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MONTELUKAST:
INDICATIONS AND SAFETY

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ABBREVIATIONS

AAAAI	American Academy of Allergy, Asthma, and Immunology
ACAAI	American College of Allergy, Asthma, and Immunology
AE(s)	Adverse event(s)
AERD	Aspirin-exacerbated respiratory disease
AR	Allergic rhinitis
ATS	American Thoracic Society
CDC	Centers for Disease Control and Prevention
CI	Confidence interval
CYP	Cytochrome
DSC	Drug safety communication
DUR	Drug Utilization Review
EIB	Exercise-induced bronchoconstriction
FAERS	FDA Adverse Event Reporting System
FDA	US Food and Drug Administration
FFS	Fee-for-service
FEV_1	Forced expiratory volume in 1 second
GINA	Global Initiative for Asthma
HR	Hazard ratio
ICD-9-CM	International Classification of Diseases, 9th Revision, Clinical Modification
ICD-10	International Classification of Diseases, 10th Revision
ICS(s)	Inhaled corticosteroid(s)
IgE	Immunoglobulin E
IL	Interleukin
LABA(s)	Long-acting beta$_2$ agonist(s)
LOE	Level of evidence
LTRA(s)	Leukotriene receptor antagonist(s)
NAEPP	National Asthma Education and Prevention Program
NHLBI	National Heart, Lung, and Blood Institute
NSAID(s)	Nonsteroidal anti-inflammatory drug(s)
OR	Odds ratio
PA	Prior authorization
PDL	Preferred Drug List
PKU	Phenylketonuria
RCT(s)	Randomized controlled trial(s)
RR	Relative risk
SABA(s)	Short-acting beta$_2$ agonist(s)
SDD	Sentinel Distributed Database
SR(s)	Systematic review(s)
SRMA	Systematic review and meta-analysis
US	United States

1.0 INTRODUCTION

The leukotriene receptor antagonist (LTRA), montelukast (Singulair), was initially approved by the United States (US) Food and Drug Administration (FDA) in 1998.[1] It is indicated for (a) **asthma** prophylaxis and chronic treatment in adults and children aged ≥1 year, (b) prevention of **exercise-induced bronchoconstriction (EIB)** in patients aged ≥6 years, (c) **seasonal allergic rhinitis (AR)** in patients aged ≥2 years, and (d) **perennial AR** in patients aged ≥6 months. Montelukast is available in a variety of oral formulations including film-coated tablets, chewable tablets, and granules. Selection of a dosage form depends on the maximum dosage recommend per indication and patient age.[1] In 2022, montelukast was prescribed to 12 million Americans, including 1.6 million pediatric patients—a sharp decline from 2.3 million in 2018.[2,3]

Post-marketing case reports of potential neuropsychiatric events associated with montelukast use have been continually received by the FDA for more than a decade, culminating in the issuance of a black box warning in March 2020.[2,4] Serious neuropsychiatric AEs including depression, irritability, and suicidal thoughts and/or behaviors have been observed in patients of all ages.[1]

Other leukotriene modulators available in the US for the treatment of asthma, zafirlukast and zileuton, also carry the risk of neuropsychiatric events.[5,6] Nonetheless, this report focuses on montelukast because it is the only agent of the 3 with a black box warning for neuropsychiatric events[4]; zafirlukast and zileuton carry only labeled warnings/precautions.[5,6]

As of April 2024, preferred products on the Utah Medicaid Preferred Drug List (PDL) include generic montelukast film-coated tablets and chewable tablets, whereas generic montelukast oral granules, the brand product of montelukast (Singulair), and other leukotriene modulators (ie, zafirlukast and zileuton) are non-preferred.[7] No drug-specific prior authorization (PA) is currently in place for montelukast.

The objective of this report is to provide information about the place in therapy for montelukast in the treatment of asthma, EIB, and AR, and to outline the concerns regarding the black box warning in order to help guide appropriate montelukast use among the Utah Medicaid population. These objectives are supplemented with montelukast utilization data among the Medicaid fee-for-service (FFS) population over the past 1-year period.

2.0 METHODS

This review focuses on the FDA-approved indications of montelukast including asthma, EIB, and AR. Because montelukast is generally not recommended to treat nonallergic rhinitis,[8] this condition is not addressed by this report.

Product prescribing information (ie, package insert) was obtained from the drug sponsor's website. Additionally, we performed a search of the following major medical organizations websites for recently published (2019−2024) clinical practice guidelines for the treatment of asthma, EIB, or AR:

- Global Initiative for Asthma (GINA): https://ginasthma.org/
- National Heart, Lung, and Blood Institute (NHLBI): https://www.nhlbi.nih.gov/
- American Academy of Allergy, Asthma, and Immunology (AAAAI): https://www.aaaai.org/

- American College of Allergy, Asthma, and Immunology (ACAAI): https://acaai.org/
- American Thoracic Society (ATS): https://www.thoracic.org/

To complement the observational evidence reviewed by the FDA regarding the potential association between neuropsychiatric events and montelukast exposure in pediatric patients, we performed a focused literature search in Epistemonikos for recently published (2023 and onward) systematic reviews (SRs). Complete details of the search strategy are provided in **Appendix A**.

3.0 MONTELUKAST MECHANISM OF ACTION

Cysteinyl leukotrienes (ie, LTC_4, LTD_4, LTE_4) are potent inflammatory mediators derived from arachidonic acid[9] that have been associated with the pathophysiology of both asthma and AR.[1] The effects mediated by leukotrienes in asthma encompass airway edema, smooth muscle contraction, and changes in inflammatory related-cellular activity, all contributing to asthma signs and symptoms.[1,10] In the setting of AR, cysteinyl leukotrienes are released from the nasal mucosa during early and late-phase reactions following allergen exposure, resulting in AR symptoms.[1,10] Montelukast is a highly selective antagonist at cysteinyl leukotriene receptor type-1, thereby inhibiting the physiologic effects of leukotrienes in asthma and AR.[1]

While the underlying mechanisms of neuropsychiatric events associated with montelukast use is not fully understood, studies in rats detected montelukast in brain tissue and cerebrospinal fluid, indicating montelukast is able to cross the blood-brain barrier and may have a direct effect in the brain.[1,2,4]

4.0 BLACK BOX WARNING

Since 2007, post-marketing reports have documented neuropsychiatric events in patients exposed to montelukast, including adults, adolescents, and children, with or without a history of psychiatric conditions.[1,4,11] Prior to implementing the more recent black box warning for neuropsychiatric events, FDA safety reviews led to several revisions to the product labeling for montelukast.[4] While these revisions were aimed at disseminating the risk of neuropsychiatric events to patients and healthcare providers,[4] there remained concern for the lack of awareness, particularly in pediatric patients.[2,11] In response, in 2019, the FDA re-evaluated data from the FDA Adverse Event Reporting System (FAERS), from February 1998 (date of montelukast approval) through May 2019, and published observational studies for neuropsychiatric events.[2,4] Additionally, the FDA conducted an observational study using claims data from 2000 to 2015 in the Sentinel Distributed Database, a national monitoring system.[4,11,12]

The current black box warning for montelukast advises providers to discuss the risks and benefits of montelukast with patients and caregivers, including counseling to monitor for changes in behavior and onset of new neuropsychiatric symptoms, when prescribing montelukast.[1,2] If any alterations in behavior or new neuropsychiatric symptoms emerge (eg, attention problems, agitation, depression, hallucination, insomnia), patients should discontinue montelukast immediately and seek prompt attention from their provider.[1,2] Of note, some patients may continue to experience neuropsychiatric events after discontinuing montelukast, and therefore, it is advised to provide continual monitoring and support until symptoms completely resolve.[1] If re-treatment with montelukast is desired, the risks and benefits should be considered.[1]

Because the potential benefits of montelukast may not outweigh the potential risks of neuropsychiatric events in some patients (eg, those with mild disease able to be treated with other medications), it is advised to reserve montelukast for patients with AR who have an inadequate response or intolerance to alternative treatments.[1] Benefits and risks should be considered before prescribing montelukast for asthma or EIB. Montelukast labeling notes that regardless of age, children, adolescents, and adults are at risk for neuropsychiatric events. There are no unique precautions specific to children and adolescents.[1]

The following sections review the data considered before issuance of the black box warning in 2019. **Appendix B** provides additional warnings/precautions and adverse effects for montelukast, and other labeled information.

4.1 Montelukast FAERS Data

Overall, reported neuropsychiatric events in montelukast-exposed patients were highly variable, including but not limited to, hostility, depression, dream abnormalities, hallucinations, insomnia, and suicidal thoughts and behaviors, and ranged widely in severity.[1,11] Of the 19,685 FAERS case reports of *any adverse effect* in patients taking montelukast, over 21 years of prescribing in the US, 52% had a keyword of interest related to a potential neuropsychiatric event (ie, nervous system disorder, psychiatric disorder); of these, approximately 84% of adult (≥17 years old) and pediatric (<17 years old) cases were serious*.[4] Mortality of any cause was reported in approximately 6.3% and 1.0% of potential neuropsychiatric event reports among adults and pediatric patients, respectively, exposed to montelukast. Temporal trends from montelukast case reports revealed increased reporting of neuropsychiatric events in 1999, 2008, 2013, and 2018, but this was likely attributable to heightened public awareness as a result of FDA safety communications, and increases in duplicate or foreign reports.[2,4]

Over the 21 years of montelukast FAERS case reports, there were 82 cases of completed suicide, many of which documented the onset of neuropsychiatric symptoms before the event.[4] Of these, about 55% involved patients >17 years of age and approximately 23% occurred in those ≤17 years of age (the remaining 22% did not report patient age).[2,4] Most of these reported cases (59%) lacked adequate information for assessing the association between montelukast and the suicidal event (ie, confounders may have been present such as concomitant medications and psychiatric history), but among the reports with more comprehensive details, it was noted that other potentially contributing risk factors for suicide were present (eg, medication usage, psychiatric comorbidities) in the majority of reports.[2,4] Notably, 6 cases described a lack of provider counseling on the neuropsychiatric risk with montelukast use.[2] While most events were reported during montelukast use, there were 2 cases in which events occurred after montelukast was discontinued, and overall conclusions regarding causality were limited by the lack of reported information.[4]

* Serious potential neuropsychiatric events were defined as events that were life-threatening, resulted in death, hospitalization, disability, or congenital defect, or required medical intervention, "and other serious important medical events" (page 43).[4]

4.2 Observational Studies in Pediatric Patients

Although children and adults are potentially at risk of a neuropsychiatric event with montelukast use based on the FAERS data, the FDA's analysis of observational studies on the risks of neuropsychiatric events with montelukast primarily addressed pediatric patients, possibly because the safety concern was brought to the FDA pediatric advisory council in response to citizen petitions from parent advocacy groups.[4] The FDA performed a formal literature search in PubMed, Web of Science, Google Scholar, and EBSCOHost in December 2017, January 2018, and July 2019.[4] The FDA evaluated 4 published observational studies regarding montelukast use and neuropsychiatric events: 1 cohort study (Benard et al)[13] and 3 nested case-control studies (Schumock et al, Ali et al, and Glockler-Lauf et al),[14-16] all of which included **children with asthma**.[4] Notably, higher quality studies in the adult population may have existed at that time but were not fully considered in the FDA's assessment which focused on pediatric montelukast exposure[†].

Results from the 4 reviewed observational studies were mixed regarding whether montelukast was associated with neuropsychiatric events.[4] Studies judged to be of higher quality by the FDA (Schumock et al and Ali et al) did not find a statistically significant association. Overall, the FDA decided that the reviewed observational studies did not provide definitive evidence linking montelukast use to the development of neuropsychiatric events in pediatric patients. These observational studies had important limitations (eg, study design, unadjusted confounding factors related to pre-existing psychiatric conditions or concomitant medications with possible neuropsychiatric effect; or potential influence of montelukast FDA drug safety communications [DSC] or labeling changes), which motivated the FDA to conduct its own observational study using data from the Sentinel Distributed Database (see **Section 4.3**).[4] **Table 1** provides an overview of each of these studies, including results. Additional details for each observational study are discussed after the table.

[†] See **Section 4.6** for recently published evidence, including a systemic review and meta-analysis (SRMA) of randomized controlled trials (RCTs) on the association between montelukast exposure and neuropsychiatric events.

Table 1. Overview of FDA-reviewed Observational Studies Evaluating Neuropsychiatric Risks with Montelukast[4]

Study author (published year)	Select outcome of interest	Study population	Study groups: number of patients	Select results for neuropsychiatric outcome with montelukast (or LTMA) vs. control group (95% CI)
Cohort studies (nested matched results shown)				
Benard et al (2017)[13]	• Neuropsychiatric events leading to montelukast discontinuation	• Children aged 1–17 years with asthma	• Montelukast ± ICS: 84 ○ 36 (43%): montelukast monotherapy ○ 36 (43%): montelukast + ICS ○ 12 (14%): montelukast + ICS/LABA • ICS monotherapy: 84	• Montelukast (± ICS) vs. ICS alone (matched): ○ **Relative risk for any neuropsychiatric events: 12.0 (1.6–90.2)** ○ **Relative risk for probably/definitely drug-related neuropsychiatric events: 9.0 (1.2–69.5)** • Montelukast monotherapy vs. ICS alone (unmatched; *post-hoc* analysis): ○ **Relative risk for any neuropsychiatric events: 5.9 (1.5–22.5)**[a] • Any montelukast regimen (± ICS or ± ICS/LABA) vs. ICS alone (unmatched; *post-hoc* analysis): ○ **Relative risk for any neuropsychiatric events: 7.1 (2.1–23.4)**[a]
Nested case-control studies				
Glockler-Lauf et al (2019)[16]	• Neuropsychiatric events	• Children aged 5–18 years with asthma treated with at least 1 maintenance medication (eg, ICS, montelukast) in the previous year	• Cases: 898 ○ Had a neuropsychiatric event after being diagnosed with asthma ○ 73 cases (8.1%) had at least 1 montelukast prescription • Matched controls[b]: 3497 ○ Did not experience a neuropsychiatric event during the study period between 2004 and 2016 ○ 74 controls (2.1%) had at least 1 montelukast prescription	Adjusted odds ratio (aOR) for neuropsychiatric events: • **Montelukast exposure vs. no montelukast exposure: aOR: 1.91 (1.15–3.18)** • Number of montelukast prescriptions received vs. no montelukast exposure ○ 1 montelukast prescription vs none: aOR: 2.38 (0.98–5.77) ○ 2 or more montelukast prescriptions vs none: aOR: 1.74 (0.96–3.16)
Schumock et al (2012)[14]	• Suicide attempts	• Patients aged 5–24 years with asthma • Started a LTMA (ie, montelukast, zafirlukast, or zileuton) or another asthma medication (eg, ICS, LABA)	• Cases: 344 ○ Cases who had a suicide attempt and were currently exposed to any LTMA: 19 ▪ All 19 cases received montelukast • Matched[c] controls: 3438 ○ Controls who were at risk of a suicide attempt and were currently exposed to any LTMA: 224 ▪ 219 controls received montelukast	Adjusted odds ratio (aOR) for suicide attempts: • Current use of any LTMA vs. no LTMA exposure within the past 180 days: aOR: 0.70 (0.36–1.39) • Current use of any LTMA vs. no LTMA exposure within the past 180 days (subgroup analysis): ○ 5–11 year olds (cases: 1; controls: 13): aOR: 0.78 (0.03–18.09) ○ 12–18 year olds (cases: 12; controls: 179): aOR: 0.47 (0.20–1.09) ○ **19–24 year olds** (cases: 6; controls: 32)**: aOR: 5.15 (1.16–22.86)** ▪ When also controlling for medications: aOR: 5.64 (0.87–36.66)
Ali et al (2015)[15]	• Neuropsychiatric events	• Children aged 1–17 years with asthma	• Cases: 1007 ○ Had a neuropsychiatric event based on psychiatric diagnosis or recipient of a psychotropic medication within 1 year of the asthma diagnosis date • Matched controls[c]: 3021 ○ Did not experience a neuropsychiatric event during the study period between 1998–2009	Adjusted odds ratio (aOR) for neuropsychiatric events: • Montelukast exposure in past year vs no exposure: aOR: 0.96 (0.80–1.14) ○ Subgroup with montelukast exposure in the past month vs no exposure: aOR: 1.02 (0.82–1.26) ○ **Subgroup with high dose (>1080 mg) montelukast exposure vs no exposure: aOR: 0.67 (0.48–0.93)** ○ Subgroup with moderate dose (481–1080 mg) montelukast exposure vs no exposure: aOR: 1.28 (0.96–1.69) ○ Subgroup with 91–180 days of montelukast exposure vs no exposure: aOR: 1.15 (0.83–1.59) ○ Subgroup with >180 days of montelukast exposure vs no exposure: aOR: 0.83 (0.61–1.13)

*Statistically significant results are **bolded**.*

[a] *Although it is unclear, it appears that the reported relative risk considers all neuropsychiatric events, instead of events probably or definitely drug related only.*

[b] *Cases and controls were matched on birth year, sex, and year of asthma diagnosis.*

[c] *Cases and controls were matched on sex, age, and geographic region.*

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; FDA, US Food and Drug Administration; ICS, inhaled corticosteroid; LABA(s), long-acting beta$_2$ agonist; LTMA, leukotriene-modifying agent; US, United States

4.2.1 Bernard et al

Bernard et al conducted a retrospective cohort study with a nested matched cohort study.[13] Eligible participants were 1−17 years of age with an asthma diagnosis. For the nested matched cohort study, participants were started on either daily montelukast, as monotherapy or in combination with an inhaled corticosteroid (ICS), or ICS monotherapy. Both treatment groups had not previously received montelukast. After matching, 84 participants were included in each treatment group.[13] In the montelukast group, 43% of participants were treated with montelukast plus an ICS, 14% were treated with montelukast plus an ICS/long-acting beta$_2$ agonist (LABA), and 43% were treated with montelukast only.[4] Parents of eligible participants were interviewed by phone or in person to inquire about the occurrence of neuropsychiatric events after starting the medication.[13] Neuropsychiatric events were classified based on their probability of being associated with montelukast, as determined by a blinded adjudication committee using the Naranjo causality scale,[17] with probabilities ranging from unlikely to definitely.[4,13] The primary outcome was the incidence of parent-reported neuropsychiatric events leading to drug discontinuation in the montelukast treatment group.[13]

This study found a 9- to 12-fold increased risk of neuropsychiatric events resulting in drug discontinuation associated with montelukast (with or without ICS) compared to ICS alone, with the magnitude of increased risk dependent on the assigned Naranjo causality likelihood (relative risk [RR] for any reported neuropsychiatric events: 12; 95% confidence interval [CI]: 1.6−90.2; RR for neuropsychiatric events probably [Naranjo score of 5−8] or definitely [Naranjo score of ≥9] related to montelukast only: 9; 95% CI: 1.2−69.5).[13] A *post hoc* subgroup analysis among unmatched participants was congruent with the primary analysis, finding a higher risk of neuropsychiatric events that led to drug discontinuation with montelukast, regardless of the type of montelukast regimen used (ie, with or without ICS or ICS/LABA; RR for montelukast monotherapy: 5.9; 95% CI: 1.5−22.5; and RR for montelukast monotherapy or a montelukast-containing regimen with or without ICS or ICS/LABA: 7.1; 95% CI: 2.1−23.4), compared to ICS only.[13]

Although this study controlled for various factors such as age, sex, asthma control, duration between starting the drug and parent interview, among others,[4] the large CIs for these findings indicate little reliability in the results. The FDA noted that this study had significant recall bias, which may have led to overestimating the risk of neuropsychiatric events.[4] For example, the study occurred after the 2008 FDA DSC and labeling changes for montelukast, potentially resulting in more parents perceiving neuropsychiatric symptoms were related to montelukast use, and therefore, an increased likelihood of attributing an event to montelukast rather than an ICS.[4]

4.2.2 Glockler-Lauf et al

A nested case-control study by Glockler-Lauf et al found that children (ages 5−18 years) with treated asthma who had a new-onset neuropsychiatric event (cases; n=898) were twice as likely to have been prescribed montelukast within the year preceding the event compared to controls (n=3497) who did not experience a neuropsychiatric event during the study period between 2004 and 2016 (adjusted odds ratio [OR]: 1.91; 95% CI: 1.15−3.18)[4,16]; most events among cases were anxiety (48.6%) and/or sleep disturbance (26.1%).[16] Nonetheless, compared to no prescriptions for montelukast, the number of montelukast prescriptions received in the previous year was not significantly associated with new-onset

neuropsychiatric events (1 vs 0 prescriptions: adjusted OR: 2.38; 95% CI: 0.98−5.77; 2+ vs 0 prescriptions: adjusted OR: 1.74; 95% CI: 0.96−3.16).[16] Cases were defined as those who experienced a neuropsychiatric event, as documented by a visit to a hospital, emergency room, or same-day surgery, after being diagnosed with asthma. Cases and controls were required to be prescribed at least 1 maintenance medication for asthma in the previous year before the index date (ie, the date of the patient's first neuropsychiatric event after being diagnosed with asthma). Notably, cases had significantly more exposure to montelukast than controls based on the proportion of those who had received at least 1 montelukast prescription: 8.1% of cases versus 2.1% of controls.[16]

As noted by the FDA, a major limitation of this study design was the uncertainty of whether exposure (ie, montelukast treatment) preceded the initial neuropsychiatric diagnosis for all cases, as some could have had a pre-existing psychiatric condition given the lack of information regarding the reason for the medical visit.[4]

4.2.3 Schumock et al and Ali et al

Schumock et al and Ali et al were both insurance claims-based nested case-control studies that included patients with asthma.[4] Eligible participants were 1−17 years for Ali et al and 5−24 years for Schumock et al. The primary objective of these studies was to evaluate the association between montelukast exposure and neuropsychiatric events (for Ali et al) or suicide attempts (for Schumock et al).[4]

In the study by Ali et al, cases (which were defined as having a neuropsychiatric event based on psychiatric diagnosis or recipient of a psychotropic medication within 1 year of the asthma diagnosis date; n=1007) were matched to controls (n=3021) who did not experience a neuropsychiatric event during the study period between 1998−2009.[4,15] This study found no positive association between any montelukast exposure (ie, at least 1 montelukast prescription within 30, 90, 180, or 365 days before the index date) in the previous year and neuropsychiatric events (adjusted OR: 0.96; 95% CI: 0.80−1.14), compared to no montelukast exposure. Patients exposed to higher cumulative doses of montelukast (>1080 mg) in the previous year had significantly lower odds for a neuropsychiatric event (adjusted OR: 0.67; 95% CI: 0.48−0.93) compared to no exposure to montelukast, but there was not a consistent dose-response relationship. Although results for moderate cumulative montelukast doses (481−1080 mg) showed a numerically higher odds for a neuropsychiatric event (adjusted OR: 1.28; 95% CI: 0.96−1.69), this finding, as well as for treatment duration (90 to 180 days, or 180 days or longer), was not statistically significant compared to no montelukast exposure.[4,15]

The other nested case-control study, Schumock et al, addressed the association between leukotriene modifying agents and attempted suicides among children and young adults.[4,14] Included patients were those with asthma who started a leukotriene modifying agent (ie, montelukast, zafirlukast, or zileuton) or another controller agent for asthma (eg, ICS, LABA, mast cell stabilizer, inhaled anticholinergic) between 1997−2006.[4,14] Cases (defined as those with a suicide attempt occurring ≥1 day after the date of the first claim for an asthma medication; n=344) were matched to controls (those at risk for a suicide attempt; n=3438) based on age, geographic region, and sex.[4,14] Most controls and all cases who received a leukotriene modifying agent were exposed to montelukast at the time of the event (ie, current use).[4,14] Compared to controls, cases were significantly more likely to have a previous suicide attempt, psychological counseling, a mental health condition (eg, depression, schizophrenia), or use of

medications potentially related to suicide (eg, antipsychotics, antidepressants); there were potentially pre-existing confounding factors.[14]

Overall results from Schumock et al showed a numerically lower odds of suicide attempt with current use of any leukotriene modifying agent (adjusted OR: 0.70; 95% CI: 0.36−1.39) compared to no recent exposure within the past 180 days.[4,14] However, a subgroup analysis of 19−24 year old patients found a statistically significant higher risk of suicide (adjusted OR: 5.15; CI: 1.16−22.86) with current use of any leukotriene modifying agent versus no recent use within the past 180 days.[14] Nonetheless, the wide CIs suggest low reliability in the result. Notably, this exploratory finding was no longer significant (adjusted OR: 5.64; CI: 0.87−36.66) after accounting for additional covariates, such as prior use of medications for asthma and other medications associated with suicide.[14] Subgroup analysis among pediatric patients aged 5−11 years and 12−18 years showed no significant suicide risk associated with exposure to any leukotriene modifying agent compared to no recent exposure within the previous 180 days.[14] According to the 2019 FDA review, an increased suicide risk associated with montelukast among young adults has not been duplicated in other studies.[4]

4.3 FDA Observational Analysis using Sentinel Distributed Database (SDD) Data

The objective of the FDA's observational analysis using Sentinel Distributed Database (SDD) data was to address (a) whether montelukast use for asthma was associated with an increased risk of self-harm, suicide, or depressive disorders relative to ICSs, and (b) if neuropsychiatric events associated with montelukast, in comparison to ICSs, were influenced by the 2008 DSC (first FDA communication released about the potential for neuropsychiatric events, including suicidality, potentially related to montelukast exposure) and subsequent montelukast labeling changes; or other factors such as age, psychiatric history, and sex.[4,12]

The study included patients with asthma (without chronic obstructive pulmonary disease) at least 6 years of age; the asthma diagnosis was based on International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) code claims, which could have occurred in any care setting.[4,12] The observation period for the study was January 1, 2000 to September 30, 2015. Patients with AR were also included, but only if asthma was the primary diagnosis. Patients needed to be without recent exposure to montelukast or any ICS-containing therapy within the previous 183 days. To account for potential drug-related neuropsychiatric events, up to a 15-day gap was allowed between dispensings of montelukast or an ICS (plus a 15-day episode extension period) and events of inpatient treated depression or self-harm, whereas a 30-day gap and episode extension period were used for the drug-exposure and events of treated outpatient depressive disorder. Only the first treatment fulfilling these criteria were considered[4,12]; exposures where montelukast and an ICS were started on the same day were excluded.[4]

Patients who received either montelukast or ICS monotherapy were matched[‡] in a 1:1 ratio using propensity scores.[4,12] After propensity score matching, 457,377 patients were included in each exposure

[‡] Propensity score matching paired patients based on sex, age, psychiatric history, prior comorbidities, medication usage, index year, and asthma severity.

group (montelukast or ICS). Included patients in the matched cohort were primarily female, with a mean age of 38.5 years. Approximately 37% of patients had a history of a psychiatric disorder and 43% had a concurrent diagnosis of AR.[4,12] Additionally, about 63% and 20% of patients had a history of using short-acting beta$_2$ agonists (SABAs) and/or oral corticosteroids, respectively.[12]

A total of 20,245 (out of 38,870) neuropsychiatric events of interest (ie, claims related to depression and/or self-harm) were identified among patients who received montelukast monotherapy.[4] Of these events among montelukast recipients, approximately 19,598 (97%) were for outpatient depressive disorder (ie, depression that required treatment with an antidepressant or psychotherapy within 30 days after the diagnosis date), 381 (2%) were for inpatient depressive disorder (ie, depression was the primary reason for inpatient admission on the claim), 124 (0.5%) were for hospitalization due to self-harm, and 142 (0.7%) were for modified self-harm (ie, hospitalization due to self-harm or relevant E-codes for self-harm [E950-E958]).[4] Notably, it was undetermined whether these neuropsychiatric events were for ongoing treatment of chronic pre-existing conditions, or related to an exacerbation or undertreatment of pre-existing conditions. The majority of depression or self-harm events among montelukast recipients occurred in patients with a history of a psychiatric disorder.[12] The average length of follow-up from the start of the medication to the neuropsychiatric event varied from 54−70 days for ICS recipients and 81−100 days for montelukast recipients.[4,12]

Compared to ICS monotherapy, montelukast monotherapy was associated with a significantly *reduced risk* for outpatient treatment of a depressive disorder (overall hazard ratio [HR]: 0.91; 95% CI: 0.89−0.93), even among patients with a psychiatric condition or psychotropic drug use preceding the ICS or montelukast exposure (HR: 0.89; 95% CI: 0.88−0.91), and pediatric patients 12−17 years of age (HR: 0.82; 95% CI: 0.76−0.89) and adults (HR: 0.90; 95% CI: 0.88−0.92).[4,12] There was no significantly increased risk of inpatient-treated depressive disorder with montelukast monotherapy compared to ICS monotherapy in the overall population, and among the subgroups of patients with a history of a psychiatric disorder, pediatric patients, or those treated in the period after the 2008 DSC and changes to montelukast product labeling. Moreover, the risk of self-harm, including when using the modified self-harm approach, associated with montelukast monotherapy was not significantly increased compared to ICS monotherapy. Two completed suicides occurred during the follow-up period, both in the montelukast cohort; both cases were female adults (>18 years of age) with a psychiatric history.[4,12] **Table 2** summarizes the results from the FDA's observational analysis.

Authors of this observational analysis mentioned that the finding of a significantly *decreased risk* of outpatient treatment for a depressive disorder with montelukast monotherapy compared to ICS-only use should be interpreted cautiously, as it could be due to the following reasons[4,12]:

- **Effect of 2008 DSC and labeling changes**: Most patients (90%) started on montelukast after the 2008 DSC and subsequent montelukast labeling changes, which advised providers to be alert for neuropsychiatric events and if such events occur, to evaluate the risks and benefits of continuing montelukast. Therefore, patients receiving montelukast could have discontinued the agent upon experiencing depressive symptoms without seeking outpatient treatment, or ICS therapy may have been preferred rather than montelukast for patients already undergoing depression treatment.
- **Patients may have continued treatment for a pre-existing depressive disorder (ie, depressive events may not have started after starting ICS or montelukast)**: A considerable number of patients with a pre-existing depressive disorder may have been continuing treatment, making it difficult to

determine if the outpatient depression diagnosis occurred after starting ICS or montelukast monotherapy for asthma.

Table 2. Results from the FDA's 2019 Observational Analysis on Neuropsychiatric Events Associated With Montelukast Use[4,12]

Neuropsychiatric event of interest (number of events)	Select results for montelukast monotherapy vs. ICS monotherapy
Outpatient depressive disorder • Montelukast monotherapy: 19,598 ○ Occurring in patients with a psychiatric history: 18,077 • ICS monotherapy: 18,142 ○ Occurring in patients with a psychiatric history: 17,105	**Outpatient depressive disorder HR (95% CI)** • **Overall: 0.91 (0.89–0.93)** • Subgroup analysis: ○ **Psychiatric history: 0.89 (0.88–0.91)** ○ 6–11 year olds: 1.02 (0.87–1.19) ○ **12–17 year olds: 0.82 (0.76–0.89)** ○ **≥18 year olds: 0.90 (0.88–0.92)** ○ **Use before DSC/montelukast labeling change (2000–2007): 0.90 (0.83–0.98)** ○ **Use after DSC/montelukast labeling change (2008–2015): 0.91 (0.89–0.93)**
Inpatient depressive disorder • Montelukast monotherapy: 381 ○ Occurring in patients with a psychiatric history: 350 • ICS monotherapy: 266 ○ Occurring in patients with a psychiatric history: 231	**Inpatient depressive disorder HR (95% CI)** • Overall: 1.06 (0.90–1.24) • Subgroup analysis: ○ Psychiatric history: 1.10 (0.93–1.31) ○ 6–11 year olds: 0.62 (0.26–1.48) ○ 12–17 year olds: 1.09 (0.73–1.61) ○ ≥18 year olds: 1.08 (0.90–1.29) ○ Use before DSC/montelukast labeling change (2000–2007): 0.94 (0.60–1.48) ○ Use after DSC/montelukast labeling change (2008–2015): 1.08 (0.91–1.29)
Self-harm (resulting in hospitalization)[a] • Montelukast monotherapy: 124 ○ Occurring in patients with a psychiatric history: NR • ICS monotherapy: 95 ○ Occurring in patients with a psychiatric history: NR	**Self-harm**[a] **HR (95% CI)** • Overall: 0.92 (0.69–1.21) • Subgroup analysis: ○ Psychiatric history: 0.89 (0.66–1.18) ○ 6–11 year olds: NR ○ 12–17 year olds: 1.04 (0.41–2.66) ○ ≥18 year olds: 0.91 (0.68–1.22) ○ Use before DSC/montelukast labeling change (2000–2007): 1.16 (0.49–2.74) ○ Use after DSC/montelukast labeling change (2008–2015): 0.90 (0.67–1.21)
Modified self-harm (resulting in hospitalization or a relevant E-code)[a] • Montelukast monotherapy: 142 ○ Occurring in patients with a psychiatric history: NR • ICS monotherapy: 122 ○ Occurring in patients with a psychiatric history: NR	**Modified self-harm**[a] **HR (95% CI)** • Overall: 0.81 (0.63–1.05) • Subgroup analysis: ○ Psychiatric history: 0.80 (0.61–1.04) ○ 6–11 year olds: NR ○ 12–17 year olds: 1.23 (0.57–2.68) ○ ≥18 year olds: 0.78 (0.60–1.03) ○ Use before DSC/montelukast labeling change (2000–2007): 1.06 (0.53–2.15) ○ Use after DSC/montelukast labeling change (2008–2015): 0.78 (0.60–1.03)

*Statistically significant results are **bolded**.*

[a] *Self-harm was defined "as a combination of inpatient, outpatient, or emergency room discharge diagnosis of poisoning, toxicity of non-medical substance, asphyxiation or an open wound to the elbow/wrist/forearm and an inpatient discharge diagnosis of depression, personality disorder, mania, adjustment reaction, or an unspecified nonpsychotic mental disorder on the same day."*[12] *(page 20); in addition to these outcomes, the modified self-harm also included relevant E-codes (E950–E958) in order to capture additional cases.*

Abbreviations: CI, confidence interval; DSC, drug safety communication; FDA, US Food and Drug Administration; HR, hazard ratio; ICS, inhaled corticosteroid; NR, not reported; US, United States

4.4 Select Limitations of the FAERS and SDD Data Sources

The FAERS neuropsychiatric events data was primarily from voluntarily submitted post-marketing case reports that are frequently limited by a lack of details about the neuropsychiatric event, making it difficult to establish montelukast as a contributor to the event.[4,11] Moreover, it is challenging, if not impossible, to determine the true incidence of neuropsychiatric events among all montelukast-exposed patients since the total number of people exposed to montelukast is unknown.[11] Additionally, the FDA's observational study using SDD data was unable to capture all depression and self-harm events, because only events in which patients presented for medical care were captured by claims data.[4]

4.5 FDA Conclusions About Montelukast Safety

After reviewing the observational evidence about the possible neuropsychiatric risks with montelukast and convening an advisory meeting in 2019, **the FDA ultimately decided to make 2 changes to the montelukast prescribing information: (1) neuropsychiatric risks were elevated from a warning/precaution to a black box warning; and (2) the FDA-indication for AR was changed to recommend against montelukast as a first-line treatment for AR.[11] The FDA highlighted that these changes were made primarily to increase awareness about the possibility of neuropsychiatric events in general and that these events can be severe, but also to maintain access to montelukast for patients who benefit from this therapy.** The FDA expressed that the labeling changes may prompt providers to weigh the risks versus benefits of montelukast treatment for the individual patient. Moreover, risks may outweigh the benefits for off-label use if the benefits are not established. Labeling changes were made to improve communication between patients and providers about the potential risk of neuropsychiatric events with montelukast, despite the inconclusive observational evidence.[11]

It was evident from public feedback received during a 2019 FDA pediatric advisory council meeting that montelukast's existing label at that time, with the precaution/warning for neuropsychiatric events, did not garner a sufficient level of awareness about the possible risk and severity of neuropsychiatric events with montelukast use.[11,18] For example, despite the labeled warning, caregivers and patients described how their provider did not discuss with them the potential for neuropsychiatric effects with montelukast use.[11] To heighten awareness, the FDA decided to elevate the warning for neuropsychiatric events to a black box warning, and they performed a risk-benefit assessment of montelukast for each approved indication to inform the black box warning. The FDA concluded that the potential neuropsychiatric risks of montelukast outweighed the potential benefit as a first-line treatment for AR, since AR is usually a mild disease that is treatable with other safe and effective options including over-the-counter medications (eg, loratadine, fexofenadine).[11] Thus, the current montelukast black box warning for neuropsychiatric events and the indication labeling advises to reserve montelukast for patients with AR who inadequately respond or cannot tolerate alternative therapies.[1] The FDA's risk-benefit analysis determined that changes to the asthma and EIB indications for montelukast were not necessary, with appropriate montelukast use for these conditions to be determined by provider discretion on an individual basis,[11] considering that other options may also be associated with psychiatric risks (eg, ICS) or other issues (eg, tolerance development with frequent beta-agonist use).[19-22]

Because of the seriousness of neuropsychiatric events, the need to consider the risks when prescribing montelukast, and changes to montelukast's indication for AR, the FDA decided to escalate the warning

of potential neuropsychiatric events to a black box warning.[11] A new medication guide for patients and caregivers was also required to reflect the safety changes.[2] No labeling changes were made for zafirlukast or zileuton because they are structurally and mechanistically dissimilar from montelukast, not approved for AR, and there was a paucity of post-marketing reports for neuropsychiatric events with either agent.[11]

4.6 Newer Evidence for Neuropsychiatric Risks Potentially Related to Montelukast Exposure

We identified 1 SR, and 1 SR and meta-analysis (SRMA), both published in 2023, that evaluated the association between montelukast and neuropsychiatric events.[23,24] The SR (Lo et al) included observational studies, reviews of randomized controlled trials (RCTs), pharmacovigilance studies, and case reports/series in adults and children with asthma,[23] whereas the SRMA (Mou et al) included RCTs only in adults and children with asthma and/or AR.[24] Literature searches were conducted in several bibliographic databases (eg, Embase, PubMed) generally from inception up to 2022 or 2023 for Lou et al and Mou et al, respectively.[23,24] In total, 59 studies were included by Lo et al with comparisons between montelukast and non-montelukast users (eg, placebo, ICS, ICS/LABA), and 18 RCTs were included by Mou et al with comparisons between montelukast and placebo or active comparator.[23-25] Six of the 18 included RCTs by Mou et al compared montelukast as adjunctive therapy to loratadine or budesonide, versus loratadine or budesonide monotherapy, respectively.[24] Of all observational studies and reviews of RCTs included by Lo et al, 8 included children and young adults (<24 years of age), and 3 studies included older adults (>50 years of age) only.[23] The quality of observational studies included by Lo et al varied from poor quality to high quality based on the Newcastle-Ottawa scores, with 7 out of 16 observational studies considered to be high quality (score of 7–9).[23,25] Most RCTs included by Mou et al were in patients ≥15 year of age, and 11 RCTs were in patients with asthma only, 6 RCTs were in patients with AR only, and 1 RCT was in patients with asthma and AR.[24] Risk of bias of the 18 included RCTs by Mou et al was evaluated using the Jadad scale: 12 RCTs had a low risk of bias; 4 RCTs had a moderate risk of bias; and 2 RCTs had a high risk of bias.[24] While Mou et al tended to describe results related to neuropsychiatric events in general,[24] Lou et al described results with respect to specific neuropsychiatric outcomes including suicide, depression, anxiety, and sleep disorders.[23]

Lo et al summarized findings from individual studies, overall finding mixed results for an association between montelukast use and neuropsychiatric diagnoses.[23] Montelukast exposure was not statistically associated with an increased risk of suicide-related events based on 6 observational studies of pediatric and adult patients. Results from studies of pediatric and adult patients were inconsistent based on the definition of depression: no significant association was found between montelukast use and depression (as defined by ICD-10 codes) based on 3 observational studies and 1 review of RCTs, but among the 4 studies that used antidepressants as a proxy for depression, the association between montelukast and an antidepressant prescription was significant. In some, but not all studies, montelukast use in adults, especially older adults, was associated with an increased risk of anxiety, other anxiety-related disorders, and sleep disorders/disturbances (eg, insomnia, nightmares) based on observational studies and pharmacovigilance studies (case reports/series).[23] Overall, while several case reports described neuropsychiatric events among children administered montelukast, conflicting results were found for an association between montelukast use and the risk of neuropsychiatric events in observational studies exclusively of pediatric patients with asthma, including those reviewed by the FDA in 2019.[4,23]

In the SRMA conducted by Mou et al that included 18 RCTs with follow-up durations ranging from 2−24 weeks, no significant association was found between montelukast exposure and the risk of neuropsychiatric events compared to placebo in patients with asthma and/or AR (RR: 0.88; 95% CI: 0.75−1.03) by the meta-analysis of 11 RCTs.[24] Likewise, compared to placebo, montelukast was not associated with a significantly increased risk of neuropsychiatric events among analyzed subgroups of: <1 month of montelukast exposure (RR: 0.78; 95% CI: 0.51−1.21) based on 4 RCTs; ≥1 month of montelukast exposure (RR: 0.91; 95% CI: 0.68−1.22) based on 7 RCTs; patients ≥15 years of age (0.87; 95% CI: 0.73−1.02) based on 9 RCTs; or pediatric patients ≤14 years of age (RR: 0.97; 95% CI: 0.64−1.47) based on 2 RCTs. Moreover, there was no significant association between montelukast versus placebo for the risk of neuropsychiatric events in patients with asthma only (RR: 0.86; 95% CI: 0.73−1.02) based on 7 RCTs, or AR only (RR: 1.04; 95% CI: 0.55−1.98) based on 3 RCTs.[24]

5.0 DOSING AND ADMINISTRATION OF MONTELUKAST

Montelukast is available in several oral dosage formulations, including film-coated tablets (10 mg), chewable tablets (4 mg and 5 mg), and granules (4 mg packet).[1] Selection of an appropriate dosage form depends on the patient's age and the FDA-approved indication (ie, asthma, EIB, AR).

- Asthma: prophylaxis and chronic treatment in adults and children aged ≥1 year
- EIB: for prevention in patients aged ≥6 years
- AR: for relief of symptoms associated with (a) seasonal AR in patients aged ≥2 years, or (b) perennial AR in patients aged ≥6 months

Treatment of AR with montelukast should be reserved for patients who are intolerant or have an inadequate response to other treatments, including over-the-counter medicines (eg, loratadine, cetirizine, fexofenadine) and/or nasal sprays (eg, fluticasone, triamcinolone), due to the potential for neuropsychiatric symptoms.[1,2]

The recommended daily dosages of montelukast vary by age: 4 mg for patients 6 months (for AR) or 12 months (for asthma) to 5 years of age; 5 mg for patients 6−14 years of age; and 10 mg for patients ≥15 years of age.[1] Notably, for children ages 2−5 years, the 4 mg oral granule can be used as an alternative to the 4 mg chewable tablet.[1]

Montelukast should be given once daily for asthma and AR (seasonal or perennial), whereas for EIB prevention, the dose should be taken as-needed at least 2 hours before exercise (refer to **Table 3** for administration details).[1] Daily use of montelukast for chronic asthma management has not been proven to prevent EIB episodes. Nonetheless, patients with EIB already taking montelukast daily for another indication, including asthma, should continue to take it as directed, and not take an additional dose for EIB prevention.[1]

Table 3 summarizes the FDA-approved indications for montelukast and dosing/administration information, according to prescribing information.

Table 3. Montelukast (Singulair) FDA-approved Indications and Dosing/Administration Information[1]

FDA-approved indications
1. Prophylaxis and chronic treatment of asthma in patients aged ≥1 year (12 months) *Limitation of use:* should not be used to treat an acute asthma attack
2. Prevention of exercise-induced bronchoconstriction in patients aged ≥6 years
3. Alleviation of allergic rhinitis (seasonal or perennial) symptoms: Seasonal allergic rhinitis in patients aged ≥2 years Perennial allergic rhinitis in patients aged ≥6 months *Use for allergic rhinitis should be reserved for patients who are intolerant or have an inadequate response to other treatments due to the risk of neuropsychiatric events, which may potentially outweigh the therapeutic benefits*
Dosing and administration information[a]
1. Asthma[b]: taken once daily by mouth in the evening, with or without food (*see below for the recommended dosage form and strength based on the patient's age*)
▪ Patients aged 12–23 months: one 4 mg oral granule packet[c] ▪ Patients aged 2–5 years: one 4 mg chewable tablet OR one 4 mg oral granule packet[c] ▪ Patients aged 6–14 years: one 5 mg chewable tablet ▪ Patients aged ≥15 years (including adults): one 10 mg tablet ○ If a dose is missed, the next dose should be taken as regularly scheduled; do not take 2 doses simultaneously
2. Prevention of exercise-induced bronchoconstriction: taken by mouth at least 2 hours before exercise (*see below for the recommended dosage form and strength based on the patient's age*)
▪ Patients aged 6–14 years: one 5 mg chewable tablet ▪ Patients aged ≥15 years (including adults): one 10 mg tablet ○ Do not take an additional dose within 24 hours of a previous dose ○ Patients using montelukast on a daily basis for a different indication (eg, chronic asthma) should not take an extra dose for the prevention of exercise-induced bronchoconstriction ▪ Patients should have access to a short-acting inhaled $beta_2$ agonist for rescue treatment ○ Daily use of montelukast for managing chronic asthma has not been proven to prevent acute episodes of exercise-induced bronchoconstriction
3. Allergic rhinitis (seasonal or perennial)[b]: taken once daily by mouth, regardless of meal times; time of dose can be individualized based on patient needs (*see below for the recommended dosage form and strength based on the patient's age*)
▪ Patients aged 6–23 months: one 4 mg oral granule packet[c] (**for perennial allergic rhinitis only**) ▪ Patients aged 2–5 years: one 4 mg chewable tablet OR one 4 mg oral granule packet[c] ▪ Patients aged 6–14 years: one 5 mg chewable tablet ▪ Patients aged ≥15 years (including adults): one 10 mg tablet ○ If a dose is missed, the next dose should be taken as regularly scheduled; do not take 2 doses simultaneously

[a] *Montelukast is available in 10 mg film-coated tablets, 5 mg and 4 mg chewable tablets, and 4 mg oral granule packets. Notably, the 4 mg and 5 mg chewable tablets contain phenylalanine, which can be harmful for patients with phenylketonuria (see* ***Appendix B****).*

[b] *A single oral dose of montelukast, administered once daily by mouth in the evening, should be used in patients with both asthma and allergic rhinitis. If a dose is missed, the next dose should be taken as regularly scheduled.*

[c] *Oral granules can be given directly in the mouth, dissolved in 5 mL (1 teaspoonful) of baby formula or breast milk, or mixed with certain soft foods (ie, applesauce, rice, carrots, ice cream). Only open the packet upon intended use, with the full dose administered within 15 minutes after opening, and any unused portion discarded if mixed with baby formula, breast milk, or food. While the granules can be dissolved in baby formula or breast milk, they should not be dissolved in any other liquid; however, any liquid can be consumed after administration. Oral granules can be taken regardless of meal times.*

Abbreviations: FDA, US Food and Drug Administration; US, United States

6.0 DISEASE OVERVIEW AND TREATMENT GUIDELINES

Asthma, EIB, and AR are related conditions that are characterized by inflammation of the upper or lower respiratory airways, and often coincide with each other.

- Asthma is a chronic inflammatory disorder of the respiratory airways, often presenting with symptoms such as shortness of breath, wheezing, chest tightness, and cough.[19]
- EIB refers to the transient narrowing of the respiratory airways during or after physical exertion, leading to nonspecific respiratory symptoms (eg, wheezing, shortness of breath).[20,26]
- AR is an immune-mediated allergic reaction caused by exposure to environmental allergens, resulting in nasal congestion, nasal pruritis, sneezing, and rhinorrhea.[27-29]

Predisposing risk factors for EIB include a history of AR or asthma, either of which can co-occur with EIB[22,26,30]; EIB has been observed in up to 90% of individuals with asthma,[26,31] including children.[30] Additionally, most patients who suffer from asthma also experience AR (about 80%),[27] and up to 40% of patients with AR have comorbid asthma.[19] In children, inadequately managed AR is associated with greater severity and earlier onset of asthma.[32] For patients with asthma, the presence of either EIB or AR can indicate poor asthma control.[19,28]

For pharmacologic recommendations, especially those pertaining to LTRAs, for the treatment of asthma, EIB, and AR, we reviewed guidelines from Global Initiative for Asthma (GINA),[19] National Heart, Lung, and Blood Institute (NHLBI)/ National Asthma Education and Prevention Program (NAEPP),[33,34] American Academy of Allergy, Asthma, and Immunology (AAAAI),[20] AAAAI/ American College of Allergy, Asthma, and Immunology (ACAAI),[8,22] and American Thoracic Society (ATS).[21]

The following subsections provide additional details about the disease and guideline-recommended treatments for asthma (**Section 6.1**), EIB (**Section 6.2**), and AR (**Section 6.3**).

6.1 Asthma

Asthma is a heterogeneous condition, typically associated with chronic inflammation in the respiratory airways.[19] It is characterized by respiratory symptoms, including shortness of breath, wheezing, chest tightness, and cough, which fluctuate in frequency and severity over time. Additionally, intermittent airflow restriction can occur, which may eventually progress to a chronic state. Exacerbating factors that trigger symptom fluctuations include exercise, weather condition changes, exposure to allergens or irritants, or viral respiratory infections. Asthma commonly manifests in early childhood.[19]

According to 2021 data from the Centers for Disease Control and Prevention (CDC), asthma affects approximately 8% of US adults (20.2 million) and 6.5% of US children (4.6 million).[35] In Utah, the estimated prevalence is 9.7% in adults and 5.5% in those <17 years of age.[36,37] Asthma poses a significant economic burden to the US healthcare system, costing roughly 50 billion dollars yearly.[38,39] Additionally, in 2020, asthma was attributed to more than 900,000 emergency department visits and 94,000 hospitalizations in the US.[35] Asthma has a substantial impact on patients' quality of life, affecting aspects such as sleep, school, work, and physical activity.[26]

6.1.1 Overview of Asthma Treatment

Pharmacotherapies for asthma include inhaled corticosteroids (ICSs), short-acting beta$_2$ agonists (SABAs), and long-acting beta$_2$ agonists (LABAs).[19] Reliever products are used for acute symptoms and exacerbations; these products contain SABAs, ICS, and/or formoterol. Controller products, also known as maintenance therapy, are used on a daily, scheduled basis to maintain control of symptoms. Controllers mainly contain ICS, LABAs, or LTRAs. Montelukast, an LTRA, is a controller medication used daily regardless if symptoms are present; it can be used as monotherapy or add-on treatment (eg, in combination with an ICS for some asthma patients).[19]

6.1.2 Guidelines for Asthma Management

We reviewed 2 recent clinical practice guidelines for asthma management: the GINA guideline published in 2023,[19] and the NHLBI/ NAEPP guideline initially published in 2007,[34] with a focused updated released in 2020.[33] However, the 2020 NAEPP focused update did not consider updated evidence for LTRAs or other agents (eg, cromolyn, theophylline), and instead carried forward prior recommendations for the place in therapy of these agents, while updating recommendations for other therapies.[33] While the NAEPP 2020 focused update addressed several pre-selected questions, it noted that LTRAs had limited availability in the US and/or an elevated risk of adverse effects, including neuropsychiatric events for montelukast, making them less preferable options in general.[33]

Both GINA and the NAEPP provide a stepwise treatment approach for asthma management across various age groups, tailoring pharmacologic therapy based on the patient's level of asthma symptom control and risk factors for exacerbations (see **Appendix C** for additional details).[19,33,34] Treatment steps tend to correspond to asthma severity, generally categorized as mild (steps 1 or 2), moderate (steps 3 or 4), or severe (step 5[+]).[19,33,34] For GINA, preferred, and in some cases, alternative controller and reliever options are given for each step, in addition to "other controller options", which may have significantly lower efficacy, pose increased risks, or lack substantial supportive evidence relative to the preferred or alternative controllers.[19] The NAEPP also specifies preferred and alternative choices for each treatment step, with alternatives being less efficacious or having limited evidence to support use compared to preferred options.[33,34] However, clinicians and patients might opt for an alternative option based on patient preference or if the preferred treatment is unavailable or too expensive.[33] Patients with well-controlled asthma already taking an alternative agent may continue the therapy, rather than switching to another medication.[33]

6.1.2.1 Guideline Recommendations for LTRAs in the Treatment of Asthma

GINA (2023) considers LTRA monotherapy or add-on therapy as an alternative option to other controller therapies due to inferior efficacy and the risk of neuropsychiatric events with montelukast[19,40]:

- GINA recommends LTRAs as an "other controller option" for adults, adolescents (≥12 years), and children (≤11 years), as an alternative monotherapy option for step 2 or an alternative add-on option to ICS-containing regimens at higher treatment steps.
- As monotherapy, LTRAs are not as effective as daily ICS for the treatment of asthma, especially for reducing exacerbations. Combine use of an LTRA and ICS has also been shown to be less effective than ICS-LABA combination regimens.

- Specifically for montelukast, there is a risk of neuropsychiatric events, which applies to children and adults. The GINA guideline advises that the adverse effect potential of montelukast be weighed against potential benefits, particularly in younger children, before its prescribed.

According to GINA, LTRAs are reserved for adults and adolescents aged ≥12 years on treatment steps 2−5, typically as add-on therapy to an existing regimen.[19] For the management of difficult-to-treat asthma in adults and adolescents, adding a non-biologic agent, such as an LTRA, to a medium- or high-dose ICS can be considered before adding a targeted biologic therapy (eg, anti-immunoglobulin E [anti-IgE] agent, anti-interleukin 5 receptor [anti-IL5/5R] agent, anti-interleukin 4 receptor [anti-IL4R] agent), if appropriate. For children 11 years of age or younger, GINA reserves LTRA therapy for treatment steps 2−4, either as monotherapy or in combination with an ICS.[19]

Similar to the GINA guideline,[19] the NAEPP guideline generally considered LTRAs, either as monotherapy or an adjunct to ICS, as an alternative option for adults, adolescents, and children (≤11 years) with persistent asthma (for treatment step 2 or above).[33]

With respect to managing asthma in patients with aspirin-exacerbated respiratory disease (AERD), formerly known as aspirin-induced asthma, an LTRA may be a suitable option, even though ICSs are the mainstay treatment.[19] Patients with AERD should avoid aspirin- or nonsteroidal anti-inflammatory drug (NSAID)-containing products, in addition to other agents that block cyclooxygenase-1, due to the potential for asthma exacerbation. Aspirin desensitization is another treatment option, but its implementation should be supervised by a specialist in a medical setting.[19]

Table 4 summarizes the guideline recommendations for the use of LTRAs in the treatment of asthma. For additional information on other pharmacologic interventions, see **Appendix C**.

Table 4. Recommendations for the Use of Leukotriene Receptor Antagonists by Age and Treatment Step in Recent US/International Asthma Guidelines

Global Initiative for Asthma (GINA); 2023[19]				
Population	**Treatment step #**	**Preferred controller + reliever option(s):**		**Alternative or other controller option (LTRAs[a])**
		Track 1[b]	**Track 2[b]**	
Adults and adolescents (≥12 years of age)	**2**	• As-needed low-dose ICS-formoterol	• Low-dose maintenance ICS + as-needed SABA or as-needed ICS-SABA	• Daily **LTRA**
	3	• Low-dose ICS-formoterol as MART	• Low-dose maintenance ICS-LABA + as-needed SABA or as-needed ICS-SABA	• **Adding** an **LTRA** to an existing therapeutic regimen
	4	• Medium-dose maintenance ICS-formoterol + as-needed low-dose ICS-formoterol	• Medium- or high-dose maintenance ICS-LABA + as-needed ICS-SABA or as-needed SABA	
	5	• Adding a LAMA, considering high-dose ICS-formoterol, or consulting for phenotypic evaluation ± add-on biologic therapy		• If not previously tried, **add-on therapy with an LTRA**
Children (6–11 years of age)	**2**	• Daily low-dose ICS + as-needed SABA		• Daily **LTRA**
	3	• Daily low-dose ICS-LABA + as-needed SABA (or ICS-formoterol as MART), or • Medium-dose ICS + as-needed SABA (or ICS-formoterol as MART), or • Very-low dose ICS-formoterol as MART		• Low dose ICS **+ LTRA**
	4	• Medium-dose ICS-LABA + as-needed SABA (or ICS-formoterol as MART), or • Low-dose ICS-formoterol as MART		• If not previously tried, **add-on therapy with an LTRA**
Children (≤5 years of age)	**2**	• Daily low-dose ICS + as-needed SABA		• Daily **LTRA**
	3	• Medium-dose ICS (ie, doubling the initial low dose ICS) + as-needed SABA		• Low dose ICS **+ LTRA**
	4	• Continue medium dose ICS + as-needed SABA and refer to a specialist		• **Adding** an **LTRA** to an existing therapeutic regimen
Other key points or recommendations (Strength; LOE, if available)[c]:				
• Although ICS is the mainstay treatment for AERD, **LTRAs** may be beneficial (Evidence B)				

See Appendix C for additional details on the stepwise treatment approach for asthma management in patients aged ≥12 years, and ≤ 11 years, as recommended by GINA (2023) and NAEPP (2007/2020).

[a] *Leukotriene receptor antagonists (LTRAs), including montelukast, are considered an alternative option across all age ranges, which may have significantly lower efficacy, pose increased risks, or lack substantial supportive evidence relative to the preferred or alternative controllers.*

[b] *Track 1 is preferred over Track 2 given the demonstrated reduction for severe exacerbations with as-needed ICS-formoterol compared to as-needed SABA reliever, and offers a less complex regimen. Track 2 is an alternative if Track 1 is not feasible or is not favored by a patient with no previous exacerbations on their current therapeutic regimen. Treatment may be individualized by switching between tracks based on the patient's needs or may be stepped up or down within a track using the same reliever.*

[c] *GINA evidence levels: A, based on a large number of well-conducted randomized controlled trials (RCTs), systematic reviews (SRs), or observational studies, with consistent results; B, based on a limited number of RCTs or SRS, which may be potentially flawed (eg, results are inconsistent, small sample size); C, based on observational or non-randomized studies; D, based on panel consensus according to clinical expertise.*

[d] *LTRAs, along with other agents such as cromolyn, nedocromil, and theophylline were not considered in the 2020 guideline update; nonetheless, the guideline mentions these agents have limited availability in the US and/or an elevated risk of adverse effects, including neuropsychiatric events for montelukast, making them less preferable options in general.*

Abbreviations: AERD, aspirin-exacerbated respiratory disease; GINA, Global Initiative for Asthma; ICS(s), inhaled corticosteroid(s); LABA(s), long-acting beta$_2$ agonist(s); LAMA(s), long-acting muscarinic antagonist(s); LOE, level of evidence; LTRA(s), leukotriene receptor antagonist(s); MART, maintenance-and-reliever therapy; NAEPP, National Asthma Education and Prevention Program; NHLBI, National Heart, Lung, and Blood Institute; OSC(s), oral systemic corticosteroid(s); RCT(s), randomized controlled trial(s); SABA(s), short-acting beta$_2$ agonist(s); SR(s), systematic review(s); US, United States

Table 4. Recommendations for the Use of Leukotriene Receptor Antagonists by Age and Treatment Step in Recent US/International Asthma Guidelines

National Heart, Lung, and Blood Institute (NHLBI)/ National Asthma Education and Prevention Program (NAEPP); 2020[33] [e]			
Population	**Treatment step #**	**Preferred controller + reliever option(s):**	**Alternative controller option (LTRAs[a])**
Adults and adolescents (≥12 years of age)	**2**	• Daily low-dose ICS + as-needed SABA, or as-needed concomitant ICS + SABA	• Daily **LTRA**
	3	• Daily + as-needed low-dose ICS-formoterol (combination)	• Daily low-dose ICS **+ LTRA**
	4	• Daily + as-needed medium-dose ICS-formoterol (combination)	• Daily medium-dose ICS **+ LTRA**
	5	• Daily medium-high dose ICS-LABA + LAMA, and as-needed SABA	• Daily high-dose ICS **+ LTRA**
Children (5–11 years of age)	**2**	• Daily low-dose ICS + as-needed SABA	• Daily **LTRA**
	3	• Daily + as-needed low-dose ICS-formoterol (combination)	• Daily low-dose ICS **+ LTRA**
	4	• Daily + as-needed medium-dose ICS-formoterol (combination)	• Daily medium-dose ICS **+ LTRA**
	5	• Daily high-dose ICS-LABA + as-needed SABA	• Daily high-dose ICS **+ LTRA**
	6	• Daily high-dose ICS-LABA + OSC + as-needed SABA	• Daily high-dose ICS **+ LTRA** + OSC
Children (≤4 years of age)	**2**	• Daily low-dose ICS + as-needed SABA	• Daily **montelukast**
	4	• Daily medium-dose ICS-LABA + as-needed SABA	• Daily medium-dose ICS **+ montelukast**
	5	• Daily high-dose ICS-LABA + as-needed SABA	• Daily high-dose ICS **+ montelukast**
	6	• Daily high-dose ICS-LABA + OSC + as-needed SABA	• Daily high-dose ICS **+ montelukast** + OSC

See Appendix C for additional details on the stepwise treatment approach for asthma management in patients aged ≥12 years, and ≤ 11 years, as recommended by GINA (2023) and NAEPP (2007/2020).

[a] Leukotriene receptor antagonists (LTRAs), including montelukast, are considered an alternative option across all age ranges, which may have significantly lower efficacy, pose increased risks, or lack substantial supportive evidence relative to the preferred or alternative controllers.

[b] Track 1 is preferred over Track 2 given the demonstrated reduction for severe exacerbations with as-needed ICS-formoterol compared to as-needed SABA reliever, and offers a less complex regimen. Track 2 is an alternative if Track 1 is not feasible or is not favored by a patient with no previous exacerbations on their current therapeutic regimen. Treatment may be individualized by switching between tracks based on the patient's needs or may be stepped up or down within a track using the same reliever.

[c] GINA evidence levels: A, based on a large number of well-conducted randomized controlled trials (RCTs), systematic reviews (SRs), or observational studies, with consistent results; B, based on a limited number of RCTs or SRS, which may be potentially flawed (eg, results are inconsistent, small sample size); C, based on observational or non-randomized studies; D, based on panel consensus according to clinical expertise.

[d] LTRAs, along with other agents such as cromolyn, nedocromil, and theophylline were not considered in the 2020 guideline update; nonetheless, the guideline mentions these agents have limited availability in the US and/or an elevated risk of adverse effects, including neuropsychiatric events for montelukast, making them less preferable options in general.

Abbreviations: AERD, aspirin-exacerbated respiratory disease; GINA, Global Initiative for Asthma; ICS(s), inhaled corticosteroid(s); LABA(s), long-acting beta$_2$ agonist(s); LAMA(s), long-acting muscarinic antagonist(s); LOE, level of evidence; LTRA(s), leukotriene receptor antagonist(s); MART, maintenance-and-reliever therapy; NAEPP, National Asthma Education and Prevention Program; NHLBI, National Heart, Lung, and Blood Institute; OSC(s), oral systemic corticosteroid(s); RCT(s), randomized controlled trial(s); SABA(s), short-acting beta$_2$ agonist(s); SR(s), systematic review(s); US, United States

6.2 Exercise-induced Bronchoconstriction (EIB)

EIB, previously referred to as exercise-induced asthma, manifests during or after periods of physical exertion (usually within 15 minutes), leading to transient narrowing of the respiratory airways.[20,26] EIB commonly occurs with asthma. [26,30,31] The prevalence of EIB tends to be higher among elite athletes (up to 70%) than the general population (up to 20%), but varies based on the specific sport, environmental factors, and level of physical exertion.[20,26,31] While exercise has been shown to be beneficial in improving EIB severity and pulmonary function, some individuals with EIB may avoid physical activity due to symptoms (eg, shortness of breath, cough, wheezing, chest tightness), which may contribute to poor health outcomes.[26] Symptoms may manifest more frequently in particular settings with cold, dry air, or elevated airborne irritants/pollutants.[26] Typically, symptoms resolve spontaneously within 30 to 90 minutes, accompanied by a subsequent refractory period lasting <4 hours, during which bronchoconstriction is less likely to occur after exercise.[20,30,31]

Because EIB symptoms are often nonspecific, diagnosis relies on evaluating the changes in lung function, measured by the forced expiratory volume in 1 second (FEV_1), with direct or indirect bronchial provocation tests (eg, exercise challenge, mannitol inhalation, eucapnic voluntary hyperventilation).[20,21,31] When employing an exercise challenge test or a surrogate provocation test, diagnostic criterion for EIB is typically an FEV_1 percent decrease of ≥10% from the pre-exercise baseline,[21] although this threshold may vary based on the specific test.[20] In elite athletes, confirming the diagnosis of EIB requires a positive bronchoprovocation test or, unlike other patient populations, positive bronchodilator reversibility after SABA inhalation.[20,31]

6.2.1 Overview of EIB Treatment

Because EIB is an asthmatic condition, its pharmacologic management closely aligns with that of asthma, and the overall approach tends to be similar for patients with EIB only and those with EIB and coexisting asthma.[20] Pharmacologic options for EIB include SABAs, ICSs, LABAs, and LTRAs.[21] As-needed (ie, intermittent) reliever medications, primarily SABAs, are typically the first-line therapy to prevent EIB.[20-22] LTRAs are an alternative prophylactic option for intermittent use before exercise, for daily use, or as an add-on option for some patients (eg, those with an insufficient response to SABA monotherapy).[20-22] An estimated 15% to 20% of patients are non-responsive to SABA monotherapy.[20] ICS, added to as-needed SABA, tends to be preferred for patients with EIB and comorbid asthma[20,21]; LTRA can also be added to these therapies.[22]

In individuals with asthma, the presence of EIB may be an indicator of suboptimal asthma control[19]; addressing the uncontrolled asthma is essential to mitigate the manifestations of EIB (see **Section 6.1.2.1** for guideline recommendations related to the use of LTRAs in asthma management).[22,31]

6.2.2 Guidelines for EIB Prevention

Regarding the pharmacologic management of EIB, we reviewed a 2020 guideline published by the AAAAI; however, this guideline addressed the management of EIB in athletes only, and did not provide formal graded recommendations.[20] To provide comprehensive insight into the utilization of LTRAs for

EIB prevention in the general population, we supplemented this information with 2 earlier guidelines: one from AAAAI/ ACAAI (2016)[22] and the other from the ATS (2013).[21]

6.2.2.1 Guideline Recommendations for LTRAs in the Treatment of EIB

The AAAAI strongly recommended (2016; for the general population) or considered (2020; for athletes) LTRAs as intermittent (ie, as-needed 1−2 hours before exercise) or maintenance (ie, daily) option for EIB prophylaxis, but SABAs are generally considered first-line therapy because $beta_2$ agonists are the most effective class for acute prevention of intermittent EIB in athletes and the general population.[20,22] ATS (2013) tended to reserve LTRAs (and ICSs) as add-on therapies to an as-needed SABA in patients with or without asthma who require regular SABA use or continue to exhibit respiratory symptoms even with intermittent SABA monotherapy.[21] Typically, the choice of adding a daily LTRA or ICS to an as-needed SABA depends on patient preferences and lung function.[20,21] Adding an ICS may be preferred over an LTRA in patients with EIB and comorbid asthma given the greater anti-inflammatory effects.[20,21] While the 2023 GINA asthma guideline addresses the treatment of EIB, it does not specifically include LTRA therapy in the context of this condition, instead emphasizing daily use of an ICS for patients with EIB and asthma based on recommendations from the 2013 ATS guideline.[19]

Overall, LTRAs can be combined with as-needed SABA for patients with EIB. Unlike SABAs and LABAs, tolerance to LTRAs does not develop with daily use; however, patients respond variably to LTRA treatment, with approximately 50% achieving some degree of EIB attenuation.[20,22] Montelukast can prevent EIB within 1−2 hours of ingestion; and the bronchoprotective effects can last for 12−24 hours, while also hastening recovery from EIB.[22] However, unlike $beta_2$ agonists, LTRAs cannot reverse existing airway obstruction. While $beta_2$ agonists are considered by the AAAAI to be more effective than LTRAs, it is strongly advised limiting use of SABAs/LABAs before exercise to <4 times per week to maintain effectiveness.[22] Notably, not all patients who frequently use a SABA or LABA will develop tolerance.[22]

Table 5 summarizes the guideline treatment recommendations for EIB, including for other treatment options not previously discussed above.

Table 5. Guideline Recommendations for the Pharmacologic Treatment of Exercise-induced Bronchoconstriction

American Academy of Allergy, Asthma, and Immunology (AAAAI); 2020[20] Target age group/population for recommendations: athletes of all skill levels (eg, high school and college athletes, recreational athletes, professional athletes)
Key points for beta$_2$ agonists (Strength; LOE, if available):
• SABAs are considered first-line therapy for all patients with EIB, administered shortly before exercise (15–20 minutes) ○ LABAs can also be used in the treatment of EIB prevention (as-needed) and have a longer duration of action compared to SABAs, but should not be used alone ○ Chronic or frequent use of SABAs or LABAs may cause tolerance to develop, resulting in reduced efficacy and duration of effect
Key points for LTRAs (Strength; LOE, if available):
• LTRAs can be used for EIB prophylaxis, given daily or as-needed (ie, 1–2 hours before exercise), and can be used in combination with ICS therapy ○ Unlike beta$_2$ agonists, LTRAs do not cause the development of tolerance when taken daily, but they are unable to reverse existing airway obstruction
Key points for ICSs (Strength; LOE, if available):
• For patients with EIB and underlying asthma, ICSs are the preferred choice over other therapies, but should still be used with as-needed SABA or LABA therapy ○ Even when used in combination with an ICS, daily use of a SABA or LABA can result in tolerance. Therefore, daily ICS as maintenance prophylaxis for EIB is preferred over ICS in combination with a LABA.
Key points for other agents (eg, mast cell stabilizers, muscarinic receptor antagonists) (Strength; LOE, if available):
• Mast cell stabilizers (eg, cromolyn, nedocromil) can be used in the management of EIB if taken before exercise, but availability of these agents is limited in the US • Short-acting muscarinic receptor antagonists (eg, ipratropium bromide) have conflicting evidence in the prevention of EIB • Caution should be used with antihistamines and methylxanthines (eg, theophylline) due to conflicting evidence in the management of EIB
AAAAI/American College of Allergy, Asthma, and Immunology (ACAAI); 2016[22] [a] Target age group/population for recommendations: unspecified
General recommendations (Strength; LOE, if available):
• In individuals with asthma, the presence of EIB may signify inadequate management of underlying asthma; addressing the uncontrolled asthma is essential to achieving EIB control. (Strong; Evidence D) • Regular medical visits are encouraged, as medication efficacy may vary over time due to the fluctuating nature of asthma (if present), environmental factors, exercise intensity, and the potential for tolerance (if taking a beta$_2$ agonist). (Strong; Evidence A)
Recommendations for beta$_2$ agonists (Strength; LOE, if available):
• Intermittent use (ie, <4 times per week) of a SABA and/or LABA prior to exercise is recommended to prevent or mitigate EIB. (Strong; Evidence A) ○ SABAs have shown benefits against EIB, including as a preventive measure and expediting pulmonary function recovery when administered following a decline in pulmonary function post-exercise. (Strong; Evidence A) ○ Daily use of beta$_2$ agonists, either as monotherapy or adjunct to ICSs, may result in the development of tolerance (ie, diminished duration of EIB protection and extended recovery period in treatment response post-exercise; Strong; Evidence A)
Recommendations for LTRAs (Strength; LOE, if available):
• Daily LTRA therapy can be considered for EIB prevention, as this approach avoids tolerance development and has demonstrated efficacy in mitigating EIB in 50% of patients. Notably, LTRAs, taken either daily or as-needed, offer partial protection and cannot reverse airway obstruction. **(Strong; Evidence A)**
Recommendations for ICSs (Strength; LOE, if available):
• Because ICSs have the potential to reduce the frequency and severity of EIB in a dose-response manner, an ICS in conjunction with other therapies can be considered; EIB may not be completely eliminated with ICS therapy alone (Strong; Evidence A)

[a] AAAAI/ACAAI guideline evidence rating: A, based on meta-analysis of randomized controlled trials (RCTs) or at least one RCT; B, based on at least 1 non-randomized study or other type of quasi-experimental study or extrapolated from A evidence; C, based on non-experimental descriptive studies or extrapolated from A or B evidence; D, based on expert opinion and/or clinical experience or extrapolated based on A, B, or C evidence. Generally, recommendations assigned a strong rating are based on A or B evidence and moderate recommendations are based on B or C evidence, but if unavailable, lower quality evidence can be used, if benefits outweigh the risks. Weak recommendations are based on D evidence or well-conducted studies (A, B, or C) that demonstrate about equal benefit of one intervention to another.

[b] Recommendations were assigned a strength and evidence rating based on the GRADE approach, with the evidence quality as follows: High, based on RCTs; Moderate, based on well-conducted observational studies showing a large estimate of effect or flawed RCTs; Low, controlled observational studies; Very low, other study designs or uncontrolled observations (eg, case series, case reports); evidence quality could be downgraded or upgraded based on several factors (eg, bias). Strong recommendations represent that most patients should receive the intervention and the benefits outweigh the risks, whereas weak recommendations should incorporate additional decision aids to align with patient preferences and values, and the benefits likely outweigh the risks, but there is uncertainty.

Abbreviations: AAAAI, American Academy of Allergy, Asthma, and Immunology; ACAAI, American College of Allergy, Asthma, and Immunology; ATS, American Thoracic Society; EIB, exercise-induced bronchoconstriction; GRADE, Grades of Recommendation, Assessment, Development, and Evaluation; ICS(s), inhaled corticosteroid(s); LABA(s), long-acting beta$_2$ agonist(s); LOE, level of evidence; LTRA(s), leukotriene receptor antagonist(s); RCT(s), randomized controlled trial(s); SABA(s), short-acting beta$_2$ agonist(s); US, United States

Table 5. Guideline Recommendations for the Pharmacologic Treatment of Exercise-induced Bronchoconstriction

• Unless needed for comorbid moderate-to-severe persistent asthma, daily LABAs in combination with an ICS should not be used to treat EIB. Daily LABA use may result in tolerance, potentially even in combination with an ICS. (Strong; Evidence A)
Recommendations for other agents (ie, mast cell stabilizers, short-acting muscarinic receptor antagonists) (Strength; LOE, if available):
• Although availability in the US is limited, mast cell stabilizers can be considered to prevent EIB, either alone or in combination with other agents, administered shortly before exercise. Notably, these agents have a short duration of action and no bronchodilator properties. (Strong; Evidence A) • Inhaled ipratropium bromide can be considered for patients who are unresponsive to other agents for EIB; notably, effectiveness is variable. (Weak; Evidence A)
American Thoracic Society (ATS); 2013[21,41,42 b] Target age group/population for recommendations: unspecified
First-line treatment for all patients with EIB (Strength; LOE, if available):
• SABA prior to exercise (Strong; High)
For patients who require regular SABA use (ie, daily or more often) or continue to exhibit respiratory symptoms even with intermittent SABA monotherapy, the following options are recommended to be added (Strength; LOE, if available):
• **LTRA**, on a daily basis (Strong; Moderate) • Daily ICS, with or without LABA (Strong; Moderate); after starting, it may take 2–4 weeks to achieve maximal benefit • Mast cell stabilizing agent (Strong; High) or inhaled anticholinergic agent (Weak; Low) prior to exercise • Antihistamine, for patients with EIB and allergies only (Weak; Moderate)
The following is recommended against (Strength; LOE, if available):
• Daily LABA monotherapy (Strong; Moderate) • ICS monotherapy given as-needed prior to exercise only (Strong; Moderate) • Antihistamine in patients without allergies (Strong; Moderate)

[a] *AAAAI/ACAAI guideline evidence rating: A, based on meta-analysis of randomized controlled trials (RCTs) or at least one RCT; B, based on at least 1 non-randomized study or other type of quasi-experimental study or extrapolated from A evidence; C, based on non-experimental descriptive studies or extrapolated from A or B evidence; D, based on expert opinion and/or clinical experience or extrapolated based on A, B, or C evidence. Generally, recommendations assigned a strong rating are based on A or B evidence and moderate recommendations are based on B or C evidence, but if unavailable, lower quality evidence can be used, if benefits outweigh the risks. Weak recommendations are based on D evidence or well-conducted studies (A, B, or C) that demonstrate about equal benefit of one intervention to another.*

[b] *Recommendations were assigned a strength and evidence rating based on the GRADE approach, with the evidence quality as follows: High, based on RCTs; Moderate, based on well-conducted observational studies showing a large estimate of effect or flawed RCTs; Low, controlled observational studies; Very low, other study designs or uncontrolled observations (eg, case series, case reports); evidence quality could be downgraded or upgraded based on several factors (eg, bias). Strong recommendations represent that most patients should receive the intervention and the benefits outweigh the risks, whereas weak recommendations should incorporate additional decision aids to align with patient preferences and values, and the benefits likely outweigh the risks, but there is uncertainty.*

Abbreviations: AAAAI, American Academy of Allergy, Asthma, and Immunology; ACAAI, American College of Allergy, Asthma, and Immunology; ATS, American Thoracic Society; EIB, exercise-induced bronchoconstriction; GRADE, Grades of Recommendation, Assessment, Development, and Evaluation; ICS(s), inhaled corticosteroid(s); LABA(s), long-acting beta$_2$ agonist(s); LOE, level of evidence; LTRA(s), leukotriene receptor antagonist(s); RCT(s), randomized controlled trial(s); SABA(s), short-acting beta$_2$ agonist(s); US, United States

6.3 Allergic Rhinitis (AR)

AR, also referred to as hay fever, is a common inflammatory disorder of the nasal passages.[27-29] It is characterized by chronic, fluctuating symptoms (eg, nasal pruritis, sneezing, nasal congestion, rhinorrhea) triggered by exposure to environmental allergens.[27-29] Approximately 60 million people in the US suffer from AR, with self-reported rates up to 30% in adults and 40% in children.[8,43] Prevalence of AR tends to be highest around the second to fourth decade of life, after which it tends to gradually decline.[44] Notably, AR typically emerges following several years of allergen exposure, rendering it less common among children <2 years of age,[45] but almost half of patients experience symptoms before 6 years of age.[32]

Based on the timing pattern of the allergen trigger, AR can be classified as either seasonal or perennial, representing 20% and 40% of cases, respectively.[44] Usually seasonal allergens are various types of outdoor pollens or molds that are prevalent during specific times of the year (eg, spring, summer), whereas perennial allergens are dust mites, pet dander, or molds that are present year-round indoors.[27,29,44] Nearly 40% of individuals with AR experience an allergic response to both seasonal and perennial allergens, which in some instances can be the same trigger.[8,44] Notably, there are no explicit, consensus definitions for AR severity or frequency, but some clinicians generally classify symptoms as intermittent (ie, occurring <4 days per week or <4 consecutive weeks per year) or persistent (ie, occurring ≥4 days per week or ≥4 consecutive weeks per year); and mild (ie, symptoms do not disrupt patient's quality of life) or moderate/severe (ie, symptoms affect patient's quality of life including sleep, academic or work productivity, ability to perform daily activities, or are troublesome).[8,32,46]

AR can significantly affect a patient's quality of life by interfering with sleep, work, and other daily activities, and cause mood changes (eg, irritability), especially in children who may be unable to verbalize symptoms.[8,29,32] The economic burden of AR is substantial, amounting to approximately 3.4 billion dollars in direct healthcare expenses, with more than half of this cost attributable to medication costs.[43]

Diagnosis of AR includes conducting a clinical history, which is vital to ensuring an accurate diagnosis by evaluating potential triggers, family history, age at onset, prior treatment failures, comorbidities, and symptom frequency or duration.[8] In addition, the diagnostic evaluation also includes a physical examination, which can be used to observe suggestive symptoms (eg, frequent sniffling, mouth breathing) and/or rule out other conditions.[8,44] If AR is suspected, allergen testing via either skin prick testing or serum-specific immunoglobulin E (IgE) assessment are recommended to confirm the diagnosis.[8] Validated questionnaires (eg, Rhinitis Control Assessment Test[§])[47] can be used to help determine AR symptom severity or control.[8]

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§ The Rhinitis Control Assessment Test is a patient-administered 6-item question that evaluates the frequency of AR symptoms over a 1-week timeframe using a 5-point Likert scale, ranging from "never" to "extremely often", with lower scores indicating poorer symptom control.

6.3.1 Overview of AR Treatment

Pharmacologic management of AR tends to be dictated by symptom severity and persistence, and includes oral or intranasal antihistamines, oral or intranasal corticosteroids, mast cell stabilizers, and LTRAs.[8,32,45] Subcutaneous or sublingual allergen immunotherapy are other available options, but often require referral to an allergist.[32] For most patients, AR is usually persistent, necessitating ongoing therapy.[45] Nonetheless, pharmacotherapy can be stepped down/discontinued if symptoms are adequately controlled and the triggering allergen is no longer present.[8]

6.3.2 Guidelines for AR

For the management of AR, we reviewed a 2020 guideline published by AAAAI/ACAAI.[8] Although this guideline denotes that most pharmacologic options listed in their treatment algorithms are FDA-approved for children younger than 12 years old, many of the comparative studies were limited to children 12 years of age or older; therefore guideline recommendations for treatment are specified for children aged ≥12 years and adults.[8] **Appendix D** provides the stepwise pharmacologic treatment approach for AR management, as recommended by the 2020 AAAAI/ACAAI guideline.

6.3.2.1 Guideline Recommendations for LTRAs in the Treatment of AR

Guideline-recommended first-line treatments for intermittent and persistent AR include oral or intranasal antihistamines and intranasal corticosteroids.[8] If an oral antihistamine is used, it is preferred to use a second-generation rather than a first-generation to minimize potential sedating adverse effects. Generally, for the treatment of any severity of intermittent AR, oral or intranasal antihistamines are favored over intranasal corticosteroids. Conversely, intranasal corticosteroids tend to be preferred over antihistamines for treating persistent AR of any severity. Combination use of an intranasal corticosteroid with an intranasal antihistamine (administered in separate devices or a single device) may be an initial treatment option for patients with moderate to severe intermittent or persistent AR.[8]

Due to lower or similar efficacy to certain first-line treatments (eg, intranasal corticosteroids, oral antihistamines) **and the risk of neuropsychiatric events, AAAAI/ACAAI conditionally recommended against LTRAs, including montelukast, as initial first-line treatment for any severity of intermittent or persistent AR**, based on very low certainty evidence.[8] The conditional recommendation suggests that montelukast monotherapy may be an option for patients with AR, particularly for patients with comorbid asthma, but the provider should weigh the risks and benefits of therapy with the patient, especially in the context of preferred therapies.[8] Nonetheless, it is suggested that clinicians reserve montelukast for patients who are intolerant or unresponsive to alternative treatments,[8] consistent with montelukast FDA labeling.[1]

Combined treatment with an LTRA and another agent for moderate or severe intermittent or persistent AR is conditionally recommended against by the AAAAI/ACAAI.[8] Due to a paucity of supporting evidence, AAAAI/ACAAI suggests avoiding LTRAs, specifically montelukast, in combination with an intranasal corticosteroid for the treatment of AR. Additionally, despite some studies showing improved symptom reduction and quality of life among patients with seasonal AR taking an LTRA in combination with an oral antihistamine, it tends to be less effective than intranasal corticosteroids alone; therefore, it is suggested to avoid combining montelukast with an oral antihistamine in patients with seasonal AR,

inadequately controlled on an oral antihistamine. According to the guideline treatment algorithm, an LTRA in combination with an oral antihistamine is also recommended against for initial treatment of moderate or severe, persistent AR, and subsequent treatment of moderate or severe, intermittent or persistent AR.[8]

Table 6 summarizes the pharmacologic guideline recommendations for the treatment of AR. Refer to this table or **Appendix D** for additional options for second-line or later-line therapy.

Table 6. Guideline Recommendations for the Pharmacologic Treatment of Allergic Rhinitis

American Academy of Allergy, Asthma, and Immunology (AAAAI)/American College of Allergy, Asthma, and Immunology (ACAAI); 2020[8] [a] Target age group/population for recommendations: patients aged ≥12 years with allergic and/or nonallergic rhinitis[b]
Recommendations for oral or intranasal antihistamines and intranasal corticosteroids (Strength; LOE, if available):
• Intranasal antihistamines are recommended as first-line treatment for patients with seasonal AR (Strong; High) or intermittent AR (Conditional; Ungraded) • Intranasal corticosteroid monotherapy is preferred to combination use with an oral antihistamine in patients with seasonal and/or perennial AR (Conditional; Very low), including as initial treatment for symptomatic seasonal AR in patients ≥12 years of age (Strong; Moderate) • For persistent AR, intranasal corticosteroids are the preferred monotherapy choice (Strong; High) • Combined use of an intranasal antihistamine and intranasal corticosteroid can be considered for: ○ Patients at least 12 years of age with seasonal AR, and moderate/severe symptoms, as an initial treatment option (Conditional; High) ○ Patients suffering from moderate/severe seasonal or perennial AR that is unresponsive to pharmacologic interventions alone (Conditional; Moderate) • When using an oral antihistamine for the treatment of AR, second-generation antihistamines are preferred over first-generation antihistamines (Strong; High)
Recommendations for LTRAs (Strength; LOE, if available):
• Oral LTRAs, including montelukast, **should not be used as first-line treatment** for AR due to lower efficacy relative to other therapies. Additionally, given the post-marketing reports of serious neuropsychiatric events (eg, suicidal thoughts or behaviors) with montelukast, it is advised to reserve montelukast use for patients who are intolerant or unresponsive to alternative treatments (Conditional; Very low); this is consistent with montelukast FDA labeling.[1] ○ **As initial treatment for moderate/severe seasonal AR, an intranasal corticosteroid is preferred over an LTRA in patients aged ≥15 years** (Strong; High) • For seasonal AR, using montelukast in combination with an oral antihistamine **should be avoided** in patients with an inadequate response to an oral antihistamine alone (Conditional; Moderate) • Due to the insufficient evidence supporting efficacy and the potential risk of serious neuropsychiatric events, it is suggested to **avoid** adding montelukast to an intranasal corticosteroid for the treatment of AR (Conditional; Very low)
Recommendations for very severe or refractory AR (Strength; LOE, if available):
• May consider short-term use (5 to 7 days) of an OCS (Conditional; Very low) • Due to the potential for adverse effects, the use of depot parenteral corticosteroids are suggested against for the treatment of AR (Conditional; Low)
Recommendations for other agents (eg, mast cell stabilizers, short-acting muscarinic receptor antagonists; Strength; LOE, if available):
• To minimize AR symptoms, patients with episodic allergen exposures may benefit from intranasal cromolyn, taken immediately before exposure (Conditional; Very low) • Patients with perennial AR can be offered intranasal ipratropium, provided rhinorrhea is their primary nasal symptom (Conditional; Low) • Can consider adding intranasal ipratropium to patients who have persistent rhinorrhea despite intranasal corticosteroid use (Conditional; Moderate) • If tolerated, adding pseudoephedrine (a decongestant) can be considered for patients with AR who experience nasal congestion despite using an oral antihistamine (Conditional; Moderate)
Recommendations for allergen immunotherapy (ie, subcutaneous or sublingual tablets; Strength; LOE, if available):
• For patients with moderate/severe AR, can consider allergen immunotherapy in those who (a) have an inadequate response to allergen avoidance and/or pharmacotherapy or (b) prefer immunotherapy to pharmacotherapy for various reasons (eg, cost, adverse effects), and/or (c) seek the prospective advantages of immunotherapy in preventing or mitigating the severity of comorbidities (Conditional; Moderate) • For patients with mild/moderate asthma and comorbid AR, can consider allergen immunotherapy (Conditional; Moderate)

See Appendix D for additional details on the stepwise treatment approach for AR management, as recommended by AAAAI/ACAAI (2020).

[a] Guideline evidence rating: High, based on several well-conducted RCTs, systematic reviews, or meta-analyses, with the confidence in the effect estimate most likely unchanged with additional evidence; Moderate, based on fewer RCTs or non-randomized trials, with the confidence in the effect estimate likely to change with additional evidence; Low, based on nonexperimental studies, comparative studies, or registries, with the confidence in the effect estimate very likely to change with additional evidence; Very low, based on expert opinion or studies deemed to be very low quality, with the estimated effect to be very uncertain. Generally, recommendations assigned a strong strength would apply to most patients, with benefits outweighing harms; whereas, recommendations assigned a conditional strength may apply to most patients, but many may not desire the recommended course of action, with benefits most likely outweighing the risks. Guideline authors use the wording "we recommend" to refer to strong recommendations, and "we suggest" to refer to conditional recommendations.

[b] Only recommendations for allergic rhinitis (AR) were extracted, although the guideline also includes recommendations for nonallergic rhinitis; oral leukotriene receptor antagonists (LTRAs) are conditionally recommended against for the treatment of nonallergic rhinitis.

Abbreviations: AAAAI, American Academy of Allergy, Asthma, and Immunology; ACAAI, American College of Allergy, Asthma, and Immunology; AR, allergic rhinitis; FDA, US Food and Drug Administration; LOE, level of evidence; LTRA(s), leukotriene receptor antagonist(s); OCS(s), oral corticosteroid(s); RCT(s), randomized controlled trial(s); US, United States

7.0 OFF-LABEL USE OF MONTELUKAST

Off-label uses for montelukast in pediatric and adult patients, as indexed in the drug compendia Micromedex and Lexidrug, are summarized in **Table 7**. For Micromedex, only non-FDA approved indications designated as "effective" or "evidence favors efficacy" were extracted.

Except for urticaria, all of the listed off-label uses indexed in Lexidrug pertain to the adult population.[48] According to Lexidrug, some off-label uses are guideline-recommended (denoted as level of evidence [LOE] G in **Table 7**), including for aspirin desensitization in patients with AERD, and chronic or delayed-pressure urticaria in patients unresponsive to second-generation antihistamine monotherapy.[48] Notably, based on a limited number of RCTs or SRs, GINA mentions that an LTRA may be a suitable option for patients with AERD, even though ICSs are the mainstay treatment.[19] Yet AERD is uncommon in the pediatric population, especially since the use of aspirin is typically recommended to be avoided in patients <14 years of age due to the potential for Reye syndrome, and use in children aged ≥14 years should be determined on a case-by-case basis.[49]

Chronic, refractory urticaria and aspirin-induced asthma were listed as adult off-label uses[**] by Micromedex, in addition to atopic dermatitis and seasonal allergic conjunctivitis; of all which have supportive evidence for efficacy, graded *Category B* (based on RCTs with significant limitations, meta-analyses of RCTs with conflicting results, or non-randomized studies).[50] Pediatric, off-label uses for montelukast indexed in Micromedex are for the management of non-severe obstructive sleep apnea, aspirin-induced asthma, and seasonal allergic conjunctivitis, each with supportive evidence graded *Category B*.[50] Notably, only non-severe obstructive sleep apnea had a designation of "effective", whereas the other pediatric non-FDA uses were designated as "evidence favors efficacy".[50]

[**] Similar to Lexidrug, Micromedex also notes that montelukast can be used as adjunctive therapy for chronic urticaria in adults who are unresponsive to second-generation antihistamines, based on guideline recommendations.

Table 7. Off-label Indications for Montelukast, Per Micromedex and Lexidrug[48,50]

Micromedex[a]		Lexidrug[b]
Pediatric off-label indications		
Effective (Category B): • Non-severe obstructive sleep apnea	*Evidence favors efficacy (Category B):* • Aspirin-induced asthma • Seasonal allergic conjunctivitis	*Limited data available*[c]*:* • Urticaria (NSAID-induced)
Adult off-label indications		
Evidence favors efficacy (Category B): • Aspirin-induced asthma • Atopic dermatitis • Seasonal allergic conjunctivitis • Chronic, refractory urticaria (adjunct)		***LOE G****:* • Chronic or delayed-pressure urticaria (adjunct) *LOE B and* ***LOE G****:* • Aspirin-exacerbated respiratory disease, including aspirin desensitization *LOE C:* • Hypersensitivity reactions, rapid chemotherapy/biologics desensitization (premedication) • Infusion-related reactions, daratumumab-based regimens (premedication)

[a] *Only off-label indications indexed as "effective" or "evidence favors efficacy" were extracted; some off-label uses are displayed in the "In-depth Answers" view of the database only.*

Micromedex categories for the strength of evidence:

- *Category A: based on consistent results from meta-analyses of RCTs or several well-conducted, large RCTs*
- *Category B: based on meta-analyses of RCTs with conflicting results, RCTs with critical limitations (eg, bias, small sample size), or non-randomized studies*
- *Category C: based on expert consensus or opinion, case series, or case reports*

[b] ***Lexidrug level of evidence (LOE):***

- *B: based on RCTs with critical limitations (eg, flawed methods, inconsistent results), or very strong evidence from an alternative study design. Estimate of effect may change with future research.*
- *C: based on evidence from observational studies, unsystematic clinical experience, or potentially flawed RCTs. Estimate of effect is uncertain.*
- *G: supported by inclusion in at least one evidence- or consensus-based clinical practice guideline.*

[c] *Although Lexidrug lists no off-label uses of montelukast for pediatric patients, pediatric dosing recommendations were provided for montelukast in the treatment of urticaria.*

Abbreviations: LOE, level of evidence; RCT(s), randomized controlled trial(s)

8.0 OVERALL MONTELUKAST PLACE-IN-THERAPY

While the risk of neuropsychiatric events should be weighed before using montelukast,[19] first-line therapies for asthma, EIB, and AR also carry a risk of adverse effects or other factors that make them less favorable for some patients. Examples of situations in which montelukast therapy may be favorable are briefly discussed below:

- **Tolerance to SABAs/LABAs**: Patients with EIB who exercise frequently may require other preventative treatments (LTRA or ICS) to supplement the first-line treatment with SABAs because tolerance to beta$_2$ agonist bronchodilator effects can develop with daily use.[20,22] Compared to ICS that is recommended for daily use, LTRAs have the option to be taken as-needed 1−2 hours before exercise.[20,22]
- **Side effects with ICS**: ICS is typically preferred for patients with EIB and asthma,[20,21] but LTRAs may be an attractive option for children given that long-term ICS use in pediatric patients may reduce linear growth.[20] Additionally, older adults, especially those with comorbidities such as osteoporosis and/or glaucoma, may have increased susceptibility to certain side effects associated with ICS.[51] The benefits of prolonged administration of high-dose ICS, a necessary therapy for few asthma patients, must be weighed against potential risks.[51]
- **Patients with multiple comorbidities treatable with montelukast:** Depending on the conditions and availability of other options, montelukast may be a useful treatment to minimize polypharmacy in patients with multiple conditions treatable with montelukast.
- **Ease of administration:** Because montelukast is taken orally, and is available in a variety of dosage formulations, it may have greater ease of administration compared to inhaled medications, particularly in younger children who may be unable to appropriately use an inhaler.
- **Add-on therapy**: If response is inadequate with first-line treatments alone, LTRAs may be added to other agents, particularly for EIB and asthma.[19,21,33]

9.0 MONTELUKAST UTILIZATION DATA

Tables 8–10 provide pharmacy claims data for the fee-for-service (FFS) Utah Medicaid population over the past 1-year period, from March 2023 through February 2024.

The age group with the greatest proportion of patients receiving montelukast was adults ≥18 years of age (56.6%), followed by similar proportions in children ≤5 years of age (13.8%) and 6−10 years of age (13.5%). **Table 8** provides the age distribution of patients filling a montelukast prescription, of any formulation, in the last year.

Table 8. Age Distribution of Patients Receiving Montelukast from March 2023 through February 2024 (Fee-for-service Claims)

Age ranges	Patients	
	Number of patients	Percentage of patients
18 years and older	1143	56.6%
15–17 years	147	7.3%
11–14 years	177	8.8%
6–10 years	274	13.5%
5 years and younger	279	13.8%
Total	**2020**	**100%**

With respect to specific montelukast strengths and formulations, the 10 mg montelukast tablets had the highest utilization based on patient and claim counts, followed by the 5 mg and then 4 mg chewable tablets, and lastly, the 4 mg oral granules. **Table 9** shows the number of patients and claims for each dosage strength and formulation of montelukast in the last year.

Table 9. Patient and Claim Counts by Montelukast Strength/Formulation Filled from March 2023 through February 2024

Montelukast formulation and strength	Patients[a]	Claims
Fim-coated tablet, 10 mg	1434	5546
Chewable tablet, 5 mg	403	1351
Chewable tablet, 4 mg	211	676
Oral granule, 4 mg	<11	11
Total	2020 (unique patients)	7584

[a] *Some patients may have received more than one dosage form of montelukast during the 12-month period, and therefore, may be represented in more than 1 row.*

Table 10 provides the patient distribution for pertinent diagnosis codes (per International Classification of Diseases, 10th Revision [ICD-10]) for disease states related to approved uses of montelukast; codes of interest within 1 year before or after each montelukast claim were queried. Most patients filling montelukast across all age ranges (ie, ≤5 years, 6–14 years, and ≥15 years) had at least one ICD-10 diagnosis code related to an approved use of montelukast (ie, ICD-10 codes specific to AR or asthma, including EIB). While a considerable amount of patients lacked an ICD-10 claim code specific to asthma or AR, it is possible some patients had an indicated use but it was not represented in their ICD-10 claims record in the past year or was reflected by less specific coding. Notably, a claims record may not fully reflect the patient's medical chart for various reasons (eg, their diagnosis claim code may have been entered more than 1 year ago, or more recently, the patient may have not been Medicaid eligible at the time of their diagnosis claim or were seen for other chief complaints).

Table 10. Patient Distribution by ICD-10 Codes Related to Montelukast Approved Uses (for Patients Receiving Montelukast from March 2023 through February 2024)

ICD-10 codes of interest for patients filling montelukast over the last year[a]	Number of patients (%)		
	≤5 years	6–14 years	≥15 years
Patients with any asthma-related diagnosis (**J45.XXX**)	125	230	613
Patients with exercise-induced asthma diagnosis (**J45.990**)	<11	13	11
Patients with allergic rhinitis-related diagnosis (**J30.1X to J30.9**)	80	181	431
Patients filling montelukast *without* *any* of the above diagnoses	114	132	467

[a] *ICD-10 codes associated with an approved use of montelukast appearing in the patient's record* ***up to 1 year before or after*** *each montelukast claim. Patients could have multiple montelukast claims during the 1-year observation period and therefore multiple observation periods for capturing pertinent ICD-10 codes. Notably, patients could also have more than one ICD-10 code of interest.*

Abbreviations: ICD-10, International Classification of Disease, 10th Revision

Table 11 provides ICD-10 codes potentially related to an on-label or off-label use of montelukast in the subset of pediatric patients 14 years of age and younger *without* asthma-specific or AR-specific ICD-10 codes of interest (as listed in **Table 10**; N=246). While we cannot interpret that patients were certainly using montelukast to treat these conditions without investigating the patient's chart on an individual level, Table 11 provides an idea of *potential* indications for which these patients *might* be using montelukast. Codes are grouped in the table as (a) non-specific respiratory symptoms possibly related to asthma or other conditions (eg, wheezing), (b) respiratory infections (eg, that could exacerbate existing asthma or theoretically cause new-onset bronchoconstriction), (c) ICD-10 codes potentially related to compendia-recognized off-label uses of montelukast, and (d) other ICD-10 codes that might be related to other potential off-label uses of montelukast.

Table 11. Patient Distribution for Other Potentially Pertinent ICD-10 Codes in Patients 14 Years or Younger who Filled Montelukast and Lacked a Specific Asthma or AR Diagnosis Claim in the Previous Year[a]

ICD-10 code[b]	Description	Number of patients
Non-specific respiratory symptoms possibly related to asthma or other conditions		
R059	Cough, unspecified	17
R051	Acute cough	<11
R053	Chronic cough	<11
R062	Wheezing	<11
R0981	Nasal congestion	<11
R0602	Shortness of breath	<11
Respiratory infections		
J069	Acute upper respiratory infection, unspecified	25
J029	Acute pharyngitis, unspecified	23
J020	Streptococcal pharyngitis	14
J0190	Acute sinusitis, unspecified	<11
J329	Chronic sinusitis, unspecified	<11
J050	Acute obstructive laryngitis (Croup)	<11
J00	Acute nasopharyngitis (common cold)	<11
J040	Acute laryngitis	<11
J310	Chronic rhinitis	<11
J209	Acute bronchitis, unspecified	<11
J40	Bronchitis, not specified as acute or chronic	<11
U071	COVID-19	<11
Indications potentially related to a compendia-recognized off-label use of montelukast		
G4733	Obstructive sleep apnea	<11
G4730	Sleep apnea, unspecified	<11
L309	Dermatitis, unspecified	<11
R21	Rash and other nonspecific skin eruption	<11

[a] *This is not a comprehensive list; although we extracted ICD-10 codes for diagnoses most closely related to a potential off-label use of montelukast or non-specific codes that might indicate asthma symptoms (on-label), there may be unlisted ICD-10 diagnosis codes that are possibly related to montelukast use. Claims are among patients without a claim for an ICD-10 code specific to asthma, EIB, or AR from March 2023 through February 2024.*

[b] *ICD-10 codes appearing in the patient's record* ***up to 2 months before or after*** *each montelukast claim. Patients could have multiple montelukast claims during the 2-month observation period and therefore multiple observation periods for capturing pertinent ICD-10 codes. Notably, patients could also have more than one ICD-10 code.*

Abbreviations: AR, allergic rhinitis; EIB, exercise-induced bronchoconstriction; ICD-10, International Classification of Disease, 10th Revision

Table 11. Patient Distribution for Other Potentially Pertinent ICD-10 Codes in Patients 14 Years or Younger who Filled Montelukast and Lacked a Specific Asthma or AR Diagnosis Claim in the Previous Year[a]

ICD-10 code[b]	Description	Number of patients
L209	Atopic dermatitis, unspecified	<11
L2089	Other atopic dermatitis	<11
L259	Unspecified contact dermatitis, unspecified cause	<11
L500	Allergic urticaria	<11
L501	Idiopathic urticaria	<11
L509	Urticaria, unspecified	<11
H1033	Unspecified acute conjunctivitis, bilateral	<11
H1031	Unspecified acute conjunctivitis, right eye	<11
H109	Unspecified conjunctivitis	<11
Other indications that might be related to other potential off-label uses of montelukast		
H6693	Otitis media, unspecified, bilateral	<11
H6690	Otitis media, unspecified, unspecified ear	<11
H6692	Otitis media, unspecified, left ear	<11
H6691	Otitis media, unspecified, right ear	<11
J441	Chronic obstructive pulmonary disease with acute exacerbation, unspecified	<11
J449	Chronic obstructive pulmonary disease, unspecified	<11
K200	Eosinophilic esophagitis	<11

[a] *This is not a comprehensive list; although we extracted ICD-10 codes for diagnoses most closely related to a potential off-label use of montelukast or non-specific codes that might indicate asthma symptoms (on-label), there may be unlisted ICD-10 diagnosis codes that are possibly related to montelukast use. Claims are among patients without a claim for an ICD-10 code specific to asthma, EIB, or AR from March 2023 through February 2024.*

[b] *ICD-10 codes appearing in the patient's record* ***up to 2 months before or after*** *each montelukast claim. Patients could have multiple montelukast claims during the 2-month observation period and therefore multiple observation periods for capturing pertinent ICD-10 codes. Notably, patients could also have more than one ICD-10 code.*

Abbreviations: AR, allergic rhinitis; EIB, exercise-induced bronchoconstriction; ICD-10, International Classification of Disease, 10th Revision

10.0 CONSIDERATIONS FOR MONTELUKAST USE

Reviewed descriptive (eg, case reports), observational, and RCT evidence, primarily among patients with asthma, is mixed about the possible association between montelukast use and neuropsychiatric events.[4,13-16] Although the FDA concluded that evidence for the risk of neuropsychiatric events with montelukast was inconclusive, given the possible severity of the events and testimonies from patients and caregivers about the lack of education from their provider about the potential risk for such events, the FDA decided to elevate the level of warning about neuropsychiatric events to a black box warning in 2020.[11]

According to the FDA, the black box warning is intended to increase patient and provider awareness about the potential risk of neuropsychiatric events with montelukast, and to help ensure that use of montelukast is limited to patients in which the anticipated benefits outweigh the risks.[11] Clinical practice guidelines and the black box warning for montelukast advise that montelukast should not be used as first-line treatment for AR.[1,8]

The Utah Medicaid Drug Utilization Review (DUR) Board may consider discussing and/or recommending the interventions described below. Considering that the association between montelukast and the risk of neuropsychiatric events has been inconsistently demonstrated, with some evidence suggesting reduced risk with montelukast use, along with the FDA's intention of the black box warning primarily being to encourage awareness about the *potential* risk of neuropsychiatric events while maintaining patient access to montelukast for those in need, we suggest prioritizing retrospective DUR or educational interventions rather than stricter approaches/restrictions. For any policy or interventions, implementation feasibility should be considered, given the high frequency of montelukast use in the Utah Medicaid FFS population.

1. Consider implementing educational outreach or a retrospective DUR to notify providers (eg, by fax) of patients who are filling montelukast of the potential risk of neuropsychiatric events with montelukast exposure.
    a. Healthcare providers should be educated to counsel *all* patients/caregivers about the risk of neuropsychiatric events, which may include suicidal thoughts and/or behaviors, when prescribing montelukast.[1,2] Additionally, patients should be counseled to stop montelukast immediately if any neuropsychiatric symptoms or behavioral changes occur.[1,2]
    b. Neuropsychiatric events with montelukast use have been observed in patients with and without a pre-existing psychiatric condition; therefore, providers should be educated to monitor all treated patients for neuropsychiatric symptoms during montelukast use, and after discontinuation.
        i. Although neuropsychiatric symptoms usually resolve after discontinuing montelukast, some cases have reported a persistence or emergence of neuropsychiatric symptoms following montelukast discontinuation.[2]
    c. Prescribers should limit the use of montelukast for patients in which the potential benefits outweigh the risks. The FDA, montelukast labeling, and a clinical practice guideline advise to not use montelukast as first-line treatment for AR because this condition is usually mild and is treatable with other safe and effective options, including over-the-counter medications.[1,8,11]

d. Providers as well as patients/caregivers should be encouraged to voluntarily report any adverse effects related to montelukast to the FDA MedWatch program[††] to facilitate the continual monitoring of neuropsychiatric events by the FDA.[2]

e. Providers should urge patients/caregivers to review the medication guide that accompanies their montelukast prescription, as it delineates important safety considerations.[2]

2. If desired, a prior authorization (PA) for montelukast could be implemented to ensure that montelukast is prescribed for conditions where the potential benefits outweigh the risks. Consider the following caveat and criteria:

a. Caveat: The PA workload to meet patient needs for montelukast may be overwhelming for prescriber offices, given that it is currently utilized by many patients in the Medicaid FFS population (N=2020 patients from March 2023 through February 2024).

b. Montelukast should be prescribed in accordance with FDA labeling, including not exceeding the recommended daily dosage based on the indication and patient's age.[1]

c. Montelukast use should be reserved for clinical situations in which the potential benefits outweigh the risks. Before prescribing or continuing montelukast, the individual benefits and risks should be evaluated by the provider.[1]

i. Reviewed asthma guidelines recommended LTRAs, either as monotherapy or an adjunct to ICS, as an alternative option to other controller therapies (eg, ICS) for adults, adolescents, and children (≤11 years) due to inferior efficacy and the potential risk of neuropsychiatric events with montelukast use.[19,40]

ii. For the treatment of AR, montelukast should be reserved for patients with an inadequate response or intolerance to first-line therpies.[1]

(1) Based on a benefit-risk assessment, in 2019, the FDA concluded that the potential neuropsychiatric risks of montelukast outweighed the potential benefit as a first-line treatment for AR, which is usually a mild disease that is treatable with other safe and effective options, including over-the-counter medications.[11]

(2) The AAAAI/ACAAI guideline conditionally recommended against LTRAs, including montelukast, as initial first-line treatment for any severity of intermittent or persistent AR, due to lower or similar efficacy to first-line agents of other drug classes and the risk of neuropsychiatric events.[8]

iii. Although SABAs are generally considered first-line therapy for EIB prophylaxis, the AAAAI strongly recommended LTRAs for the general population or considered LTRAs for athletes as an intermittent (ie, as-needed 1–2 hours before exercise) or daily maintenance option.[20,22] However, an older guideline by ATS (2013; potentially based on older data) tended to reserve LTRAs (and ICSs) as add-on therapies to an as-needed SABA in patients with or without asthma who require regular SABA use or continue to exhibit respiratory symptoms even with intermittent SABA monotherapy.[21]

[††] MedWatch forms for reporting adverse events (AEs) are available at: https://www.fda.gov/safety/medical-product-safety-information/medwatch-forms-fda-safety-reporting

d. Off-label use of montelukast should be considered cautiously, and only for indications in which there is sufficient evidence for benefit and/or insufficient alternatives with a superior efficacy and/or safety profile.
e. Require providers to acknowledge that they counseled patients about the potential neuropsychiatric risks (eg, depression, sleep disturbances, suicidal thoughts and/or behaviors) associated with montelukast use, and that the patient/provider will monitor for such events.

11.0 SUMMARY

Montelukast (Singulair) has been approved by the US Food and Drug Administration (FDA) since 1998.[1] It is indicated for the treatment of: (a) asthma in patients aged ≥1 year, (b) seasonal and perennial allergic rhinitis (AR) in patients as young as 2 years or 6 months of age, respectively, with an inadequate response or intolerance to other treatments, and (c) prevention of exercise-induced bronchoconstriction (EIB) in patients aged ≥6 years.[1] Montelukast is a leukotriene receptor antagonist (LTRA) available in various oral formulations, with the recommended dosage and formulation based on age: 4 mg for patients 6 months (for AR) or 12 months (for asthma) to 5 years of age; 5 mg for patients 6−14 years of age; and 10 mg for patients ≥15 years of age. Montelukast is taken daily for asthma and AR, or may be taken as-needed ≥2 hours before exercise for EIB prophylaxis (to not exceed the maximum daily dose).[1] Asthma, EIB, and AR are related conditions that are characterized by inflammation of the upper or lower respiratory airways, and often coincide with each other.

Post-marketing reports of neuropsychiatric events in patients exposed to montelukast have been continually received by the FDA since 2007.[1,4,11] According to these case reports in the FDA Adverse Event Reporting System (FAERS), neuropsychiatric events were highly variable, some were serious (eg, suicidal thoughts and/or behaviors), and events occurred in patients of all ages with or without a history of psychiatric conditions.[1,4,11] Yet, a clear association/causal effect of neuropsychiatric events due to montelukast was largely unconfirmable because case reports did not contain enough information or occurred in the context of many confounding factors.[2,4] In 2019, the FDA reviewed additional observational evidence, primarily in pediatric patients.[4] Because the available evidence had considerable limitations and no clear association of neuropsychiatric risk in pediatric patients exposed to montelukast could be established,[4] the FDA pursued its own observational study, using claims data from the Sentinel Distributed Database (SDD).[12] This study included 457,377 patients (aged 6 years or older) in each exposure group (montelukast or ICS), and found no significantly increased risk of inpatient-treated depressive disorder or self-harm associated with montelukast monotherapy compared to ICS monotherapy.[12] Compared to ICS monotherapy, montelukast monotherapy was associated with a significantly *reduced risk* of outpatient-treated depressive disorder, even among pediatric patients 12−17 years of age, but authors of this observational analysis mentioned this finding should be interpreted cautiously.[12]

In 2020, the FDA made 2 major changes to the montelukast labeling to increase patient/provider awareness about the possibility and potential seriousness of neuropsychiatric events, while maintaining access to montelukast for patients who benefit from this therapy. The first change was to elevate the level of warning for neuropsychiatric events to a black box warning, and the second change was to recommended against montelukast as a first-line treatment for AR, and restrict its use to patients with an inadequate response to other treatments for AR.[11] No changes were made to the asthma and EIB

indications, with appropriate montelukast use for these conditions to be determined by provider discretion on an individual basis,[11] considering that other options may also be associated with psychiatric risks (eg, ICS) or other issues (eg, tolerance development with frequent beta-agonist use).[19-22] Regardless of age, the current montelukast labeling advises that providers inform patients of the potential for neuropsychiatric risks, and that patients and caregivers monitor for behavioral changes and new neuropsychiatric symptoms and discontinue treatment if they occur.[1]

A more recent systematic review found that montelukast exposure was not associated with a significant increased risk of suicide-related events, and mixed results for an association to depression.[23] In some, but not all studies, montelukast use in adults, especially older adults, was associated with an increased risk of anxiety, other anxiety-related disorders, and sleep disorders/disturbances. Overall, while several case reports described neuropsychiatric events among children administered montelukast, conflicting results were found for an association between montelukast use and the risk of neuropsychiatric events in observational studies exclusively of pediatric patients with asthma.[23] A 2023 systematic review and meta-analysis of randomized controlled trials found no significant association between montelukast exposure and the risk of neuropsychiatric events, compared to placebo, in patients with asthma and/or AR, including among pediatric patients ≤14 years of age.[24]

Frequent off-label use of montelukast, especially among younger patients, was a concern highlighted by the FDA in 2019 because the potential risks of montelukast may not outweigh the benefits for unestablished indications.[11] According to the drug compendia Micromedex and Lexidrug, recognized off-label uses include non-severe obstructive sleep apnea, aspirin-induced asthma, seasonal allergic conjunctivitis, and urticaria in pediatric patients; and atopic dermatitis, seasonal allergic conjunctivitis, urticaria, and aspirin-exacerbated respiratory disease (AERD), among others, in adults (see **Table 7**).[48,50]

For its FDA-approved uses, reviewed guidelines tend to recommend montelukast as a second-line or alternative option as monotherapy, and/or an optional for add-on therapy to first-line treatments.[8,19-22,33] Guidelines typically recommend selecting alternative options in place of first-line or preferred options for patient-specific situations, such as tolerability concerns, failure of first-line agents, or patient preference for a particular dosage form.[19,33] The following is an overview of the place-in-therapy of montelukast for its FDA-approved uses according to reviewed guidelines:

- For the treatment of asthma in children, adolescents, and adults, LTRAs are an alternative option as maintenance monotherapy for mild persistent asthma (ie, at treatment step 2), and one of several alternative options for add-on therapy to an ICS-based maintenance regimen for moderate to severe asthma.[19,33]
- For EIB prevention, montelukast is typically an alternative first-line option or an add-on option to first-line therapy, which is generally a short-acting $beta_2$ agonist (SABA).[20-22] Because tolerance may potentially develop with frequent or prolonged $beta_2$ agonist use, LTRAs could be helpful for patients with EIB who exercise frequently to supplement the first-line treatment with SABAs.[20,22] Compared to ICS, which is recommended for daily use, LTRAs have the option to be taken as-needed 1–2 hours before exercise.[20,22] Notably, while LTRAs reduce the risk of EIB, they cannot reverse existing airway obstruction.[20]
- In agreement with the FDA's guidance and required montelukast labeling changes to the AR indication, the reviewed AR guideline conditionally recommended against LTRAs as initial first-line

treatment for any severity of intermittent or persistent AR in patients ≥12 years of age (the only age group addressed by the guideline).[8]

Based on FDA guidance and reviewed clinical practice guidelines, we provide potential policy recommendations for montelukast interventions that may be considered for discussion by the Utah Medicaid Drug Utilization Review (DUR) Board (see **Section 10.0**).

REFERENCES

1. Singulair (montelukast sodium), for oral use. Package Insert. Organon LLC; 2021. Accessed February 27, 2024. Available at https://www.organon.com/product/usa/pi_circulars/s/singulair/singulair_pi.pdf

2. FDA requires boxed warning about serious mental health side effects for asthma and allergy drug montelukast (Singulair); advises restricting use for allergic rhinitis. Drug safety communication. U.S. Food and Drug Administration. March 4, 2020. Accessed February 27, 2024. Available at https://www.fda.gov/media/135840/download

3. Jewett C, Mueller B. The FDA Warned an Asthma Drug Could Induce Despair. Many Were Never Told. *The New York Times*. January 9, 2024. Accessed February 27, 2024. Available at https://www.nytimes.com/2024/01/09/health/fda-singulair-asthma-drug-warning.html

4. U.S. Food and Drug Administration. *FDA Briefing Document: Pediatric Advisory Committee Meeting - Neuropsychiatric Events with Use of Montelukast in Pediatric Patients*. U.S. Food and Drug Administration; 2019: 194 pages. Last Updated September 27, 2019. Accessed February 27, 2024. Available at https://www.fda.gov/media/131035/download

5. Zafirlukast (Lexi-Drugs): Label uses. Lexidrug.com; 2024. Last Updated February 24, 2024. Accessed March 21, 2024. Available at http://online.lexi.com

6. Zileuton (Lexi-Drugs): Label uses. Lexidrug.com; 2024. Last Updated February 24, 2024. Accessed March 21, 2024. Available at http://online.lexi.com

7. Utah Department of Health and Human Services. *Preferred Drug List & Pharmacy Coverage Resources*. Utah Department of Health and Human Services; 2024: 115 pages. Last Updated April 1, 2024. Accessed April 9, 2024. Available at https://medicaid.utah.gov/pharmacy/preferred-drug-list/

8. Dykewicz MS, Wallace DV, Amrol DJ, et al. Rhinitis 2020: A practice parameter update. *J Allergy Clin Immunol*. 2020;146(4):721-767. doi:10.1016/j.jaci.2020.07.007

9. Kanaoka Y, Boyce JA. Cysteinyl leukotrienes and their receptors; emerging concepts. *Allergy Asthma Immunol Res*. 2014;6(4):288-295. doi:10.4168/aair.2014.6.4.288

10. Montelukast (Lexi-Drugs): Mechanism of action. Lexidrug.com; 2024. Last Updated February 24, 2024. Accessed March 4, 2024. Available at http://online.lexi.com

11. Clarridge K, Chin S, Eworuke E, Seymour S. A Boxed Warning for Montelukast: The FDA Perspective. *J Allergy Clin Immunol Pract*. 2021;9(7):2638-2641. doi:10.1016/j.jaip.2021.02.057

12. Sansing-Foster V, Haug N, Mosholder A, et al. Risk of Psychiatric Adverse Events Among Montelukast Users. *J Allergy Clin Immunol Pract*. 2021;9(1):385-393.e312. doi:10.1016/j.jaip.2020.07.052

13. Benard B, Bastien V, Vinet B, Yang R, Krajinovic M, Ducharme FM. Neuropsychiatric adverse drug reactions in children initiated on montelukast in real-life practice. *Eur Respir J*. 2017;50(2)doi:10.1183/13993003.00148-2017

14. Schumock GT, Stayner LT, Valuck RJ, Joo MJ, Gibbons RD, Lee TA. Risk of suicide attempt in asthmatic children and young adults prescribed leukotriene-modifying agents: a nested case-control study. *J Allergy Clin Immunol*. 2012;130(2):368-375. doi:10.1016/j.jaci.2012.04.035

15. Ali MM, O'Brien CE, Cleves MA, Martin BC. Exploring the possible association between montelukast and neuropsychiatric events among children with asthma: a matched nested case-control study. *Pharmacoepidemiol Drug Saf*. 2015;24(4):435-445. doi:10.1002/pds.3758

16. Glockler-Lauf SD, Finkelstein Y, Zhu J, Feldman LY, To T. Montelukast and Neuropsychiatric Events in Children with Asthma: A Nested Case-Control Study. *J Pediatr*. 2019;209:176-182.e174. doi:10.1016/j.jpeds.2019.02.009

17. Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther*. 1981;30(2):239-245. doi:10.1038/clpt.1981.154

18. U.S. Food and Drug Administration. *Transcript of the September 27, 2019 joint meeting of the Pediatric and Drug Safety and Risk Management Advisory Committees*. U.S. Food and Drug Administration; 2019: 152 pages. Accessed March 25, 2024. Available at https://www.fda.gov/media/132560/download

19. Global Initiative for Asthma. *Global Strategy for Asthma Management and Prevention (2023 update)*. Global Initiative for Asthma; 2023: 246 pages. Last Updated July 10, 2023. Accessed March 4, 2024. Available at https://ginasthma.org/wp-content/uploads/2023/07/GINA-2023-Full-report-23_07_06-WMS.pdf

20. Greiwe J, Cooke A, Nanda A, et al. Work Group Report: Perspectives in Diagnosis and Management of Exercise-Induced Bronchoconstriction in Athletes. *J Allergy Clin Immunol Pract*. 2020;8(8):2542-2555. doi:10.1016/j.jaip.2020.05.020

21. Parsons JP, Hallstrand TS, Mastronarde JG, et al. An official American Thoracic Society clinical practice guideline: exercise-induced bronchoconstriction. *Am J Respir Crit Care Med*. 2013;187(9):1016-1027. doi:10.1164/rccm.201303-0437ST

22. Weiler JM, Brannan JD, Randolph CC, et al. Exercise-induced bronchoconstriction update-2016. *J Allergy Clin Immunol*. 2016;138(5):1292-1295.e1236. doi:10.1016/j.jaci.2016.05.029

23. Lo CWH, Pathadka S, Qin SX, et al. Neuropsychiatric events associated with montelukast in patients with asthma: a systematic review. *Eur Respir Rev*. 2023;32(169)doi:10.1183/16000617.0079-2023

24. Mou Y, Song Q, Zhao C, Fang H, Ren C, Song X. Meta-analysis of the relationship between montelukast use and neuropsychiatric events in patients with allergic airway disease. *Heliyon*. 2023;9(11):e21842. doi:10.1016/j.heliyon.2023.e21842

25. Lo CWH, Pathadka S, Qin SX, et al. Neuropsychiatric events associated with montelukast in patients with asthma: a systematic review: Supplement. *Eur Respir Rev*. 2023;32(169)doi:10.1183/16000617.0079-2023

26. Gerow M, Bruner PJ. Exercise-Induced Asthma. StatPearls Publishing Copyright © 2024, StatPearls Publishing LLC.; 2024.

27. Schuler Iv CF, Montejo JM. Allergic Rhinitis in Children and Adolescents. *Pediatr Clin North Am*. 2019;66(5):981-993. doi:10.1016/j.pcl.2019.06.004

28. Greiner AN, Hellings PW, Rotiroti G, Scadding GK. Allergic rhinitis. *Lancet*. 2011;378(9809):2112-2122. doi:10.1016/s0140-6736(11)60130-x

29. American College of Allergy Asthma and Immunology. Hay fever. acaai.org. Accessed March 15, 2024. Available at https://acaai.org/allergies/allergic-conditions/hay-fever/

30. Tong R, Caliendo T. Managing Exercise-Induced Bronchoconstriction. *US Pharm*. 2023;48(7):7-12. Accessed March 14, 2024. Available at https://www.uspharmacist.com/article/managing-exerciseinduced-bronchoconstriction

31. O'Byrne P. Exercise-induced bronchoconstriction. UpToDate.com; 2023. Last Updated May 8, 2023. Accessed March 11, 2024. Available at https://www.uptodate.com/contents/exercise-induced-bronchoconstriction

32. Cohen B. Allergic Rhinitis. *Pediatr Rev*. 2023;44(10):537-550. doi:10.1542/pir.2022-005618

33. National Asthma Education and Prevention Program Coordinating Committee. *2020 Focused Updates to the Asthma Management Guidelines: A Report from the National Asthma Education and Prevention Program Coordinating Committee Expert Panel Working Group*. National Heart Lung and Blood Institute; 2020: 322 pages. Accessed March 6, 2024. Available at https://www.nhlbi.nih.gov/resources/2020-focused-updates-asthma-management-guidelines

34. National Asthma Education and Prevention Program. *Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma*. National Heart Lung and Blood Institute; 2007: 440 pages. Accessed March 6, 2024. Available at https://www.nhlbi.nih.gov/sites/default/files/media/docs/EPR-3_Asthma_Full_Report_2007.pdf

35. Centers for Disease Control and Prevention. Most Recent National Asthma Data. CDC.gov; 2023. Accessed March 5, 2024. Available at https://www.cdc.gov/asthma/most_recent_national_asthma_data.htm

36. Centers for Disease Control and Prevention. Most Recent Asthma State or Territory Data. CDC.gov; 2023. Last Updated May 10, 2023. Accessed March 5, 2024. Available at https://www.cdc.gov/asthma/most_recent_data_states.htm

37. Utah Department of Health and Human Services. Complete Health Indicator Report of Asthma: Child Prevalence. IBIS.Health.Utah.gov; 2023. Last Updated May 24, 2023. Accessed March 6, 2024. Available at https://ibis.health.utah.gov/ibisph-view/indicator/complete_profile/AsthChiPrev.html

38. Centers for Disease Control and Prevention. Control Asthma. CDC.gov; 2022. Last Updated March 9, 2022. Accessed March 5, 2024. Available at https://www.cdc.gov/sixeighteen/asthma/index.htm#anchor_1602778120

39. American College of Allergy Asthma and Immunology. Asthma Facts. ACAAI.org. 2023. Last Updated June 28, 2023. Accessed March 5, 2024. Available at https://acaai.org/asthma/asthma-101/facts-stats/

40. Global Initiative for Asthma. *Pocket Guide for Asthma Management and Prevention for Adults, Adolescents, and Children 6-11 Years*. Global Initiative for Asthma; 2023: 51 pages. Last Updated July 2023. Accessed March 5, 2024. Available at https://ginasthma.org/wp-content/uploads/2023/07/GINA-2023-Pocket-Guide-WMS.pdf

41. Schünemann HJ, Jaeschke R, Cook DJ, et al. An official ATS statement: grading the quality of evidence and strength of recommendations in ATS guidelines and recommendations. *Am J Respir Crit Care Med*. 2006;174(5):605-614. doi:10.1164/rccm.200602-197ST

42. Parsons JP, Hallstrand TS, Mastronarde JG, et al. Supplement to an official American Thoracic Society clinical practice guideline: exercise-induced bronchoconstriction. *Am J Respir Crit Care Med*. 2013;187(9):1016-1027. doi:10.1164/rccm.201303-0437ST

43. Meltzer EO, Bukstein DA. The economic impact of allergic rhinitis and current guidelines for treatment. *Ann Allergy Asthma Immunol*. 2011;106(2 Suppl):S12-16. doi:10.1016/j.anai.2010.10.014

44. Akhouri S, House SA. Allergic Rhinitis. StatPearls Publishing Copyright © 2024, StatPearls Publishing LLC.; 2024.

45. deShazo R, Kemp S. Pharmacotherapy of allergic rhinitis. UpToDate.com; 2023. Last Updated September 15, 2023. Accessed March 18, 2024. Available at https://www.uptodate.com/contents/pharmacotherapy-of-allergic-rhinitis

46. deShazo R, Kemp S. Allergic rhinitis: Clinical manifestations, epidemiology, and diagnosis. UpToDate.com; 2022. Last Updated April 26, 2022. Accessed March 18, 2024. Available at https://www.uptodate.com/contents/allergic-rhinitis-clinical-manifestations-epidemiology-and-diagnosis

47. Is It Nasal Allergy? Find Out For Sure. allergyasthmanetwork.org. Accessed March 15, 2024. Available at https://allergyasthmanetwork.org/images/Misc/rhinitis_control_assessment_test_RCAT.pdf

48. Montelukast (Lexi-Drugs): Off-label uses. Lexidrug.com; 2024. Last Updated February 24, 2024. Accessed February 29, 2024. Available at http://online.lexi.com

49. Stevens WW, Jerschow E, Baptist AP, et al. The role of aspirin desensitization followed by oral aspirin therapy in managing patients with aspirin-exacerbated respiratory disease: A Work Group Report from the Rhinitis, Rhinosinusitis and Ocular Allergy Committee of the American Academy of Allergy, Asthma & Immunology. *J Allergy Clin Immunol*. 2021;147(3):827-844. doi:10.1016/j.jaci.2020.10.043

50. Merative Micromedex. Montelukast. IBM Micromedex.com; 2024. Accessed March 1, 2024. Available at https://www.micromedexsolutions.com/home/dispatch/

51. Drug Regimen Review Center. *Short-acting Beta-agonist Utilization Among Patients With Asthma: A Retrospective Review*. Utah Department of Health and Human Services Drug Utilization Review Board; 2024: 50 pages. Accessed April 18, 2024. Available at https://medicaid.utah.gov/pharmacy/drug-utilization-review-board/

52. Montelukast (Lexi-Drugs): Drug Interactions. Lexidrug.com; 2024. Last Updated April 12, 2024. Accessed April 14, 2024. Available at http://online.lexi.com

APPENDIX A: LITERATURE SEARCH STRATEGY

Epistemonikos – Systematic Reviews

Date of search: April 12, 2024
Publication type filter: Systematic Review

(title:(Montelukast OR Singulair) OR abstract:(Montelukast OR Singulair)) AND (title:(Neuropsychiatric) OR abstract:(Neuropsychiatric))

APPENDIX B: ADDITIONAL DETAILS FROM MONTELUKAST PRESCRIBING INFORMATION

Other Labeled Safety Information

Below is a summary of adverse events (AEs) and labeled warnings/precautions, according to montelukast prescribing information. Generally, the risks from montelukast are reported without regard to the montelukast dosage form, although safety evidence may have been from trials of a particular dosage form. Notably, montelukast is contraindicated in patients with hypersensitivity to the active ingredient or any of its excipients.[1]

Adverse Events (AEs)

Overall, the most common AEs (≥5% in montelukast-treated patients; higher than the placebo rate) in controlled clinical trials (across various age groups and dosage formulations) were upper respiratory infection, headache, fever, cough, pharyngitis, diarrhea, abdominal pain, influenza, otitis media, rhinorrhea, sinusitis, and otitis.[1] **Neuropsychiatric events did not emerge as a common AE in clinical studies and was identified only after montelukast came to market.**[1,18] The delay in noticing such events could have been due to the low event rate, a lack of sufficiently long-term clinical trials, and/or safety studies not being designed to specifically observe neuropsychiatric events.[4]

Although the safety profile of montelukast seems to remain generally consistent across different age groups and indications, the predominant AEs reported vary as follows[1]:

- *Adults and adolescents aged ≥15 years with:*
    - **Asthma** (N=2950): Montelukast AEs with an incidence ≥4% and occurring more frequently than placebo were headache (18.4%) and influenza (4.2%).
    - **Seasonal AR** (N=2199): Upper respiratory infection was the most frequently reported AE, occurring in 1.9% of montelukast-treated patients versus 1.5% of placebo-treated patients. The safety profile was similar to placebo regardless of when montelukast was administered (daily in the morning versus evening).
    - **Perennial AR** (N=3357): Montelukast AEs with an incidence ≥1% occurring more frequently than placebo were upper respiratory infection, sinusitis, cough, sinus headache, epistaxis, and elevated alanine aminotransaminase levels.
- *Pediatric patients up to 14 years of age with:*
    - **Asthma** (N=476; ages 6–14 years): Frequently reported AEs (≥2%; higher than the placebo rate) were influenza, pharyngitis, fever, nausea, sinusitis, diarrhea, otitis, dyspepsia, laryngitis, and viral infection.
        - Additional AEs, not previously reported in this age group, were observed in a 56-week, double-blind, placebo-controlled trial evaluating montelukast effects on growth rate among pediatric patients 6–8 years old (≥2%; higher than the placebo rate), included rhinitis, headache, varicella, atopic dermatitis, gastroenteritis, acute bronchitis, skin infection, tooth infection, and myopia.

- **Seasonal AR** (N=280; 2−14 years of age): Montelukast AEs with an incidence ≥2% and occurring more often than placebo were otitis media, headache, pharyngitis, and upper respiratory infection.
- **Perennial AR**: The safety profile in pediatric patients ages 2−14 years was extrapolated from safety data among patients within the same age range with seasonal AR.

- *Pediatric patients aged 2−5 years with:*
  - **Asthma** (N=573): Montelukast AEs with an incidence ≥2% and occurring more frequently than placebo were cough, fever, abdominal pain, headache, diarrhea, sinusitis, rhinorrhea, influenza, rash, otitis, ear pain, eczema, gastroenteritis, varicella, urticaria, dermatitis, pneumonia, and conjunctivitis.
- *Pediatric patients aged 6−23 months with:*
  - **Asthma** (N=175): Montelukast AEs with an incidence ≥2% and occurring more frequently than placebo were upper respiratory infection, otitis media, wheezing, pharyngitis, cough, tonsillitis, and rhinitis.
  - **Perennial AR:** The safety profile in pediatric patients aged 6−23 months was extrapolated from pharmacokinetic and safety studies among patients within the same age range with asthma, as well as from pharmacokinetic studies involving adults.

Additional Warnings and Precautions

In addition to the black box warning for neuropsychiatric events, the following warnings/precautions are labeled for montelukast[1]:

- **Acute asthma episodes**: Montelukast is not intended to treat acute asthma episodes, including status asthmaticus. However, montelukast can be continued during acute asthma exacerbations, and patients should be instructed to have rescue treatment readily accessible, such as an inhaled short-acting $beta_2$ agonist (SABA).
- **Concomitant corticosteroid use**: Montelukast should not be abruptly switched in place of an oral or inhaled corticosteroid. If an inhaled corticosteroid is to be discontinued when starting montelukast in a patient established on a corticosteroid, the corticosteroid dose should be gradually tapered before discontinuation, under provider supervision.
- **Aspirin sensitivity**: While undergoing treatment with montelukast, patients with a known sensitivity to aspirin should continue to avoid aspirin or nonsteroidal anti-inflammatory drugs (NSAIDs). Despite its efficacy in enhancing airway function, montelukast has not demonstrated an ability to diminish the bronchoconstrictor reaction to aspirin and other NSAIDs among individuals with asthma and aspirin sensitivity.
- **Eosinophilic conditions**: A causal relationship has not been established, but patients with asthma receiving montelukast may exhibit systemic eosinophilia, occasionally manifesting clinical features of vasculitis suggestive of Churg-Strauss syndrome. Healthcare providers should be alert for signs of the following in their patients: eosinophilia, worsening pulmonary symptoms, vasculitic rash, cardiac issues, and/or neuropathy.
- **Patients with phenylketonuria (PKU)**: Montelukast chewable tablets (4 mg and 5 mg) contain phenylalanine, posing potential harm to individuals with PKU. Prior to prescribing montelukast to a

patient with PKU, it is crucial to evaluate the total daily consumption of phenylalanine from all sources, including montelukast.

Drug Interactions

No specific drug-drug interactions are provided in the montelukast prescribing information.[1] It is noted that no dosage adjustment is needed if montelukast is concomitantly administered with the following agents or drug classes: prednisone, theophylline, prednisolone, fexofenadine, oral contraceptives, digoxin, warfarin, itraconazole, gemfibrozil, sedative hypnotics, thyroid hormones, NSAIDs, decongestants, benzodiazepines, and cytochrome (CYP) P450 inducers.[1] Nonetheless, because montelukast is a CYP substrate (predominantly CYP1A2), it may be suitable to consider monitoring therapy when co-administering montelukast with potent CYP inducers (eg, rifampin, phenobarbital), which may decrease montelukast exposure, or inhibitors (eg, gemfibrozil), which may increase montelukast exposure.[1,52]

Special Populations

Montelukast use in special populations, including pregnant patients, children, and older adults, may necessitate careful consideration in order to optimize benefits while minimizing potential risks. The following bullet points provide details regarding montelukast use in these special populations:

- **Pregnancy**: Based on human data from published cohort studies spanning several decades, an association between montelukast use during pregnancy and risk of major birth defects has not been established.[1] Additionally, animal studies have not revealed any adverse developmental effects when pregnant rats and rabbits were administered oral montelukast at doses approximately 100 and 110 times the maximum recommended human daily oral dose, respectively, during organogenesis.[1] Notably, inadequately managed asthma during pregnancy heightens the risk of maternal complications such as preeclampsia, as well as adverse perinatal outcomes including preterm birth, mortality, and low birth weight.[1,19] However, the likelihood of encountering adverse maternal or fetal complications is minimal, if any, if asthma remains effectively controlled during pregnancy.[19] Although disease control and safety must be carefully balanced, montelukast may be a suitable option during pregnancy.
- **Breastfeeding**: Montelukast is present in human breast milk; nonetheless, the likelihood of adverse reactions associated with montelukast in infants, whether through direct exposure or breastfeeding, seems to be minimal based on available evidence.[1] The impact of montelukast on milk production is uncertain. Healthcare providers should carefully weigh the developmental and health benefits of breastfeeding against the maternal requirement for montelukast, and any potential adverse effects on the breastfed infant.[1]
- **Older adults, hepatic or renal impairment**: Across all montelukast clinical studies, 3.5% of participants were aged ≥65 years, with 0.4% ≥75 years.[1] Although no discernible differences in safety or efficacy were observed between older adults and younger patients, some older adults may have greater sensitivity to montelukast. Compared to younger adults, the plasma half-life of montelukast is marginally longer in older adults, but no dosage adjustment is necessary for this patient population. Similarly, no adjustments to the dosage of montelukast is required for patients with mild-to-moderate hepatic impairment or renal insufficiency.[1]

- **Pediatric patients**: Safety and efficacy for montelukast has yet to be established for pediatric patients younger than 12 months of age for asthma; 6 months of age for perennial AR; 2 years of age for seasonal AR; and 6 years of age for EIB.[1] However, the directness of the efficacy and safety evidence supporting these pediatric uses varies (see **Table B1**). The safety of montelukast has been demonstrated in at least 1 controlled trial for all FDA-approved indications (ie, asthma, EIB, seasonal and perennial AR) and ages, except for children ≤14 years of age with perennial AR. Support for use in patients 6 months to 14 years of age with perennial AR was extrapolated from pediatric patients 2−14 years of age with seasonal AR and those with asthma 6−23 months of age.[1] Except for children ages ≥6 years with asthma or EIB, or those ≥15 years with seasonal or perennial AR, the efficacy evidence for other indications/ages was extrapolated from either older patients with the same indication or patients within the same age range but with a different indication; in some cases, pharmacokinetic studies were also considered.[1] Notably, since the initial approval of montelukast, more clinical studies may have been completed regarding the efficacy and/or safety of montelukast in the pediatric population, but we did not search for such follow-up evidence. **Table B1** provides a summary of the directness of the controlled trial evidence supporting the use of montelukast for its FDA-approved uses, primarily based on the montelukast prescribing information (ie, package insert).

Table B1. Evidence Basis for Montelukast Use in Pediatric Patients for FDA-approved Indications[1,4] [a]

FDA-approved indication	Pediatric age ranges	Montelukast dosage formulation and strength	Effectiveness evidence for approval		Safety evidence for approval	
			Controlled trial?	Extrapolated?	Controlled trial?	Extrapolated?
Asthma	≥15 years	Film-coated tablet (10 mg)	Yes	No	Yes	No
	6–14 years	Chewable tablet (5 mg)	Yes	No	Yes	No
	2–5 years	Chewable tablet (4 mg)	No	Yes, ages ≥6 years with asthma[b]	Yes	No
	12–23 months	Oral granules (4 mg)	No	Yes, ages ≥6 years with asthma[b]	Yes	No
Exercise-induced bronchoconstriction	≥15 years	Film-coated tablet (10 mg)	Yes	No	Yes	No
	6–14 years	Chewable tablet (5 mg)	Yes	No	Yes	No
Seasonal allergic rhinitis	≥15 years	Film-coated tablet (10 mg)	Yes	No	Yes	No
	2–14 years	Chewable tablet (5 mg and 4 mg)	No	Yes, ages ≥15 years with allergic rhinitis[c]	Yes	No
Perennial allergic rhinitis	≥15 years	Film-coated tablet (10 mg)	Yes	No	Yes	No
	6 months–14 years	–	No	Yes, ages ≥15 years with allergic rhinitis[c]	No	Yes, ages as young as 6 months with asthma and up to age 14 years with seasonal allergic rhinitis[d]

[a] Information was primarily extracted from the prescribing information for montelukast, and was supplemented by a 2019 FDA pediatric advisory committee meeting report on montelukast. Notably, since the initial approval of montelukast, more clinical studies may have been completed regarding the efficacy and/or safety of montelukast in the pediatric population, but we did not search for such follow-up evidence.

[b] Extrapolated data based on pediatric patients ≥6 years of age with asthma, supported by exploratory efficacy outcomes from a safety trial.

[c] Effectiveness is based on extrapolated data from patients ≥15 years of age with allergic rhinitis, coupled with the presumption that there are similarities in pathophysiology, disease progression, and medication effect across these age groups.

[d] Safety of montelukast for perennial allergic rhinitis for patients aged 6 months to 14 years is based on extrapolated data from pediatric patients with seasonal allergic rhinitis (2–14 years of age), and those with asthma (6–23 months of age) and pharmacokinetic studies involving adults.

Abbreviations: FDA, US Food and Drug Administration; US, United States

APPENDIX C: GUIDELINE-RECOMMENDED PHARMACOLOGIC STEPWISE TREATMENT APPROACH FOR ASTHMA

The 2023 **Global Initiative for Asthma (GINA**) stepwise treatment approach for asthma management is provided in **Table C1** for patients aged ≥12 years, and **Table C2** for pediatric patients aged ≤11 years.

Table C1. Stepwise Treatment Approach for Ongoing Asthma Management in Patients ≥12 Years of Age, According to the GINA 2023 Guideline[19] [a]

Population	Treatment step #	Reliever	Preferred controller	Other controller options[b]
			Track 1(Preferred)[c]	
Adults and adolescents (≥12 years of age)	1 and 2	As-needed low-dose ICS-formoterol	As-needed low-dose ICS-formoterol	• **Daily LTRA**, or • Low-dose ICS taken concurrently with each SABA administration, or • Add HDM SLIT[d]
	3		Low-dose maintenance ICS-formoterol	• Medium-dose ICS, or • **Add LTRA** or HDM SLIT[d]
	4		Medium-dose maintenance ICS-formoterol	• **Add LTRA**, or LAMA, or HDM SLIT[d], or • Switch to high-dose ICS
	5		• Add-on LAMA, or • Consider high-dose maintenance ICS-formoterol, or • Consult for phenotypic evaluation ± add-on biologic therapy (eg, anti-IgE, anti-IL-5/5R, anti-IL-4R	• **Add LTRA** or azithromycin (adults only) • May consider adding low-dose OCS as a last-line option, being mindful of potential adverse effects
			Track 2 (Alternative)[c]	
Adults and adolescents (≥12 years of age)	1	As-needed ICS-SABA **or** as-needed SABA	ICS taken concurrently with each SABA administration	None
	2		Low-dose maintenance ICS	• **Daily LTRA**, or • Low-dose ICS taken concurrently with each SABA administration, or • Add HDM SLIT[d]
	3		Low-dose maintenance ICS-LABA	• Medium-dose ICS, or • **Add LTRA** or HDM SLIT[d]
	4		Medium- or high-dose maintenance ICS-LABA	• **Add LTRA**, or LAMA, or HDM SLIT[d], or • Switch to high-dose ICS
	5		• Add-on LAMA, or • Consider high-dose maintenance ICS-LABA, or • Consult for phenotypic evaluation ± add-on biologic therapy (eg, anti-IgE, anti-IL-5/5R, anti-IL-4R	• **Add LTRA** or azithromycin (adults only) • May consider adding low-dose OCS as a last-line option, being mindful of potential adverse effects

[a] *Intended to provide an overview of ongoing asthma management (may not necessarily apply to initial treatment); please refer to the guideline for details.*

[b] *Other controller options may have significantly lower efficacy, pose increased risks, or lack substantial supportive evidence relative to the preferred or alternative controllers. Before advancing to the next step for patients who have inadequately controlled asthma, it may be reasonable for patients to try other controller options at their current step.*

[c] *Track 1 is preferred over Track 2 given the demonstrated reduction for severe exacerbations with as-needed ICS-formoterol compared to as-needed SABA reliever, and offers a less complex regimen. Track 2 is an alternative if Track 1 is not feasible or is not favored by a patient with no previous exacerbations on their current therapeutic regimen. Treatment may be individualized by switching between tracks based on the patient's needs or may be stepped up or down within a track using the same reliever.*

[d] *For patients with allergic rhinitis, who are allergic to house dust mite (HDM) and have a predicted forced expiratory volume in 1 second (FEV_1) >70%, consider adding sublingual allergen immunotherapy (SLIT).*

Abbreviations: anti-IgE, anti-immunoglobulin E; anti-IL4R, anti-interleukin 4 receptor; anti-IL5/5R, anti-interleukin 5 receptor; FEV_1, forced expiratory volume in 1 second; GINA, Global Initiative for Asthma; HDM, house dust mite; ICS(s), inhaled corticosteroid(s); LABA(s), long-acting beta$_2$ agonist(s); LAMA(s), long-acting muscarinic antagonist(s); LTRA(s), leukotriene receptor antagonist(s); OCS(s), oral corticosteroid(s); SABA(s), short-acting beta$_2$ agonist(s); SLIT, sublingual allergen immunotherapy

Table C2. Stepwise Treatment Approach for Ongoing Asthma Management in Pediatric Patients ≤11 Years of Age, According to the GINA 2023 Guideline[19] [a]

Population	Treatment step #	Reliever	Preferred controller	Other controller options[b]
Children (6–11 years of age)	1	As-needed SABA (or ICS-formoterol as MART, Steps 3 and 4 only)	Low-dose ICS taken concurrently with each SABA administration	Daily low-dose ICS
	2		Daily low-dose ICS	• **Daily LTRA**, or • Low-dose ICS taken concurrently with each SABA administration
	3		• Low-dose ICS-LABA, or • Medium-dose ICS, or • Very low-dose ICS-formoterol as MART	**Low-dose ICS + LTRA**
	4		• Medium-dose ICS-LABA, or • Low-dose ICS-formoterol as MART	**Add LTRA** or tiotropium
	5		Consult for phenotypic evaluation ± higher dose ICS-LABA or consider add-on biologic therapy (eg, anti-IgE, anti-IL-5/5R, anti-IL-4R)	• May consider adding low-dose OCS as a last-line option, being mindful of potential adverse effects
Children (≤5 years of age)	1	As-needed SABA	Insufficient evidence for use of a daily controller	Occasional short-duration of ICS at onset of viral illness
	2		Daily low-dose ICS	• **Daily LTRA**, or • Occasional short-duration of ICS at onset of respiratory illness
	3[c]		Medium-dose ICS (ie, doubling the initial low dose)	• **Low-dose ICS + LTRA** • Consider referral to a specialist
	4[c]		Continue using the medium-dose ICS (ie, double the initial low dose) and refer to a specialist	• **Add LTRA** or intermittent ICS • Increase ICS frequency

[a] *Intended to provide an overview of ongoing asthma management (may not necessarily apply to initial treatment); please refer to the guideline for details.*

[b] *Other controller options may have significantly lower efficacy, pose increased risks, or lack substantial supportive evidence relative to the preferred controllers. Before advancing to the next step for patients who have inadequately controlled asthma, it may be reasonable for patients to try other controller options at their current step.*

[c] *If patients have inadequate asthma control, reconsider the asthma diagnosis, and re-evaluate inhaler technique, medication adherence, and environmental exposures (if applicable) before stepping up therapy.*

Abbreviations: anti-IgE, anti-immunoglobulin E; anti-IL4R, anti-interleukin 4 receptor; anti-IL-5/5R, anti-interleukin 5 receptor; GINA, Global Initiative for Asthma; ICS(s), inhaled corticosteroid(s); LABA(s), long-acting beta$_2$ agonist(s); LTRA(s), leukotriene receptor antagonist(s); MART, maintenance-and-reliever therapy; OCS(s), oral corticosteroid(s); SABA(s), short-acting beta$_2$ agonist(s)

The 2007/2020 **National Heart, Lung, and Blood Institute (NHLBI)/ National Asthma Education and Prevention Program (NAEPP)** stepwise treatment approach for asthma management is provided in **Table C3** for patients of all ages.

Table C3. Stepwise Treatment Approach for Ongoing Asthma Management in Patients of All Ages, According to the NHLBI/NAEPP 2020 Guideline Update[33] [a]

Population	Treatment step #	Reliever	Preferred controller	Alternative controller options[b]
Adults and adolescents (≥12 years of age)	1	As-needed SABA	None	None
	2[c]	As-needed ICS-SABA **or** as-needed SABA	Daily low-dose ICS	• **Daily LTRA**, or • Cromolyn, or nedocromil, or zileuton, or theophylline
	3[c]	As-needed low-dose ICS-formoterol (preferred) **or** as-needed SABA (alternative)	Daily low-dose ICS-formoterol	• Daily medium-dose ICS, or • **Daily low-dose ICS + LTRA**, or • Daily low-dose ICS-LABA, or • Daily low-dose ICS + LAMA, or • Daily low-dose ICS + theophylline or zileuton
	4[c]	As-needed medium-dose ICS-formoterol (preferred) **or** as-needed SABA (alternative)	Daily medium-dose ICS-formoterol	• Daily medium-dose ICS-LABA, or • Daily medium-dose ICS + LAMA, or • **Daily medium-dose ICS + LTRA**, or • Daily medium-dose ICS + theophylline or zileuton
	5[d]	As-needed SABA	Daily medium-high dose ICS-LABA + LAMA	• Medium-high dose ICS-LABA, or • **Daily high-dose ICS + LTRA**
	6[d]		Daily high-dose ICS-LABA + OSC	None
Children (5–11 years of age)	1	As-needed SABA	None	None
	2[c]		Daily low-dose ICS	• **Daily LTRA**, or • Cromolyn, or nedocromil, or theophylline
	3[c]	As-needed low-dose ICS-formoterol (preferred) **or** as-needed SABA (alternative)	Daily low-dose ICS-formoterol	• Daily medium-dose ICS, or • Daily low-dose ICS-LABA, or • **Daily low-dose ICS + LTRA**, or • Daily low-dose ICS + theophylline
	4[c]	As-needed medium-dose ICS-formoterol (preferred) **or** as-needed SABA (alternative)	Daily medium-dose ICS-formoterol	• Daily medium-dose ICS-LABA, or • **Daily medium-dose ICS + LTRA**, or • Daily medium-dose ICS + theophylline
	5[d]	As-needed SABA	Daily high-dose ICS-LABA	• **Daily high-dose ICS + LTRA**, or • Daily high-dose ICS + theophylline
	6[d]		Daily high-dose ICS-LABA + OSC	• **Daily high-dose ICS + LTRA + OSC**, or • Daily high-dose ICS + theophylline + OSC

[a] *Intended to provide an overview of ongoing asthma management (may not necessarily apply to initial treatment); please refer to the guideline for details.*

[b] *Relative to the preferred options, alternative choices are less efficacious or have limited evidence to support use. However, clinicians and patients might opt for an alternative option based on patient preference or if the preferred treatment is unavailable or too expensive.*

[c] *Adjunctive subcutaneous immunotherapy may be used in patients (≥5 years of age) with mild to moderate allergic asthma, provided the asthma was well-managed during the initiation, build-up, and maintenance stages of immunotherapy.*

[d] *At treatment steps 5 and 6, consider adding biologic therapy (eg, anti-IgE, anti-IL-5/5R). Specifically for children ages 5–11 years, consider adding omalizumab, which at the time of the 2007 guideline was the only US Food and Drug Administration (FDA)-approved biologic for this age group (biologic agents were not addressed in the focused 2020 update).*

[e] *For children 4 years of age only at treatment steps 3 or 4, may also consider trying recommended treatment options for children 5–11 years old at the corresponding treatment step of 3 or 4.*

Abbreviations: anti-IgE, anti-immunoglobulin E; anti-IL-5/5R, anti-interleukin 5 receptor; FDA, US Food and Drug Administration; ICS(s), inhaled corticosteroid(s); LABA(s), long-acting beta$_2$ agonist(s); LAMA(s), long-acting muscarinic antagonist(s); LTRA(s), leukotriene receptor antagonist(s); NAEPP, National Asthma Education and Prevention Program; NHLBI, National Heart, Lung, and Blood Institute; OCS(s), oral corticosteroid(s); SABA(s), short-acting beta$_2$ agonist(s); US, United States

Table C3. Stepwise Treatment Approach for Ongoing Asthma Management in Patients of All Ages, According to the NHLBI/NAEPP 2020 Guideline Update[33] [a]

Population	Treatment step #	Reliever	Preferred controller	Alternative controller options[b]
Children (≤4 years of age)	1	As-needed SABA	Short-duration of ICS at the onset of a respiratory tract infection	None
	2		Daily low-dose ICS	• **Daily montelukast**, or • Cromolyn
	3[e]		Daily medium dose ICS	None
	4[e]		Daily medium-dose ICS-LABA	**Daily medium-dose ICS + montelukast**
	5		Daily high-dose ICS-LABA	**Daily high-dose ICS + montelukast**
	6		Daily high-dose ICS-LABA + OSC	**Daily high-dose ICS + montelukast + OSC**

[a] *Intended to provide an overview of ongoing asthma management (may not necessarily apply to initial treatment); please refer to the guideline for details.*

[b] *Relative to the preferred options, alternative choices are less efficacious or have limited evidence to support use. However, clinicians and patients might opt for an alternative option based on patient preference or if the preferred treatment is unavailable or too expensive.*

[c] *Adjunctive subcutaneous immunotherapy may be used in patients (≥5 years of age) with mild to moderate allergic asthma, provided the asthma was well-managed during the initiation, build-up, and maintenance stages of immunotherapy.*

[d] *At treatment steps 5 and 6, consider adding biologic therapy (eg, anti-IgE, anti-IL-5/5R). Specifically for children ages 5–11 years, consider adding omalizumab, which at the time of the 2007 guideline was the only US Food and Drug Administration (FDA)-approved biologic for this age group (biologic agents were not addressed in the focused 2020 update).*

[e] *For children 4 years of age only at treatment steps 3 or 4, may also consider trying recommended treatment options for children 5–11 years old at the corresponding treatment step of 3 or 4.*

Abbreviations: anti-IgE, anti-immunoglobulin E; anti-IL-5/5R, anti-interleukin 5 receptor; FDA, US Food and Drug Administration; ICS(s), inhaled corticosteroid(s); LABA(s), long-acting beta$_2$ agonist(s); LAMA(s), long-acting muscarinic antagonist(s); LTRA(s), leukotriene receptor antagonist(s); NAEPP, National Asthma Education and Prevention Program; NHLBI, National Heart, Lung, and Blood Institute; OCS(s), oral corticosteroid(s); SABA(s), short-acting beta$_2$ agonist(s); US, United States

APPENDIX D: GUIDELINE-RECOMMENDED PHARMACOLOGIC STEPWISE TREATMENT APPROACH FOR ALLERGIC RHINITIS

Table D1. Stepwise Treatment Approach for Allergic Rhinitis in Patients ≥12 Years of Age, According to the 2020 AAAAI/ACAAI Guideline[8] [a]

Intermittent allergic rhinitis		Persistent allergic rhinitis	
Mild severity (VAS <5/10)	**Moderate/severe severity (VAS ≥5/10)**	**Mild severity (VAS <5/10)**	**Moderate/severe severity (VAS ≥5/10)**
First-line, initial treatment, in order of preference[b] (± as-needed nasal saline)[c]:			
1. Oral antihistamine OR intranasal antihistamine 2. If congestion is present, oral antihistamine + pseudoephedrine (if tolerated) 3. Intranasal corticosteroid (may be preferred over intranasal antihistamines if wanting to avoid adverse taste or when used over several days)	1. Oral antihistamine OR intranasal antihistamine 2. Intranasal corticosteroid 3. Intranasal antihistamine + intranasal corticosteroid (administered in a separate device or single device) 4. Oral antihistamine + pseudoephedrine **Agents NOT recommended as first-line treatment:** • Oral antihistamine + intranasal corticosteroid • **LTRA**	1. Intranasal corticosteroid 2. Oral antihistamine OR intranasal antihistamine 3. If congestion is present, oral antihistamine + pseudoephedrine (if tolerated) 4. Intranasal cromolyn **Agents NOT recommended as first-line treatment:** • **LTRA**	1. Intranasal antihistamine + intranasal corticosteroid (administered in a separate device or single device) 2. Intranasal corticosteroid 3. Intranasal antihistamine **Agents NOT recommended as first-line treatment:** • Oral antihistamine + intranasal corticosteroid • Oral antihistamine + pseudoephedrine (if tolerated) **Agents recommended against:** • **LTRA** • Oral antihistamine + **LTRA** **Agents NOT recommended at all:** • Injected corticosteroids (intramuscular, subcutaneous, intranasal)
If symptoms not controlled after 5–7 days:			
• Preferred to use an alternative monotherapy option not previously tried, OR • Adding or changing to a symptom specific medication (ie, intranasal anticholinergic for anterior rhinorrhea, or an intranasal decongestant [up to 5 days] or pseudoephedrine [if tolerated] for nasal congestion) • If symptoms continue to be uncontrolled after reevaluating in 1–2 weeks, progress to treatment for moderate/severe intermittent allergic rhinitis	• Alternative monotherapy option not previously tried, OR • If not previously tried, intranasal antihistamine + intranasal corticosteroid (administered in a separate device or single device), AND/OR • Adding a symptom specific medication (ie, intranasal anticholinergic, intranasal decongestant, or pseudoephedrine) • If symptoms continue to be uncontrolled after reevaluating in 1–2 weeks, progress to treatment for moderate/severe persistent allergic rhinitis **Agents recommended against:** • Oral antihistamine + **LTRA** **No recommendation for or against:** • Oral antihistamine + intranasal corticosteroid	• Preferred to use an alternative monotherapy option not previously tried, OR • Adding or changing to a symptom specific medication (ie, intranasal anticholinergic for anterior rhinorrhea, or an intranasal decongestant [up to 5 days] or pseudoephedrine [if tolerated] for nasal congestion) • If symptoms continue to be uncontrolled after reevaluating in 1–2 weeks, progress to treatment for moderate/severe persistent allergic rhinitis	• Alternative monotherapy option not previously tried, OR • If not previously tried, intranasal antihistamine + intranasal corticosteroid (administered in a separate device or single device), AND/OR • Adding a symptom specific medication (ie, intranasal anticholinergic, intranasal decongestant, or pseudoephedrine) • If symptoms continue to be uncontrolled after reevaluating in 1–2 weeks, consider adding a short duration (5–7 days) of oral corticosteroids in patients with very severe or intractable allergic rhinitis **Agents recommended against:** • Oral antihistamine + **LTRA** **No recommendation for or against:** • Oral antihistamine + intranasal corticosteroid • Oral antihistamine + pseudoephedrine (if tolerated)

[a] *Although this guideline denotes that most pharmacologic options listed in their treatment algorithms are FDA-approved for children younger than 12 years old, many of the comparative studies were limited to children at least 12 years old; therefore, the guideline made treatment recommendations for children aged ≥12 years and adults.*

[b] *Although the order of preference for listed agents was based on expert opinion, the general agents recommended have supportive evidence/strength of recommendations for use (see **Table 6**).*

[c] *If symptoms are fully controlled upon reassessment, may consider maintaining treatment as-needed or stepping down/discontinuing treatment if triggering allergen is no longer present.*

Abbreviations: AAAAI, American Academy of Allergy, Asthma, and Immunology; ACAAI, American College of Asthma, Allergy, and Immunology; FDA, US Food and Drug Administration; US, United States; VAS, Visual analog scale