30 minutes of inhaled albuterol</p>	<p>N=423</p> <p>12 weeks</p>	<p>Primary: Change from baseline in pre-dose FEV₁ values</p> <p>Secondary: Morning and evening PEF values, asthma symptom score, percentage of symptom-free days, β_2-agonist use, percentage of rescue-free days, percent of nights with no asthma-related awakenings, percentage of nights with no asthma-</p>	<p>Primary: A statistically significant improvement in the percent change from baseline in FEV₁ in the fluticasone/salmeterol group was observed compared to the montelukast group ($P \leq 0.001$).</p> <p>Secondary: A statistically significant improvement in all secondary endpoints for the fluticasone/salmeterol group was observed compared to the montelukast group ($P \leq 0.001$).</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			related awakenings in patients with ≥ 2 awakenings/week at baseline, and nights/week with no awakenings	
<p>Maspero et al³³</p> <p>Montelukast 5 mg Daily vs fluticasone/salmeterol 100/50 µg BID</p>	<p>DB, DD, MC, PG, RCT</p> <p>Patients 6 to 14 years of age, with a diagnosis of asthma for ≥ 6 months, a FEV₁ between 55 to 80% of predicated normal, and $\geq 12\%$ FEV₁ reversibility, and were not on any asthma control medications except for a SABA</p>	<p>N=548</p> <p>12 weeks</p>	<p>Primary: Morning PEF values</p> <p>Secondary: FEV₁, evening PEF values, levels of symptoms and rescue medications, assessment of asthma control, asthma exacerbations, and safety</p>	<p>Primary: The mean change from baseline in morning PEF was 45.8 L/minute in the fluticasone/salmeterol group, and 28.7 L/minute in the montelukast group ($P < 0.001$).</p> <p>Secondary: The mean change from baseline in evening PEF was 46.2 L/minute in the fluticasone/salmeterol group, and 28.0 L/minute in the montelukast group ($P < 0.001$).</p> <p>The mean change from baseline in FEV₁ was 0.47 L in the fluticasone/salmeterol group, and 0.30 L in the montelukast group ($P < 0.001$).</p> <p>The fluticasone/salmeterol group had significantly greater improvements in percentage of symptom free ($P = 0.025$) and rescue free ($P < 0.001$) 24-hour periods compared with the montelukast group.</p> <p>Asthma control was higher in the fluticasone/salmeterol group (88.3%) than in the montelukast group (66.7%; $P < 0.001$).</p> <p>Twice as many patients in the montelukast group (23.2%) had asthma exacerbations than in the fluticasone/salmeterol group (10.3%).</p> <p>Fifty five percent of patients in the fluticasone/salmeterol group and 57% in the montelukast group reported an adverse event during treatment. The most common adverse event reported in both groups was headache (23% in the fluticasone/salmeterol group, and 27% in the montelukast group).</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>Sorkness et al³⁴</p> <p>Montelukast 5 mg Daily at bedtime</p> <p>vs</p> <p>fluticasone 100 µg BID</p> <p>vs</p> <p>fluticasone/salmeterol 100/50 µg Daily in the morning and salmeterol 50 µg Daily at bedtime</p> <p>vs</p> <p>placebo</p>	<p>DB, RCT</p> <p>Children ages 6 to 14 years of age with mild-moderate persistent asthma, with an FEV₁ of ≥80% predicted normal at screening and ≥70% predicted normal at randomization</p>	<p>N=285</p> <p>48 weeks</p>	<p>Primary: The percent of asthma control days</p> <p>Secondary: Percent of episode-free days, time to first exacerbation requiring prednisone, time to treatment failure, number of treatment failures, ACQ score, FEV₁%, FEV₁/FVC, morning and evening PEF, and growth</p>	<p>Primary: The percent of asthma control days were 64.2% for the fluticasone monotherapy group, 59.6% for the fluticasone/salmeterol group, and 52.5% for the montelukast group. The difference between the fluticasone monotherapy and the montelukast group was significant (<i>P</i>=0.004). The difference between the fluticasone/salmeterol group and montelukast was not significant (<i>P</i>=0.08).</p> <p>Secondary: The percent of episode-free days were 26.4% in the fluticasone group, 26.8% in the fluticasone/salmeterol group, and 17.8% in the montelukast group. The differences were significant between the fluticasone group and the montelukast group (<i>P</i>=0.040), and between the fluticasone/salmeterol and montelukast groups (<i>P</i>=0.032).</p> <p>Kaplan-Meier survival curves showed significant “superiority” of fluticasone compared with montelukast monotherapies in favor of fluticasone in both time to first exacerbation requiring prednisone (<i>P</i>=0.002) and time to treatment failure (<i>P</i>=0.015).</p> <p>Twenty eight total treatment failures occurred, five with fluticasone, eight with fluticasone/salmeterol, and 15 with montelukast. The difference between fluticasone monotherapy and montelukast was significant (<i>P</i>=0.04).</p> <p>ACQ score improved by -0.69 in the fluticasone monotherapy group, -0.55 in the fluticasone/salmeterol group, and by -0.45 in the montelukast group. There was no significant difference between the fluticasone monotherapy and fluticasone plus salmeterol therapy in ACQ score improvement, however the difference between fluticasone monotherapy and montelukast was significant (<i>P</i>=0.018).</p> <p>The mean change in FEV₁ was 6.32% with fluticasone monotherapy, 3.62% with fluticasone/salmeterol, and -0.58% with montelukast. The differences were significant between both the fluticasone monotherapy (<i>P</i><0.001) and fluticasone/salmeterol (<i>P</i>=0.010) therapy when compared to montelukast.</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				<p>The mean change for FEV₁/FVC was 3.95% for the fluticasone monotherapy group, 1.76% for the fluticasone/salmeterol group, and 0.07% for the montelukast group. The difference was significant between the fluticasone monotherapy group and montelukast ($P<0.001$).</p> <p>Morning PEF values improved by 5.18% in the fluticasone monotherapy group, 5.33% in the fluticasone/salmeterol group, and by 0.65% in the montelukast group. The differences were significant between both the fluticasone monotherapy ($P=0.002$) and fluticasone/salmeterol ($P=0.001$) therapy when compared to montelukast.</p> <p>Evening PEF values improved by 2.95% in the fluticasone monotherapy group, 4.31% in the fluticasone/salmeterol group, and worsened by -0.57% in the montelukast group. The differences were significant between both the fluticasone monotherapy ($P=0.017$) and fluticasone/salmeterol ($P<0.001$) therapy when compared to montelukast.</p> <p>The mean increase height from baseline was 5.3 cm with fluticasone monotherapy and fluticasone/salmeterol. The increase in height was 5.7 cm in the montelukast group however the differences did not reach significance ($P<0.001$) for both groups compared to montelukast.</p>
<p>Lemanske et al³⁵ (BADGER)</p> <p>Montelukast 5 or 10 mg Daily plus fluticasone propionate 100 µg BID (LTRA step-up therapy)</p> <p>vs</p> <p>fluticasone/salmeterol 100/50 µg BID (LABA step-up therapy)</p>	<p>DB, RCT, XO</p> <p>Children 6 to 17 years of age with mild to moderate asthma uncontrolled while receiving fluticasone 100 µg BID</p>	<p>N=182</p> <p>48 weeks (three 16-week periods)</p>	<p>Primary: Differential response to each of the three step-up therapies based on control measures including requirement of oral prednisone for acute exacerbations, number of asthma control days, FEV₁</p> <p>Secondary: Not reported</p>	<p>Primary: The response to LABA step-up therapy was significantly more likely to be the best response as compared to the response to LTRA step-up and ICS step-up therapy ($P=0.004$ and $P=0.002$ respectively).</p> <p>Secondary: Not reported</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs fluticasone 250 µg BID (ICS step-up therapy)				
Busse et al ³⁶ Zafirlukast 20 mg BID vs salmeterol 42 µg BID	DB, DD, MC, PG, RCT Patients 12 to 73 years with a diagnosis of asthma for at least 6 months; after the run-in period, patients were required to have FEV ₁ values of 50 to 70% predicted value with or without symptoms, or FEV ₁ values of 70.1 to 80.0% predicted value with one or more of the following criteria: average of ≥4 puffs/day of albuterol, symptom score ≥2 in any asthma symptom category on ≥2 days, ≥1 nighttime awakening due to asthma, or ≥2 days when evening to morning PEF values differed by ≥20%	N=289 4 weeks	Primary: Morning PEF values Secondary: Evening PEF values, asthma symptom scores, supplemental albuterol use, nighttime awakenings, FEV ₁ , and asthma exacerbations	Primary: A statistically significant improvement in morning PEF values in the salmeterol group was reported compared to the zafirlukast group ($P=0.001$). Secondary: A statistically significant improvement in evening PEF values in the salmeterol group was reported compared to the zafirlukast group ($P=0.019$). Statistically significant improvements in asthma symptom scores in the salmeterol group were reported compared to the zafirlukast group ($P\leq 0.026$). A statistically significant decrease in daytime and nighttime supplemental albuterol use in the salmeterol group was noted compared to the zafirlukast group ($P=0.004$ and $P=0.013$ respectively). No statistically significant difference in nighttime awakenings between the two groups was reported ($P=0.142$). A statistically significant improvement in FEV ₁ compared to baseline in both groups was reported ($P<0.001$), but no statistically significant difference between groups at the end of the treatment period was observed ($P=0.293$). Seven patients in the salmeterol group and nine patients in the zafirlukast group experienced asthma exacerbations during the treatment period (P values not reported).
Wilson et al ³⁷ Montelukast or	CE Patients 12 to 80 years	N=326 24 months	Primary: MiniAQLQ, ACQ, HR-QOL instrument	Primary: Resource use was similar between treatment groups.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
zafirlukast (doses not specified) (LTRA Group) vs beclomethasone or fluticasone (doses not specified) (ICS Group)	of age with symptoms of asthma not controlled with a short-acting β_2 -agonist and requiring initiation of regular controller therapy		(EQ-5D), resource use and costs Secondary: Not reported	The cost to society was significantly higher in the LTRA group compared to the ICS group (adjusted difference, £204; 95% CI, 74 to 308). A non-significant difference in QALYs favoring ICS was observed between the groups at 24 months. Secondary: Not reported
Wilson et al ³⁸ Montelukast 10 mg Daily or zafirlukast 20 mg BID (LTRA Group) vs salmeterol or formoterol or fluticasone/salmeterol or budesonide/formoterol (doses not specified) (ICS Group)	CE Patients 12 to 80 years of age with asthma insufficiently controlled with ICS	N=361 24 months	Primary: MiniAQLQ, ACQ, HR-QOL instrument (EQ-5D), resource use and costs Secondary: Not reported	Primary: The cost to society was significantly higher in the LTRA group compared to the ICS group (adjusted difference, £214; 95% CI, 2 to 411). Patients receiving LTRAs experienced a non-significant incremental gain of 0.009 QALYs (95% CI, -0.077 to 0.103). Secondary: Not reported
Ducharme et al ³⁹ Montelukast 10 mg Daily or zafirlukast 20 mg BID (LTRA and ICS group) vs salmeterol 50 μ g BID or formoterol 12 μ g BID or fluticasone/salmeterol (varying doses) or	MA Children or adults with recurrent or persistent asthma	N=6,030 Varying duration (4 to 48 weeks)	Primary: Number of patients with asthma exacerbations requiring short-term courses of systemic corticosteroids Secondary: Severity of exacerbations, changes in pulmonary function	Primary: The risk of having an exacerbation requiring systemic corticosteroids was 17% lower with the use of LABA and ICS compared to LTRA and ICS (RR, 0.83; 95% CI, 0.71 to 0.97). The type of LTRA used did not affect the primary outcome. The effect of children vs adults could not be evaluated. Secondary: Overall, LABA and ICS significantly improved morning PEF compared to LTRA and ICS (WMD, 15.66 L/minute; 95% CI, 13.21 to 18.11).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>fluticasone plus salmeterol (varying doses) (LABA and ICS Group)</p> <p>All participants remained on a stable dose of ICS of average 400 to 560 µg/day of beclomethasone or equivalent.</p> <p>Other long-term control medications were allowed provided the dose remained stable during the intervention.</p>			<p>tests, symptom scores, days and/or nights without symptoms, quality of life, use of rescue inhalers, patient satisfaction, changes in measures of inflammation, adverse effects, withdrawal rates</p>	<p>Overall, LABA and ICS significantly improved evening PEF compared to LTRA and ICS (WMD, 12.09 L/minute; 95% CI, 9.26 to 14.92).</p> <p>The combined overall estimate for improvement in FEV₁ was significantly in favor of LABA and ICS compared to LTRA and ICS (WMD, 0.08 L; 95% CI, 0.06 to 0.10).</p> <p>One study reported a significant percent change from baseline in FEV₁ in favor of LTRA and ICS in 40 patients.</p> <p>The combined overall estimate for percent of rescue free days showed a significant difference in favor of LABA and ICS compared to LTRA and ICS (WMD, 8.96%; 95% CI, 4.39 to 13.53) but there was significant heterogeneity in the pooled estimate.</p> <p>The combined overall estimate showed a significant improvement in the global asthma quality of life with LABA and ICS (WMD, 0.11; 95% CI, 0.05 to 0.17).</p> <p>The combined overall estimate showed a significant increase in percentage of symptom free days in favor LABA and ICS (WMD, 6.75%; 95% CI, 3.11 to 10.39). There was significant heterogeneity observed in the montelukast group.</p> <p>One study reported improvement in nighttime symptom score with LABA and ICS compared to LTRA and ICS (N=429).</p> <p>Overall combined improvement in daytime symptoms score favored LABA and ICS (SMD, -0.18; 95% CI, -0.25 to -0.12).</p> <p>The combined overall estimate was in favor of less awakenings with LABA and ICS (WMD, -0.12; 95% CI, -0.19 to -0.06).</p> <p>One study evaluated change in percentage of rescue free nights and no significant difference between groups was observed.</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				<p>The overall estimate showed a significant reduction in the risk of withdrawal with LABA and ICS (RR, 0.93; 95% CI, 0.73 to 0.95).</p> <p>The overall estimate showed no significant difference between groups on the risk of withdrawal due to an adverse event (RR, 1.02; 95% CI, 0.80 to 1.32).</p> <p>The overall estimate showed no significant difference between groups on the risk of withdrawal due to poor asthma control or exacerbation (RR, 0.87; 95% CI, 0.49 to 1.56). Heterogeneity was present.</p> <p>No significant difference was observed between groups in patients with one or more exacerbations requiring hospitalizations (RR, 1.31; 95% CI, 0.58 to 2.98).</p>
Allergic Rhinitis				
<p>Cingi et al⁴⁰</p> <p>Montelukast 10 mg Daily</p> <p>vs</p> <p>placebo</p>	<p>DB, PC, RCT</p> <p>Patients with persistent allergic rhinitis</p>	<p>N=78</p> <p>1 month</p>	<p>Primary: RQLQ</p> <p>Secondary: Not reported</p>	<p>Primary: A significant improvement in the RQLQ was observed in the montelukast group compared to the placebo group ($P<0.001$).</p> <p>A significant improvement in the RQLQ compared to baseline was observed in both the montelukast group and the placebo group ($P<0.001$).</p> <p>The difference in change from baseline to the end of the first month was significant in favor of the montelukast group for sleep, practical problems, nasal problems, and activities that had been limited by nose or eye symptoms and for overall score ($P<0.001$).</p> <p>Secondary: Not reported</p>
<p>Li et al⁴¹</p> <p>Montelukast 5 or 10 mg Daily</p> <p>vs</p>	<p>DB, PC, RCT</p> <p>Patients 6 to 18 years of age with persistent allergic rhinitis for at least 2 years not previously treated with</p>	<p>N=44</p> <p>26 weeks (2 week run-in, 16 week treatment phase and 8</p>	<p>Primary: Composite nasal symptom score</p> <p>Secondary: Adenoidal size, nasal and blood</p>	<p>Primary: Significant between-group differences were observed in daytime sneezing score, nighttime sneezing score, and daytime composite score at week four of treatment ($P\leq 0.013$).*</p> <p>Eventually patients in the placebo group would experience symptom relief but this took a longer time when compared to the montelukast group.</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>placebo</p> <p>All patients were also administered fexofenadine 60 or 120 mg Daily.</p>	LTRAs	weeks of follow-up)	cytokine levels	<p>No significant differences were observed between groups during the follow-up period.</p> <p>Secondary: No significant differences were observed between groups.</p>
<p>Esteitie et al⁴²</p> <p>Montelukast 10 mg Daily</p> <p>vs</p> <p>placebo</p> <p>All patients were also administered fluticasone nasal spray 200 µg daily.</p>	<p>DB, PC, RCT</p> <p>Patients 18 to 55 years of age with symptoms of PAR</p>	<p>N=54</p> <p>4 weeks</p>	<p>Primary: RQLQ, nasal symptoms</p> <p>Secondary: Not reported</p>	<p>Primary: No significant differences were observed between groups in RQLQ or nasal symptoms.</p> <p>Secondary: Not reported</p>
<p>Pullerits et al⁴³</p> <p>Montelukast 10 mg Daily</p> <p>vs</p> <p>fluticasone nasal spray 200 µg Daily</p> <p>vs</p> <p>montelukast 10 mg Daily and loratadine 10 mg Daily</p> <p>vs</p>	<p>DB, DD, PC, PG, RCT</p> <p>Patients 15 to 50 years with a diagnosis of allergic rhinitis during the grass pollen season for at least the 2 previous years</p>	<p>N=62</p> <p>50 days</p>	<p>Primary: Daytime and nighttime nasal symptom score as reported by patient (analysis divided into three periods: weeks one to two [period 1], weeks three to five [period 2], and week six to end of study [period 3])</p> <p>Secondary: EG²⁺ eosinophilic inflammation</p>	<p>Primary: No statistically significant differences were noted in any of the primary endpoints between montelukast monotherapy and placebo.</p> <p>A significant decrease in the development of nasal allergy symptoms in both the fluticasone and the montelukast and loratadine groups compared to placebo during all three treatment periods for daytime symptoms was reported for period 1 (fluticasone; <i>P</i>=0.003, montelukast and loratadine; <i>P</i>=0.04), period 2 (fluticasone; <i>P</i>=0.001, montelukast and loratadine; <i>P</i>=0.04) and period 3 (fluticasone; <i>P</i><0.001, montelukast and loratadine; <i>P</i><0.001).</p> <p>No statistically significant differences in the fluticasone group and the montelukast and loratadine group in daytime nasal symptom scores were reported.</p> <p>A statistically significant decrease in development of nasal symptoms in the</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
placebo				<p>fluticasone group was reported compared to the montelukast monotherapy group ($P=0.046$).</p> <p>A statistically significant decrease in the development of nasal symptoms in the montelukast monotherapy group was observed compared to the placebo group ($P=0.03$).</p> <p>Significantly lower symptom scores in the fluticasone group was observed compared to the placebo group in all periods ($P=0.02$, $P=0.002$, and $P<0.001$ respectively).</p> <p>Significantly lower symptom scores in the fluticasone group were reported compared with the montelukast plus loratadine group during peak season in period 2 ($P=0.04$).</p> <p>Significantly lower symptom scores in the fluticasone group compared to the montelukast monotherapy group during periods 2 and 3 were observed ($P=0.01$).</p> <p>Significantly lower symptom scores in the montelukast plus loratadine group compared to the placebo during period 3 were reported ($P=0.02$).</p> <p>Secondary: A statistically significant increase in EG^{2+} eosinophils in the placebo, montelukast monotherapy, and montelukast plus loratadine groups was observed ($P<0.01$ for all groups).</p> <p>There was no significant increase in EG^{2+} eosinophils in the fluticasone group ($P=0.2$).</p>
<p>Baena-Cagnani et al⁴⁴</p> <p>Montelukast 10 mg Daily</p> <p>vs</p>	<p>DB, PC, RCT</p> <p>Patients 15 to 75 years diagnosed with seasonal allergic rhinitis for at least 2 years, clinical</p>	<p>N=924</p> <p>4 weeks</p>	<p>Primary: Total asthma symptom score, individual asthma symptom scores, FEV₁, PEF values, and use of β_2-</p>	<p>Primary: A statistically significant reduction in the total asthma symptom scores in both the montelukast and desloratadine groups compared with placebo was observed ($P\leq 0.05$).</p> <p>No statistically significant differences between montelukast and desloratadine group were noted at any time during the study for total</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
desloratadine 5 mg Daily vs placebo	symptoms of seasonal allergic rhinitis at screening, FEV ₁ ≥70% predicted value, asthma controlled with as-needed bronchodilators only, increase in FEV ₁ of at least 12% following bronchodilator use, greater than weekly but no daily asthma symptoms and/or bronchodilator use, positive skin test for seasonal allergen		agonists Secondary: Not reported	asthma symptom scores. A statistically significant reduction in individual symptom scores in both the montelukast and desloratadine groups compared to placebo was reported (<i>P</i> <0.05). No statistically significant differences between montelukast and desloratadine group were noted at any time during the study for individual asthma symptom scores. A statistically significant increase in FEV ₁ in both the montelukast and desloratadine groups was reported compared to placebo (<i>P</i> <0.01 and <i>P</i> <0.05 respectively). There was no statistically significant difference between the montelukast and desloratadine groups at any time. Secondary: Not reported
Saengpanich et al ⁴⁵ Montelukast 10 mg Daily and loratadine 10 mg Daily vs fluticasone nasal spray 200 µg daily	DB, DD, PG, RCT Patients 21 to 54 years of age with history of sensitivity to ragweed pollen for last 2 years, and had a positive skin test to ragweed pollen	N=63 2 weeks	Primary: Rhino-conjunctivitis Quality of Life Questionnaire, daily nasal symptom scores, number of eosinophils, and level of ECP found in nasal lavage fluids Secondary: Not reported	Primary: A statistically significant improvement in questionnaire answers in both the fluticasone and montelukast and loratadine groups was observed (<i>P</i> <0.01). A statistically significant reduction in nasal symptoms on the questionnaire in the fluticasone group compared to montelukast and loratadine group was observed (<i>P</i> =0.05). There was no statistically significant decrease in daily nasal symptom scores in either the fluticasone or montelukast and loratadine groups, though both did decrease from baseline. There was a statistically significant decrease in number of eosinophils in nasal lavage in the fluticasone group compared to baseline (<i>P</i> =0.05), though no significant decrease in the montelukast and loratadine group compared to baseline. When compared between groups, this was not statistically significant.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				<p>A statistically significant decrease in ECP from baseline ($P=0.009$) and between groups ($P=0.04$) favoring fluticasone was observed.</p> <p>Secondary: Not reported</p>
<p>Meltzer et al⁴⁶</p> <p>Montelukast 10 mg Daily</p> <p>vs</p> <p>montelukast 20 mg Daily</p> <p>vs</p> <p>loratadine 10 mg Daily</p> <p>vs</p> <p>montelukast 10 mg Daily and loratadine 10 mg Daily</p> <p>vs</p> <p>placebo</p>	<p>DB, MC, PC, PG, RCT</p> <p>Patients 15 to 75 years of age diagnosed with spring seasonal allergic rhinitis for 2 years, positive skin test for at least 1 of 8 allergens including oak, grass, elm, olive, walnut, and sycamore</p>	<p>N=460</p> <p>2 weeks</p>	<p>Primary: Daytime nasal symptoms score</p> <p>Secondary: Eye symptoms, nighttime symptoms, individual daytime symptoms, global evaluations, and rhinoconjunctivitis quality of life scores</p>	<p>Primary: A statistically significant improvement in daytime nasal symptom scores in the montelukast and loratadine group compared to placebo and to either agent alone was observed ($P<0.001$).</p> <p>A statistically significant improvement in all secondary endpoints in the montelukast plus loratadine group was reported compared to placebo ($P<0.05$).</p> <p>There was no statistically significant difference in the primary endpoint between montelukast or loratadine monotherapy groups compared to placebo.</p> <p>Secondary: A statistically significant improvement in rhinoconjunctivitis quality of life was reported in the montelukast 10 mg and loratadine group compared to placebo ($P<0.05$).</p> <p>A statistically significant improvement in daytime eye symptom score, nighttime symptom score, and composite daytime and nighttime symptom score was reported in the montelukast 10 mg monotherapy group compared to placebo ($P<0.05$).</p>
<p>Mucha et al⁴⁷</p> <p>Montelukast 10 mg Daily</p> <p>vs</p>	<p>DB, PG, RCT</p> <p>Patients 18 to 45 years of age with a diagnosis of allergic rhinitis during the ragweed season and a positive skin test</p>	<p>N=58</p> <p>2 weeks</p>	<p>Primary: Nasal symptoms, NPIF, quality of life scores, and tolerability profiles</p> <p>Secondary:</p>	<p>Primary: A statistically significant improvement in all primary outcome measures in both groups compared to baseline values ($P<0.05$) was observed.</p> <p>A statistically significant improvement was reported in nasal congestion in the pseudoephedrine group compared to the montelukast group ($P=0.01$).</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
pseudoephedrine 240 mg daily	to ragweed antigen extract		Not reported	Secondary: Not reported

*Level of significance adjusted to $P < 0.016$.

Study abbreviations: AC=active control, CE=cost effectiveness, DB=double-blind, DD=double-dummy, MA=meta-analysis, MC=multi-center, NI=non-inferiority, OL=open label, OS=observational study, PC=placebo-controlled, PG=parallel-group, PRO=prospective, RCT=randomized controlled trial, XO=crossover

Miscellaneous abbreviations: ACQ=Asthma Control Questionnaire, ACT=asthma control test, ALT=alanine aminotransferase, BID=twice daily, CI=confidence interval, CR=controlled release, ECP=eosinophil cationic protein, EG₂₊=mediator released by eosinophils in response to stimuli, eNO=exhaled nitric oxide, FEF_{25%-75%}=forced mid-expiratory flow, FEV₁=forced expiratory flow in 1 second, FVC=forced vital capacity, HR-QOL=Health-related quality of life, Hz=hertz, ICS=inhaled corticosteroid, IR=immediate release, LABA=long acting beta agonist, LTM=leukotriene modifier, LTRA=leukotriene receptor antagonist, Mini-AQLQ=Mini-Asthma Quality-of-Life Questionnaire, NPIF=nasal peak inspiratory flow, PAR=perennial allergic rhinitis, PEF=peak expiratory flow, PEFR=peak expiratory flow rate, QALY=quality adjusted life year, QID=four times a day, RQLQ=Rhinitis Quality of Life Questionnaire, RR=relative risk, SABA=short acting beta agonist, SMD=standardized mean difference, ULN=upper limit of normal, WMD=weighted mean difference

Special Populations

Table 5. Special Populations^{1,2,4-9,14}

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Montelukast	No dosage adjustment required in the elderly population. Approved for use in children ages 12 months and older for asthma, 15 years and older for exercise induced bronchospasm, two years and older for seasonal allergic rhinitis, and six months and older for perennial allergic rhinitis.	No dosage adjustment required.	No dosage adjustment is required in patients with mild-to-moderate hepatic insufficiency. Studies have not been conducted in patient with severe hepatic disease.	B	Unknown if excreted in human milk.
Zafirlukast	No dosage adjustment required in the elderly population. Approved for use in children ages five and older.	No dosage adjustment required.	Clearance is reduced in patients with alcoholic cirrhosis. It has not been evaluated in patients with hepatitis or in long-term studies of patients with cirrhosis.	B	Yes (% not reported)
Zileuton	No dosage adjustment required in the elderly population. Approved for use in children ages 12 and older.	No dosage adjustment required.	Contraindicated in patients with active liver disease and in patients with elevated hepatic function enzymes greater than or equal to three times the upper limit of normal.	C	Unknown if excreted in breast milk.

Adverse Drug Events

Table 6 summarizes the most common adverse events associated with the use of leukotriene modifiers. The leukotriene modifiers are generally well-tolerated with headache, nausea, upper respiratory infections, dyspepsia, abdominal pain, influenza and sinusitis reported as the most common adverse effects.^{1,2,4,5}

Table 6. Adverse Drug Events^{1,2,4-8}

Adverse Event(s)	Montelukast	Zafirlukast	Zileuton
Cardiovascular System			
Chest pain	-	-	>1
Palpitations	✓	-	-
Central Nervous System			
Agitation	✓	-	-
Anxiousness	✓	-	-
Depression	✓	<1	-
Disorientation	✓	-	-
Dizziness	1.9	1.6 to 2.0	>1
Dream abnormalities	✓	-	-
Hallucinations	✓	-	-
Headache	18.4	4.5 to 13.0	23.0 to 24.6
Insomnia	-	<1	>1
Irritability	✓	-	-
Nervousness	-	-	>1
Paresthesia	✓	-	-
Restlessness	✓	-	-
Seizures	✓	-	-
Somnambulism	✓	-	-
Somnolence	-	-	>1
Tremor	✓	-	-
Weakness	-	2	-
Dermatological			
Atopic dermatitis	≥2	-	-
Pruritus	-	<1	>1
Rash	1.6	<1	≥1
Skin infection	≥2	-	-
Urticaria	≥2	<1	✓
Gastrointestinal			
Abdominal pain	≥5	1.8 to 2.8	4.6
Constipation	-	-	>1
Diarrhea	≥5	2.8 to 3.0	5
Dyspepsia	2.1	1.0 to 1.3	8.2
Flatulence	-	-	>1
Gastroenteritis	1.5	-	-
Nausea	≥2	3.0 to 3.1	5.0 to 5.5
Pancreatitis	✓	-	-
Vomiting	≥2	1.5 to 2.0	≥1
Genitourinary			
Urinary tract infection	-	-	>1
Vaginitis	-	-	>1
Hematologic			
Agranulocytosis	-	<1	-
Decreased white blood cell count	-	-	1.0 to 2.6
Systemic eosinophilia	-	<1	-
Vasculitis (consistent with Churg-Strauss syndrome)	✓	<1	-
Laboratory Test Abnormalities			
Alanine aminotransferase elevations	2.1	1.5 to 2.0	1.8 to 3.0

Adverse Event(s)	Montelukast	Zafirlukast	Zileuton
Aspartate aminotransferase elevations	1.6	-	-
Pyuria	1	-	-
Musculoskeletal			
Arthralgia	✓	<1	>1
Back pain	-	1.5 to 2.0	-
Hypertonia	-	-	>1
Myalgia	✓	1.6 to 2.0	3.2 to 7.0
Neck pain	-	-	>1
Respiratory			
Bronchitis (acute)	≥2	-	-
Cough	≥5	-	-
Influenza	≥5	-	-
Laryngitis	≥2	-	-
Nasal congestion	1.6	-	-
Pharyngitis	≥5	-	-
Pharyngolaryngeal pain	-	-	5
Pneumonia	≥2	-	-
Rhinitis (infective)	≥2	-	-
Rhinorrhea	≥5	-	-
Sinusitis	≥5	-	6.5 to 7.0
Upper respiratory infection	≥5	-	9
Wheezing	≥2	-	-
Other			
Accidental injury	-	1.6	3.4
Anaphylaxis	✓	-	-
Angioedema	✓	<1	-
Asthenia	1.8	1.8	3.8
Bleeding	-	<1	-
Bruising	✓	<1	-
Cholestatic hepatitis	✓	-	-
Conjunctivitis	≥2	-	>1
Death	-	-	✓
Ear pain	≥2	-	-
Edema	✓	<1	-
Eosinophilic pneumonia	-	<1	-
Epistaxis	≥1	-	-
Erythema nodosum	✓	-	-
Fever	≥5	1.6 to 2.0	>1
Hepatic eosinophilic infiltration	✓	-	-
Hepatitis	-	<1	✓
Hepatocellular liver injury	✓	-	-
Hepatotoxicity	-	-	≥1
Hyperbilirubinemia	-	<1	✓
Hypersensitivity	✓	<1	≥1
Infection	-	3.5 to 4.0	-
Jaundice	-	-	✓
Malaise	-	<1	>1
Myopia	≥2	-	-
Otitis media	≥5	-	-

Adverse Event(s)	Montelukast	Zafirlukast	Zileuton
Pain (dental)	1.7	-	-
Pain (generalized)	-	1.9 to 2.0	7.8
Suicidality	✓	<1	✓
Suicide	✓	<1	✓
Trauma	1	-	-
Tonsillitis	≥2	-	-
Tooth infection	≥2	-	-
Varicella	≥2	-	-

- Event not reported.

✓ Percent not specified.

Contraindications/Precautions

Montelukast, zafirlukast, and zileuton are contraindicated in patients with hypersensitivity to any components of the respective medications.^{1,2,4,5} Additionally, zileuton is contraindicated in patients with active liver disease or hepatic function enzyme levels greater than or equal to three times the upper limit of normal.^{4,5} The leukotriene modifiers should not be used for the reversal of bronchospasm in acute asthma attacks or in status asthmaticus. The agents can be continued during acute exacerbations of asthma. Although the dose of an inhaled corticosteroid may be reduced under medical supervision, the leukotriene modifiers should not be abruptly substituted for oral or inhaled corticosteroids.^{1,2,4,5}

Neuropsychiatric events have been reported in pediatric, adolescent and adult patients taking leukotriene modifiers, including agitation, aggression, anxiousness, depression, disorientation, dream abnormalities, hallucinations, sleep disturbances, somnambulism, suicidal ideation and suicide. Patients and prescribers should watch closely for symptoms and events.^{1,2,4,5}

Patients being treated with montelukast who have a known sensitivity to aspirin should continue to avoid the use of aspirin and non-steroidal anti-inflammatory agents. Montelukast has been shown to improve airway function in patients with aspirin sensitivity, though it has not been shown to effect bronchoconstrictor response to aspirin and non-steroidal anti-inflammatory agents. Patients with phenylketonuria should be advised that the chewable montelukast tablets contain phenylalanine.¹

Patients treated with montelukast or zafirlukast may, in rare instances, present with systemic eosinophilia with clinical features of vasculitis consistent with Churg-Strauss syndrome. This may be associated with a reduction in oral corticosteroid therapy. Health care providers should be alert to the presentation of eosinophilia, vasculitic rash, worsening of pulmonary symptoms, cardiac complications, and neuropathy.^{1,2}

Caution is advised in patients who are concurrently being treated with both zafirlukast and warfarin. Concomitant use results in a clinically significant increase in prothrombin time. Prothrombin time should be monitored closely and warfarin doses adjusted accordingly.²

Zafirlukast therapy, at recommended doses, has been linked to reports of life-threatening hepatic failure. In most cases, liver enzyme values returned to normal upon discontinuation of the medication; however in some rare instances there was progression to fulminant hepatitis, and subsequently to hepatic failure, liver transplantation, and death. Although periodic serum transaminase exams have not been proven to prevent serious adverse events it is generally assumed that earlier detection of any medication-induced hepatic injury along with the immediate discontinuation of the medication can increase the possibility of recovery.²

Zileuton therapy also has the potential to cause elevations in one or more hepatic function enzymes, as well as bilirubin. These laboratory abnormalities may remain unchanged, completely resolve, or progress to significant hepatic injury. The alanine aminotransferase test is the most sensitive indicator of liver injury. Hepatic function enzymes should be assessed prior to initiating zileuton therapy, once a month for

three months while being treated with the medication, every two to three months for the remainder of the first year, and periodically thereafter in long-term therapy. If the transaminase levels are elevated five times or greater above the upper limit of normal, or signs and symptoms of liver dysfunction develop the medication should be immediately discontinued. Zileuton should be used with caution in patients who consume large quantities of alcohol or in those with a past history of liver disease.^{4,5}

Drug Interactions

Table 7. Drug Interactions^{1,2,4-9,14}

Generic Name	Interacting Medication or Disease	Potential Result
Zafirlukast, Zileuton	Warfarin	Concurrent use can result in clinically significant increases in prothrombin time. Close monitoring of prothrombin time in patients on both medications is recommended.
Zafirlukast	Theophylline	Concurrent use of zafirlukast and theophylline may result in decreased mean plasma levels of zafirlukast.
Zileuton	Theophylline	Zileuton may decrease the metabolism of theophylline compounds, and thereby increase theophylline levels. When starting zileuton, it may be necessary to decrease the dose of theophylline by 50%.
Zileuton	Pimozide	Zileuton may inhibit the metabolism of pimozide (possibly via CYP 450 3A4 enzyme), potentially causing fatal cardiac arrhythmias. Concurrent use is considered a contraindication.

Dosage and Administration

Table 8. Dosing and Administration^{1,2,4,5}

Drug(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Montelukast	<p>Asthma: Tablet: Initial, 10 mg Daily in the evening; maintenance, same as initial</p> <p><u>Exercise-induced bronchoconstriction:</u> Tablet: 10 mg at least 2 hours prior to exercise; additional doses should not be administered within 24 hours</p> <p><u>Seasonal and perennial allergic rhinitis:</u> Tablet: Initial, 10 mg Daily at any time of day; maintenance, same as initial</p>	<p>Asthma: Oral granules: 12 to 23 months of age, initial, 4 mg Daily; maintenance, same as initial</p> <p><u>Asthma, seasonal and perennial allergic rhinitis:</u> Chewable tablet or oral granules: 2 to 5 years of age, initial, 4 mg Daily in the evening; maintenance, same as initial</p> <p><u>Asthma, seasonal and perennial allergic rhinitis:</u> Chewable tablet: 6 to 14 years of age, initial, 5 mg Daily in the evening; maintenance, same as initial</p> <p><u>Perennial allergic rhinitis:</u> Oral granules: 6 to 23 months of age, initial, 4 mg Daily; maintenance, same as initial</p>	<p>Chewable tablet: 4 mg 5 mg</p> <p>Oral granules: 4 mg</p> <p>Tablet: 10 mg</p>
Zafirlukast	<p>Asthma: Tablet: initial, 20 mg BID within 1 hour before or 2 hours after meals; maintenance, same as initial</p>	<p>Asthma: Tablet: 5 to 11 years of age, initial, 10 mg twice daily; maintenance, same as initial</p>	<p>Tablet: 10 mg 20 mg</p>

Drug(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Zileuton	<p>Asthma: Extended release tablet: Initial, 1,200 mg BID within 1 hour after morning and evening meals; maintenance, same as initial</p> <p>Tablet: Initial, 600 mg QID with meals and at bedtime; maintenance, same as initial</p>	Same dosing recommendations as adults for children aged 12 years and older.	Extended release tablet: 600 mg Tablet: 600 mg

BID=twice daily, QID=four times daily

Clinical Guidelines

Table 9. Clinical Guidelines

Clinical Guideline	Recommendations
The National Heart, Lung, and Blood Institute/National Asthma Education and Prevention Program: Guidelines for the Diagnosis and Management of Asthma (2007) ¹⁰	<p><u>Diagnosis</u></p> <ul style="list-style-type: none"> To establish a diagnosis of asthma, a clinician must determine the presence of episodic symptoms or airflow obstruction, partially reversible airflow obstruction and alternative diagnoses must be excluded. The recommended methods to establish a diagnosis are a detailed medical history, physical exam focusing on the upper respiratory tract, spirometry to demonstrate obstruction and assess reversibility and additional studies to exclude alternative diagnoses. A diagnosis of asthma should be considered if any of the following indicators are present: wheezing, history of cough, recurrent wheeze, difficulty breathing or chest tightness, symptoms that occur or worsen with exercise or viral infections and symptoms that occur or worsen at night. Spirometry is needed to establish a diagnosis of asthma. Additional studies such as additional pulmonary function tests, bronchoprovocation, chest x-ray, allergy testing and biomarkers of inflammation may be useful when considering alternative diagnoses. <p><u>Treatment</u></p> <ul style="list-style-type: none"> Pharmacologic therapy is used to prevent and control asthma symptoms, improve quality of life, reduce the frequency and severity of asthma exacerbations and reverse airflow obstruction. The initial treatment of asthma should correspond to the appropriate asthma severity category. Long-term control medications such as inhaled corticosteroids (ICSs), long-acting bronchodilators, leukotriene modifiers, cromolyn, theophylline and immunomodulators should be taken daily on a long-term basis to achieve and maintain control of persistent asthma. Quick-relief medications are used to provide prompt relief of bronchoconstriction and accompanying acute symptoms such as cough, chest tightness and wheezing. Quick relief medications include short-acting β_2-adrenergic agonists (SABAs), anticholinergics and systemic corticosteroids. <p><u>Long-term control medications</u></p> <ul style="list-style-type: none"> ICSs are the most potent and consistently effective long-term control medication for asthma in patients of all ages. Short courses of oral systemic corticosteroids may be used to gain prompt

Clinical Guideline	Recommendations
	<p>control when initiating long-term therapy and chronic administration is only used for the most severe, difficult-to-control asthma.</p> <ul style="list-style-type: none"> • When patients ≥ 12 years of age require more than low-dose ICSs, the addition of a long-acting β_2-adrenergic agonists (LABAs) is recommended. Alternative, but not preferred, adjunctive therapies include leukotriene receptor antagonists, theophylline, or in adults, zileuton. • Mast cell stabilizers (cromolyn and nedocromil) are used as alternatives for the treatment of mild persistent asthma. They can also be used as preventative treatment prior to exercise or unavoidable exposure to known allergens. • Omalizumab, an immunomodulator, is used as adjunctive therapy in patients 12 years and older who have allergies and severe persistent asthma that is not adequately controlled with the combination of high-dose ICS and LABA therapy. • Leukotriene receptor antagonists (montelukast and zafirlukast) are alternative therapies for the treatment of mild persistent asthma. • LABAs (formoterol and salmeterol) are not to be used as monotherapy for long-term control of persistent asthma. • LABAs should continue to be considered for adjunctive therapy in patients five years of age or older who have asthma that require more than low-dose ICSs. For patients inadequately controlled on low-dose ICSs, the option to increase the ICS should be given equal weight to the addition of a LABA. • Methylxanthines, such as sustained-release theophylline, may be used as an alternative treatment for mild persistent asthma. • Tiotropium bromide is a long-acting inhaled anticholinergic indicated once-daily for chronic obstructive pulmonary disease and has not been studied in the long-term management of asthma. <p><u>Quick-relief medications</u></p> <ul style="list-style-type: none"> • SABAs are the therapy of choice for relief of acute symptoms and prevention of exercise induced bronchospasm. • There is inconsistent data regarding the efficacy of levalbuterol compared to albuterol. Some studies suggest an improved efficacy while other studies fail to detect any advantage of levalbuterol. • Anticholinergics may be used as an alternative bronchodilator for patients who do not tolerate SABAs and provide additive benefit to SABAs in moderate-to-severe asthma exacerbations. • Systemic corticosteroids are used for moderate and severe exacerbations as adjunct to SABAs to speed recovery and prevent recurrence of exacerbations. • The use of LABAs is not recommended to treat acute symptoms or exacerbations of asthma. <p><u>Assessment, treatment and monitoring</u></p> <ul style="list-style-type: none"> • A stepwise approach to managing asthma is recommended to gain and maintain control of asthma. • Regularly scheduled, daily, chronic use of a SABA is not recommended. Increased SABA use or SABA use more than two days a week for symptom relief generally indicates inadequate asthma control.

Clinical Guideline	Recommendations																							
	<ul style="list-style-type: none"> The stepwise approach for managing asthma is outlined below: 																							
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<p>Global Initiative for Asthma: Global Strategy for Asthma Management and Prevention (2009)¹¹</p>	<p><u>Management of exacerbations</u></p> <ul style="list-style-type: none"> Appropriate intensification of therapy by increasing inhaled SABAs and, in some cases, adding a short course of oral systemic corticosteroids is recommended. <p><u>Special populations</u></p> <ul style="list-style-type: none"> For exercise induced bronchospasm, pretreatment before exercise with either a SABA or LABA is recommended. Leukotriene receptor antagonists may also attenuate exercise induced bronchospasm, and mast cell stabilizers can be taken shortly before exercise as an alternative treatment for prevention; however, they are not as effective as SABAs. The addition of cromolyn to a SABA is helpful in some individuals who have exercise induced bronchospasm. Consideration of the risk for specific complications must be given to patients who have asthma who are undergoing surgery. Albuterol is the preferred SABA in pregnant women because of an excellent safety profile. ICSs are the preferred treatment for long-term control medication in pregnant women. Specifically, budesonide is the preferred ICS as more data is available on using budesonide in pregnant women than other ICSs. <p><u>Diagnosis</u></p> <ul style="list-style-type: none"> A clinical diagnosis of asthma is often prompted by symptoms such as episodic breathlessness, wheezing, cough and chest tightness. Measurements of lung function (spirometry or peak expiratory flow) provide an assessment of the severity, reversibility and variability of airflow limitation and provide confirmation of the diagnosis of asthma. <p><u>Treatment</u></p> <ul style="list-style-type: none"> Education should be an integral part of all interactions between health care professionals and patients, and is relevant to asthma patients of all ages. Measures to prevent the development of asthma, asthma symptoms and asthma exacerbations by avoiding or reducing exposure to risk factors should be implemented whenever possible. Controller medications are administered daily on a long-term basis and 																							

Clinical Guideline	Recommendations
	<p>include inhaled and systemic glucocorticosteroids, leukotriene receptor antagonists, LABAs in combination with ICS, sustained-released theophylline, cromones and anti-immunoglobulin E (IgE).</p> <ul style="list-style-type: none"> Reliever medications are administered on an as-needed basis to reverse bronchoconstriction and relieve symptoms and include SABAs, inhaled anticholinergics and short-acting theophylline. <p><u>Controller medications</u></p> <ul style="list-style-type: none"> ICSs are currently the most effective anti-inflammatory medications for the treatment of persistent asthma for patients of all ages. ICSs differ in potency and bioavailability, but few studies have been able to confirm the clinical relevance of these differences. To reach clinical control, add-on therapy with another class of controller is preferred over increasing the dose of ICS. Leukotriene receptor antagonists are generally less effective than ICSs and therefore may be used as an alternative treatment in patients with mild persistent asthma. Some patients with aspirin-sensitive asthma respond well to leukotriene receptor antagonists. Leukotriene receptor antagonists used as add-on therapy may reduce the dose of ICS required by patients with moderate to severe asthma and may improve asthma control in adult patients whose asthma is not controlled with low or high doses of ICS. Several studies have demonstrated that leukotriene receptor antagonists are less effective than LABAs as add-on therapy. LABAs should not be used as monotherapy in patients with asthma as these medications do not appear to influence asthma airway inflammation. When a medium-dose ICS fails to achieve control, the addition of a LABA is the preferred treatment. Controlled studies have shown that delivering a LABA and an ICS in a combination inhaler is as effective as giving each drug separately. Fixed combination inhalers are more convenient, may increase compliance and ensure that the LABA is always accompanied by an ICS. Although the guideline indicates that combination inhalers containing budesonide and formoterol may be used for rescue and maintenance therapy, this use is not approved by the Food and Drug Administration (FDA). Theophylline as add-on therapy is less effective than LABAs but may provide benefit in patients who do not achieve control on ICS alone. Cromolyn and nedocromil are less effective than a low dose of an ICS. Oral LABA therapy is used only on rare occasions when additional bronchodilation is needed. Anti-IgE treatment with omalizumab is limited to patients with elevated serum levels of IgE. Long-term oral corticosteroid therapy may be required for severely uncontrolled asthma, but is limited by the risk of significant adverse effects. Other anti-allergic compounds have limited effect in the management of asthma. <p><u>Reliever medications</u></p> <ul style="list-style-type: none"> SABAs are the medications of choice for the relief of bronchospasm during acute exacerbations and for the pretreatment of exercise induced

Clinical Guideline	Recommendations																																				
	<p>bronchospasm in patients of all ages.</p> <ul style="list-style-type: none"> • SABAs should be used only on an as-needed basis at the lowest dose and frequency required. • Although the guidelines states that formoterol, a LABA, is approved for symptom relief because of its rapid onset of action, and that it should only be used for this purpose in patients on regular controller therapy with ICS, the use of this agent as a rescue inhaler is not approved by the FDA. • Ipratropium bromide, an inhaled anticholinergic, is a less effective reliever medication in asthma than SABAs. • Short-acting theophylline may be considered for relief of asthma symptoms. • Short-acting oral β_2-adrenergic agonists (tablets, solution, etc.) are appropriate for use in patients who are unable to use inhaled medication; however, they are associated with a higher prevalence of adverse effects. • Systemic corticosteroids are important in the treatment of severe acute exacerbations. <p><u>Assessment, treatment, and monitoring</u></p> <ul style="list-style-type: none"> • The goal of asthma treatment is to achieve and maintain clinical control. • To aid in clinical management, a classification of asthma by level of control is recommended: controlled, partly controlled or uncontrolled. • Treatment should be adjusted in a continuous cycle driven by the patient's asthma control status and treatment should be stepped up until control is achieved. When control is maintained, treatment can be stepped down to the lowest step and dose of treatment that maintains control. • Asthma control is defined as: no (twice or less/week) daytime symptoms; no limitations of daily activities, including exercise; no nocturnal symptoms or awakening because of asthma; no (twice or less/week) need for reliever treatment; normal or near-normal lung function results and no exacerbations. • Increased use, especially daily use, of reliever medication is a warning of deterioration of asthma control and indicates the need to reassess treatment. • The management approach based on control is outlined below: <table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th style="background-color: #cccccc;">Step 1</th> <th style="background-color: #cccccc;">Step 2</th> <th style="background-color: #cccccc;">Step 3</th> <th style="background-color: #cccccc;">Step 4</th> <th style="background-color: #cccccc;">Step 5</th> </tr> </thead> <tbody> <tr> <td colspan="5" style="text-align: center;"><i>Asthma Education and Environmental Control</i></td> </tr> <tr> <td style="text-align: center;"><i>As Needed SABAs</i></td> <td colspan="4" style="text-align: center;"><i>As Needed SABAs</i></td> </tr> <tr> <td rowspan="4" style="background-color: #cccccc; vertical-align: middle; text-align: center;">Controller Options*</td> <td style="text-align: center;">Select One</td> <td style="text-align: center;">Select One</td> <td style="text-align: center;">To Step 3 Treatment, Select One or More</td> <td style="text-align: center;">To Step 4 Treatment, Add Either</td> </tr> <tr> <td style="text-align: center;"><u>Low-dose ICS</u></td> <td style="text-align: center;"><u>Low-dose ICS+LABA</u></td> <td style="text-align: center;"><u>Medium- or high-dose ICS+LABA</u></td> <td style="text-align: center;">Oral corticosteroid</td> </tr> <tr> <td style="text-align: center;">Leukotriene receptor antagonists</td> <td style="text-align: center;">Medium- or high-dose ICS Low-dose ICS + leukotriene receptor antagonists</td> <td style="text-align: center;">Leukotriene receptor antagonists Sustained release theophylline</td> <td style="text-align: center;">Anti-IgE treatment</td> </tr> <tr> <td style="text-align: center;">-</td> <td style="text-align: center;">Low-dose ICS + sustained-release theophylline</td> <td style="text-align: center;">-</td> <td style="text-align: center;">-</td> </tr> </tbody> </table> <p>*Preferred controller options are underlined.</p> <ul style="list-style-type: none"> • Patients who do not reach an acceptable level of control at Step 4 can be considered to have difficult-to-treat asthma. In these patients, a compromise 					Step 1	Step 2	Step 3	Step 4	Step 5	<i>Asthma Education and Environmental Control</i>					<i>As Needed SABAs</i>	<i>As Needed SABAs</i>				Controller Options*	Select One	Select One	To Step 3 Treatment, Select One or More	To Step 4 Treatment, Add Either	<u>Low-dose ICS</u>	<u>Low-dose ICS+LABA</u>	<u>Medium- or high-dose ICS+LABA</u>	Oral corticosteroid	Leukotriene receptor antagonists	Medium- or high-dose ICS Low-dose ICS + leukotriene receptor antagonists	Leukotriene receptor antagonists Sustained release theophylline	Anti-IgE treatment	-	Low-dose ICS + sustained-release theophylline	-	-
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Clinical Guideline	Recommendations
	<p>may need to be reached focusing on achieving the best level of control feasible, with as little disruption of activities and as few daily symptoms as possible, while minimizing the potential for adverse effects. Consideration of utilizing an asthma specialist should occur.</p> <p><u>Management of exacerbations</u></p> <ul style="list-style-type: none"> • Repeated administration of SABAs is the best method of achieving relief for mild to moderate exacerbations. • Systemic corticosteroids should be considered if the patient does not immediately respond to SABAs or if the episode is severe. <p><u>Special populations</u></p> <ul style="list-style-type: none"> • LABAs may also be used to prevent exercise induced bronchospasm and because of a more rapid onset of action, formoterol is more suitable for symptom relief as well as symptom prevention over salmeterol. • Appropriately monitored use of theophylline, ICS, β_2-adrenergic agonists and leukotriene receptor antagonists, specifically montelukast, are not associated with an increased incidence of fetal abnormalities. • ICS has been shown to prevent exacerbations of asthma during pregnancy. Acute exacerbations during pregnancy should be treated with nebulized SABAs and oxygen. Systemic corticosteroids should be instituted when necessary.
<p>Allergic Rhinitis and its Impact on Asthma and the Global Allergy and Asthma European Network: Guideline Revisions (2010)⁴⁸</p>	<p><u>Diagnosis</u></p> <ul style="list-style-type: none"> • The diagnosis of allergic rhinitis is based upon the concordance between typical history of allergic symptoms and diagnostic response. • Typical symptoms of allergic rhinitis include rhinorrhea, sneezing, nasal obstruction and pruritus. • Diagnostic tests are based on the demonstration of allergen-specific IgE in the skin or blood. • Many asymptomatic patients can have positive skin tests or detectable serum levels of IgE. <p><u>Treatment</u></p> <ul style="list-style-type: none"> • The treatment of allergic rhinitis should consider the severity and duration of the disease, the patient's preference, as well as the efficacy, availability and cost of the medication. • A stepwise approach depending on the severity and duration of rhinitis is proposed. • Not all patients with moderate/severe allergic rhinitis are controlled despite optimal pharmacotherapy. • Intranasal glucocorticoids are recommended over oral H1-antihistamines for the treatment of allergic rhinitis in adults and children. They are the most effective drugs for treating allergic rhinitis. In many patients with strong preferences for the oral route, an alternative choice may be reasonable. • Second-generation oral or intranasal H1-antihistamines are recommended for the treatment of allergic rhinitis and conjunctivitis in adults and children. • First generation oral H1-antihistamines are not recommended when second-generation ones are available, due to safety concerns. • Intranasal H1-antihistamines are recommended for the treatment of adults and children with seasonal allergic rhinitis, but data regarding their relative safety and efficacy is limited. Therefore, their use in persistent allergic rhinitis is not recommended.

Clinical Guideline	Recommendations
	<ul style="list-style-type: none"> • Intramuscular glucocorticoids and long-term use of oral glucocorticoids are not recommended due to safety concerns. • Topical cromones are recommended in the treatment of allergic rhinitis but they are only modestly effective. • Montelukast is recommended for adults and children with seasonal allergic rhinitis, and in pre-school children with persistent allergic rhinitis. Montelukast has limited efficacy in adults with persistent allergic rhinitis. • Intranasal ipratropium is recommended for the treatment of rhinorrhea associated with allergic rhinitis. • Intranasal decongestants may be used for a short period (<5 days) for patients with severe nasal obstruction. Nasal decongestants should not be used in pre-school aged children. • Combination oral decongestants and oral H1-antihistamines may be used for the treatment of allergic rhinitis in adults, but should not be administered regularly due to adverse effects. • For patients experiencing ocular symptoms associated with allergic rhinitis intraocular antihistamines or chromones may be considered.
<p>Joint Task Force on Practice Parameters for Allergy and Immunology: The Diagnosis and Management of Rhinitis: An Updated Practice Parameter (2008)¹²</p>	<p><u>Diagnosis</u></p> <ul style="list-style-type: none"> • An effective evaluation of a patient with rhinitis includes a determination of the pattern, chronicity, and seasonality of nasal and related symptoms; response to medications; presence of coexisting conditions; occupational exposure; and a detailed environmental history and identification of precipitating factors. • A physical examination with emphasis on the upper respiratory tract should be performed in patients with a history of rhinitis. • Skin testing is the preferred test for the diagnosis of IgE-mediated sensitivity and is indicated to provide evidence of allergic basis for the causes of the patient's symptoms. • Nasal smears for eosinophils are not necessary for routine use in diagnosing allergic rhinitis but may be useful when the diagnosis of allergic rhinitis is in question. • The measurement of total IgE should not be routinely performed. • Cytotoxic tests, provocation-neutralization, electrodermal testing, applied kinesiology, iridology, and hair analysis are not recommended diagnostic procedures. <p><u>Treatment</u></p> <ul style="list-style-type: none"> • The management and monitoring of rhinitis should be individualized and based on symptoms, physical examination findings, comorbidities, patient age and patient preferences. • Environmental control measures include avoidance of known allergic triggers when possible. • The available second-generation oral antihistamines, which are generally preferred over first-generation antihistamines, appear to be equally effective in the treatment of allergic rhinitis. • Concerning the second generation antihistamines, fexofenadine, loratadine, and desloratadine do not cause sedation at recommended doses; loratadine and desloratadine may cause sedation at doses exceeding the recommended dose; cetirizine and intranasal azelastine may cause sedation at recommended doses. • Intranasal antihistamines are efficacious and equal to or "superior" to oral second-generation antihistamines for treatment of seasonal allergic rhinitis.

Clinical Guideline	Recommendations
	<ul style="list-style-type: none"> • Intranasal antihistamines may be considered for use as first-line treatment for allergic and nonallergic rhinitis. • Leukotriene receptor antagonists alone or in combination with antihistamines are effective in the treatment of allergic rhinitis. • Topical decongestants are not recommended for regular daily use but can be considered for short-term management of nasal congestion. • Intranasal corticosteroids are the most effective medication class for controlling symptoms of allergic rhinitis and all are considered equally efficacious. • Intranasal corticosteroids can provide significant relief of symptoms when used on a regular basis as well as an as-needed basis. • Intranasal corticosteroids may be useful in the treatment of some forms of nonallergic rhinitis. • A short course of oral corticosteroids may be appropriate for very severe or intractable nasal symptoms or significant nasal polyposis. • Intranasal cromolyn sodium may be effective for the prevention and treatment of allergic rhinitis. • Intranasal anticholinergics may be effective in reducing rhinorrhea and are more effective when used in combination with intranasal corticosteroids. • Allergen immunotherapy is effective and should be considered for patients with allergic rhinitis who have demonstrable evidence of specific IgE antibodies to clinically relevant allergens. • Surgery may be indicated in the management rhinitis.
<p>Institute for Clinical Systems Improvement: Diagnosis and Treatment of Respiratory Illness in Children and Adults (2011)¹³</p>	<p><u>Diagnosis</u></p> <ul style="list-style-type: none"> • Patients can present with any of the following symptoms: congestion, rhinorrhea, pruritus, sneezing, posterior nasal discharge, and sinus pressure/pain. • A past medical history of facial trauma or surgery, asthma, rhinitis, atopic dermatitis, or thyroid disease may be suggestive of a rhinitis. In addition, a family history of atopy or other allergy associated conditions make allergic rhinitis more likely. • The most common physical findings suggestive of rhinitis tend to be swollen nasal turbinates, rhinorrhea and pruritus however allergic conjunctivitis may also be present. • Symptoms suggestive of allergic etiology include sneezing, itching of the nose, palate or eyes, and clear rhinorrhea. Nasal congestion is the most significant complaint in patients with perennial rhinitis. • Diagnostic testing should be considered if the results would change management. • Skin tests and radioallergosorbent tests identify the presence of IgE antibody to a specific allergen and are used to differentiate allergic from nonallergic rhinitis and to identify specific allergens causing allergic rhinitis. • A nasal smear for eosinophils is a good predictor of a patient's response to treatment topical nasal corticosteroids. • Peripheral blood eosinophil count, total serum IgE level, Rinkel method of skin titration and sublingual provocation testing are not recommended. <p><u>Treatment</u></p> <ul style="list-style-type: none"> • If a clinical diagnosis is obvious, symptomatic treatment, which consists of education on avoidance and medication therapy, should be initiated. • Avoidance of triggers is recommended. • Intranasal corticosteroids are the most effective single agents for controlling

Clinical Guideline	Recommendations
	<p>the spectrum of allergic rhinitis symptoms and should be considered first-line therapy in patients with moderate to severe symptoms.</p> <ul style="list-style-type: none"> • Regular daily use of intranasal corticosteroids is required to achieve optimal results. • It may be best to start treatment one week prior to the start of the allergy season for prophylaxis. • Clinical response does not seem to vary significantly between the available intranasal corticosteroids. • Systemic corticosteroids should be reserved for refractory or severe cases of rhinitis. Injectable steroids are not generally recommended. • Antihistamines are effective at controlling all symptoms associated with allergic rhinitis except nasal congestion. • Antihistamines are somewhat less effective than intranasal corticosteroids but they can be used on a daily or as needed basis. • Second-generation antihistamines are recommended because they are less sedating and cause less central nervous system impairment. • Leukotriene inhibitors may be as effective as second-generation antihistamines for the treatment of allergic rhinitis and less effective than intranasal corticosteroids. • Oral decongestants are effective in reducing nasal congestion. Oral decongestants can be a useful addition to antihistamines. • Topical decongestants, which have the potential to induce rebound congestion after three days, are effective for the short-term relief of nasal congestion. • Cromolyn is less effective than intranasal corticosteroids and is most effective when used prior to the onset of allergic symptoms. • Cromolyn is a good alternative for patients who are not candidates for corticosteroids. • Intranasal anticholinergics are effective in relieving anterior rhinorrhea in allergic and nonallergic rhinitis. • Reserve immunotherapy for patients with significant allergic rhinitis in which avoidance activities and pharmacotherapy are insufficient to control symptoms. • If adequate relief is achieved appropriate follow-up should include further education on avoidance activities and medications. • If patients anticipate unavoidable exposure to known allergens they should begin the use of medications prior to exposure. • If adequate relief is not achieved within two to four weeks consider a trial of another medication, allergen skin testing by a qualified physician, a complete nasal examination, or a diagnosis of nonallergic rhinitis. • Treatment options for nonallergic rhinitis include intranasal corticosteroids, oral decongestants and antihistamines, topical antihistamines, and nasal strips.
<p>American Academy of Family Physician: Treatment of Allergic Rhinitis (2010)⁴⁹</p>	<ul style="list-style-type: none"> • Treatment should be based on the patient's age and severity of symptoms. • Intranasal corticosteroids are the most effective treatment and should be first-line therapy for mild to moderate disease. • Moderate to severe disease not responsive to intranasal corticosteroids should be treated with second-line therapies, including antihistamines, decongestants, cromolyn, leukotriene receptor antagonists, and nonpharmacologic therapies (e.g., nasal irrigation). • Immunotherapy should be considered in patients with inadequate response to usual treatments.

Clinical Guideline	Recommendations
	<ul style="list-style-type: none"> • Omalizumab has been shown to be effective in reducing nasal symptoms and improving quality of life scores in patients with allergic rhinitis. However, its high cost (average wholesale price of \$679 to \$3,395/month) and lack of FDA approval for home administration are the main limitations to its use.

Conclusions

The leukotriene modifiers (LTMs) consist of two categories of agents; the leukotriene-receptor antagonists (LTRAs) montelukast and zafirlukast, and the 5-lipoxygenase inhibitor, zileuton. All three agents are Food and Drug Administration approved for the chronic treatment and prophylaxis of asthma. Montelukast is also indicated for prophylaxis of exercise-induced bronchoconstriction as well as for the treatment of symptoms of both seasonal and perennial allergic rhinitis.^{1,2,4,5}

Current treatment guidelines recommend the use of LTMs as one of the treatment alternatives to low-dose inhaled corticosteroids (ICSs) in patients with mild persistent asthma.^{10,11} These agents can also be considered as alternative adjunctive therapy in patients not achieving adequate symptom control with an ICS, as monotherapy or in combination with a long-acting β_2 -agonist (LABA). The allergic rhinitis guidelines consider intranasal corticosteroids to be first-line treatment for the management of allergic rhinitis and that the LTMs can be considered second-line agents along with antihistamines.^{12,13,48} Either LTRA agent is preferred compared to zileuton due to its limited efficacy data and the need for liver function monitoring.¹⁰

There are no head-to-head trials directly comparing the efficacy and safety of the LTMs to each other for any indication. In placebo controlled trials, the LTMs demonstrated efficacy in most aspects of asthma control. However, when compared to other long-term control medications, such as ICSs and LABAs, the LTMs were unable to demonstrate equivalence or significant advantages in clinical outcomes.¹⁵⁻³⁹ In regards to safety, postmarketing data appears to show that both zafirlukast and zileuton have a higher risk of hepatotoxicity than montelukast.^{2,4,5}

In patients with allergic rhinitis, montelukast has been shown to be more effective than placebo, and has demonstrated comparable efficacy to the second-generation antihistamines; however, the agent was shown to be less effective than intranasal corticosteroids.⁴⁰⁻⁴⁷

Recommendations

In recognition of the established role of the leukotriene modifiers for the treatment of asthma and allergic rhinitis, the similar efficacy between agents, and the safety concerns associated with zileuton, no changes are recommended to the current Department of Vermont Health Access approval criteria (see below). Of note, the current approval criteria were implemented on January 3rd, 2011. Prior to that date, Accolate[®] and Singulair[®] were available without a prior authorization.

Singulair[®]

- The diagnosis or indication for the requested medication is asthma.
- OR
- The diagnosis or indication for the requested medication is allergic rhinitis.
- AND
- The patient has had a documented side effect, allergy, or treatment failure to a second generation non-sedating antihistamine AND a nasal corticosteroid.

See results of RetroDUR for further recommendations regarding clinical criteria.

Zafirlukast, Accolate[®]

- The diagnosis or indication for the requested medication is asthma.
- AND
- If the request is for Accolate, the patient has a documented intolerance to generic zafirlukast.

Zyflo CR[®]

- The diagnosis or indication for the requested medication is asthma.
- AND
- The patient has had a documented side effect, allergy, or treatment failure to Accolate[®] or Singulair[®].

In addition, the following quantity limits are in place: 2 tabs/day (Accolate[®]/zafirlukast), 1 tab (or packet)/day (Singulair[®]), 4 tabs/day (Zyflo[®]).

Children five years old and under are not subject to prior authorization criteria for Singulair[®].

References

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