Cognitive Vitality Reports® are reports written by neuroscientists at the Alzheimer's Drug Discovery Foundation (ADDF). These scientific reports include analysis of drugs, drugs-in-development, drug targets, supplements, nutraceuticals, food/drink, non-pharmacologic interventions, and risk factors. Neuroscientists evaluate the potential benefit (or harm) for brain health, as well as for age-related health concerns that can affect brain health (e.g., cardiovascular diseases, cancers, diabetes/metabolic syndrome). In addition, these reports include evaluation of safety data, from clinical trials if available, and from preclinical models.

Montelukast

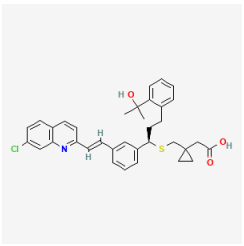
Evidence Summary

Some preclinical and observational studies suggest that montelukast could have a neuroprotective role, but clinical trial evidence is lacking. Montelukast has a black box warning for neuropsychiatric events.

Neuroprotective Benefit: There is a mechanistic basis for potential neuroprotective benefit that is mirrored in preclinical work. Some observational studies suggest a potential small benefit for dementia. Clinical trial data is lacking.

Aging and related health concerns: Montelukast is used for asthma, and untreated asthma may increase the risk of other health issues that can exacerbate aging or related health concerns. There is little evidence for benefit outside of approved indications.

Safety: While generally well-tolerated in clinical trials, there is a black box warning on montelukast for serious neuropsychiatric events from post-marketing surveillance data.

Availability: Rx	**Dose**: Montelukast is available as tablets, chewable tablets, and oral granules. Dosing is by age. Daily doses by age: 2- to 5-year-olds, 4 mg; 6- to 14-year-olds, 5 mg; 15 years and older, 10 mg.	**Chemical formula:** $C_{35}H_{36}ClNO_3S$ **MW**: 586.2 g/mol  Source: PubChem
Half-life: 2.7 to 5.5 hours	**BBB**: Penetrant	
Clinical trials: The largest review of clinical trials identified included 20,131 patients.	**Observational studies**: The largest observational study identified included 457,000 individuals who received montelukast.	

What is it?

Montelukast is a drug that is approved for prophylaxis of and treatment of chronic asthma, for exercise-induced bronchoconstriction, and for relief of symptoms of seasonal allergic rhinitis. Merck received the initial approval for and sold montelukast under the brand name Singulair; Organon then acquired Singulair in 2021.

Leukotrienes are a type of eicosanoid that act as inflammatory mediators. They are typically produced by leukocytes and released to promote inflammatory responses. There are different types of leukotrienes, and leukotrienes can have different effects. Leukotrienes overall play roles in several diseases, including asthma (Cuzzo & Lapin, 2023). Montelukast is a leukotriene receptor antagonist; montelukast specifically binds to the cysteinyl leukotriene receptor 1 (CysLTR1) as well as G-coupled protein receptor 17 (GPCR17). This binding can reduce or prevent the binding of and therefore the proinflammatory actions of leukotrienes; this reduced or blocked binding can have downstream effects such as preventing bronchoconstriction (Xiong et al., 2021; Wermuth et al., 2023). According to the Global Initiative for Asthma (GINA), montelukast and other leukotriene inhibitors are less effective for asthma symptoms than inhaled corticosteroids (ICS) and are often prescribed along with other asthma medications (GINA). There is a black box warning on montelukast for potential behavior and mood-related changes; in light of the findings, the FDA recommends that montelukast not be used for allergic rhinitis unless patients cannot be treated effectively with or cannot tolerate other allergy medications

(FDA). Both the FDA and GINA recommend that health care professionals discuss the risks and benefits of montelukast with patients with asthma before prescribing montelukast.

As proinflammatory pathways such as the leukotriene pathway have been implicated in neurological conditions such as stroke, dementia with Lewy Bodies, and AD, there has been interest in whether leukotriene receptor antagonists like montelukast may have benefit for these conditions (Sood et al., 2024).

Neuroprotective Benefit: There is a mechanistic basis for potential neuroprotective benefit that is mirrored in preclinical work. Some observational studies suggest a potential small benefit for dementia. Clinical trial data is lacking.

Types of evidence:

- 1 randomized controlled trial
- 5 observational studies
- 1 open label clinical trial
- 1 case series
- 2 reviews
- Several laboratory studies

Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function:

Overall, there is limited data on montelukast for dementia prevention or improved cognitive decline in humans. In a small trial in healthy volunteers, montelukast in combination with loratadine had no effect on multitasking ability, vigilance, or sleepiness (Valk & Simons, 2008). Another small trial found no effect of 8 weeks of montelukast on memory, attention, or mood in 12 asthma patients aged 38 to 73 years (Schwimmbeck et al., 2021).

A longitudinal observational study analyzed data from the National Alzheimer's Coordinating Center to see whether there was any association between use of leukotriene receptor antagonists and cognitive performance in cognitively intact individuals, MCI patients, and AD patients. Within each group, the researchers used propensity score matching to match leukotriene receptor antagonist users to non-

users in a 1:3 ratio. After propensity score matching, the analysis included 1,400 cognitively intact individuals, 800 individuals with MCI, and 604 with AD. The study included participants who used either montelukast or another leukotriene receptor antagonist called zafirlukast, but 99.8% of the leukotriene receptor antagonist users were using montelukast.

In patients with normal cognition, use of either leukotriene receptor antagonist was associated with a small but significant 0.8% faster rate of decline over time of immediate memory recall as compared to participants who did not use the medications. The researchers did not find any association of leukotriene receptor antagonist use and cognitive function in patients with MCI (Xiong et al., 2021).

A cohort study using health insurance claims in Japan included patients with newly diagnosed asthma and compared those who received leukotriene receptor antagonists like montelukast to those who received other drug types. They age-, sex-, and asthma diagnostic year-matched the 10,471 leukotriene receptor antagonist users 1:1 to non-leukotriene receptor antagonist users. The average age in both groups was 57 years. Of the 10,471 patients in the leukotriene receptor antagonist group, 6,576 used montelukast; the rest used pranlukast, a similar drug used in Japan. The researchers looked at the incidence of dementia diagnosis in the up to 10-year study period. The leukotriene receptor antagonist users had lower frequency of previous medical problems and serious comorbidities, including cerebrovascular disease and diabetes when compared to the non-leukotriene receptor antagonist users. It should be noted that several of these baseline differences are independently associated with increased frequency of dementia diagnosis. After statistical adjustment for these baseline differences, they found that there was a significantly lower frequency of dementia diagnosis in patients who received leukotriene receptor antagonists compared to those who did not (adjusted HR=0.42; 95% CI 0.20 to 0.87, p=0.019) (Ishikura et al., 2021).

An observational study looked at prescription drug records in Norway. The researchers looked at a group of 203,473 people 60 years and older who had received at least two prescriptions for montelukast or an inhalation type asthma medication. Approximately 23,600 of the included participants received montelukast. They also included cohorts of people who used dementia medication, those who used medication for Parkinson's disease (PD), those who had been admitted to a nursing home, those who died, and those who used type 2 diabetes medication. This study used lack of any prescriptions in a 1-year time frame while still alive as a proxy for admittance to a long-term care facility, as the Norwegian prescription drug database does not include prescription to those in long-term care. They also used this lack of prescriptions over 1 year or more as a proxy for cognitive decline, since it is estimated that 80%

of residents in nursing homes in Norway have a form of dementia. The researchers found that the prevalence of montelukast users compared to non-users was lower in certain groups. Some of the hazard ratios were trends rather than significant in the unadjusted analysis, but significant when adjusted for sex, use of medication for cardiovascular condition, and the level of consumption of prescription drugs in the follow up period; these adjustments overall control for the hypothesis that montelukast users are less healthy than people who do not use montelukast. After adjustment, montelukast users were less likely to use dementia medication (HR=0.89; 95% CI 0.81 to 0.98), less likely to have at least a 1 year gap in prescriptions / proxy for nursing home admission if the individual was 60 to 75 years of age (HR=0.67; 95% CI 0.59 to 0.77), and less likely to have a recorded death (for 60 to 75 years of age, HR=0.64; 95% CI 0.61 to 0.67; for 75+, HR=0.81; 95% CI 0.78 to 0.84). Montelukast users were slightly more prevalent than non-users in the group that received PD medication and diabetic medication. It should be noted that this study did not confirm dementia diagnosis or nursing home stay, on top of the typical caveats of an observational study (Grinde & Engdahl, 2017).

The same group published a second observational study using data from different databases. This second paper used data from the Tromsø Study, which is a prospective cohort study in Norway that includes a variety of data, including cognitive testing measures. The Tromsø study data can be linked to the Norwegian prescription database that was used in Grinde & Engdahl, 2017, thus allowing the authors to look more directly at cognitive function and prescription drug history. In this specific study, they looked at data from participants 60 years and older in the 2015-2016 window and compared the cognitive testing performance individuals who received two or more prescriptions of montelukast to those who did not. The cohort size varied by cognitive test, but was typically around 150 for montelukast users, and approximately 5,000 for non-users. The authors found that individuals who had used montelukast were more likely to perform significantly better on the Short Physical Performance Battery and Digit-symbol coding; they also performed a multivariate analysis using all 7 available cognitive and neurological tests and found that prior montelukast use was correlated with overall improved scores on these tests (p=0.03) in one of the 3 statistical models they used. The researchers also looked to see if use of other prescription drugs compared to non-use, including of other immune-modulating drugs, were associated with cognitive performance. Overall, they did not see many significant correlations between other prescription drugs and cognitive performance (Grinde et al., 2020).

Taken together, more robust studies of montelukast are needed to determine whether these observational findings reflect true biological action of montelukast or if residual confounding has influenced the results.

Human research to suggest benefits to patients with dementia:

In the study by Xiong et al., 2021, described in the previous section, the relationship between leukotriene receptor antagonist use and cognitive function was evaluated in people with Alzheimer's disease. The researchers found that in patients with AD, the use of leukotriene receptor antagonists was associated with a slower decline on language and psychomotor processing speed as compared to those who did not use the medications. The effect sizes were small, though they persisted after controlling for false discovery rate. There was no effect on memory. In a posthoc analysis, the use of leukotriene receptor antagonists by patients with MCI or AD was associated with slower decline in disease progression as measured by CDR-SB, compared to non-use of the medications (Xiong et al., 2021).

A small RCT enrolled 32 patients with MCI or AD and randomized them to receive either montelukast or placebo for 12 months. Those in the montelukast group initially received 10 mg per day, and were dose escalated to up to 40 mg per day, provided the dose was tolerated. The primary outcome measures were safety measures; the secondary outcomes included measures of cognitive function and AD biomarkers in CSF. The study results were made available on clinicaltrials.gov but do not appear to have been published as of December 2024. The montelukast group does not appear to have had an improvement from baseline in CSF biomarkers or on cognitive assessments (NCT03991988).

A clinician published a series of case reports of patients in their private practice. They included a total of 17 patients who had varying degrees of subjective or clinical memory impairment. They all received a 20 mg dose of montelukast when they woke up, and then 20 mg every 2 to 3 hours for the rest of the day for a total of 4 doses per day. The typical duration of dosing was not specified, but at least two case reports in the series reference dosing lasting for one to two weeks. Many of the patients or their families reported significant improvement of memory, agitation, or anxiety that stopped when the medication was discontinued. Not all patients reported improvement. While some patients knew what drug they were receiving and some did not, all knew they were receiving some medication from their doctor, and thus placebo effect cannot be excluded. Many did not report side effects (Rozin, 2017).

Mechanisms of action for neuroprotection identified from laboratory and clinical research:

Inflammation is a commonly recognized feature of AD. Asthma has also been suggested to be a risk factor for dementia, though the data are mixed, with some studies finding an increased risk of dementia in patients with asthma and some studies not finding any difference (Chen et al., 2014, Kim et al., 2019 and Nair et al., 2022, among others).

Montelukast is a leukotriene receptor antagonist; that is, it blocks lipid inflammatory mediators known as cysteinyl leukotrienes from binding to their receptors. While the action of cysteinyl leukotrienes and their receptors are most well-known in the respiratory system, cysteinyl leukotrienes are thought to be produced by cells in the central nervous system, and leukotriene receptors are also found in various brain regions (Wallin & Svenningsson, 2021; Sood et al., 2024). Some studies suggest that leukotriene receptors may be upregulated after injury to the brain, such as stroke, trauma, or in animal models of Parkinson's disease (PD) (Wallin & Svenningsson, 2021). Montelukast can also reduce inflammatory markers such as TNFα in the periphery (Lo et al., 2023). As montelukast acts to reduce inflammatory signaling there has been interest in whether montelukast may have repurposing potential for AD.

Preclinical studies indicate that montelukast may reduce neuroinflammation, increase neurogenesis and blood brain barrier integrity, and could modulate synaptic transmission. Moreover, montelukast may affect AD pathology, as studies have suggested montelukast can modulate Aβ formation and tau hyperphosphorylation (Ishikura et al., 2021; Xiong et al., 2021; Sood et al., 2024). Montelukast has been reported to reduce microglia activation, increase neurogenesis, and restore cognitive function in aged rats (6 weeks oral administration at 10 mg/kg) (Marschallinger et al., 2015). A study using an AD mouse model reported that montelukast improved some aspects of cognitive function and reduced neuroinflammation compared to the vehicle control (Michael et al., 2021). Co-infusion of montelukast (1-2 mg/kg) into cerebroventricles also protects against the harm induced by brain-infusion of aggregated amyloid-beta 1-42, resulting in less inflammatory and apoptotic signaling (Lai et al., 2014). Some benefits have also been seen in rodent models of stroke (Zhao et al., 2011), vascular dementia (Singh & Sharma, 2015), traumatic-brain injury (Biber et al., 2009), and animal models of synucleinopathies such as PD and dementia with Lewy bodies (reviewed in Wallin & Svenningsson, 2021 and Strempfl et al., 2022). In particular, montelukast appears to reduce blood-brain barrier permeability, which may lead to secondary protection from some injuries and age-related diseases. Zileuton, a different leukotriene receptor antagonist, has also been reported to reduce Alzheimer's pathology in aged triple transgenic mice (Di Meco et al., 2014 and others).

In summary, montelukast and similar drugs have yielded some protective benefits in animal models of neurological disease. Whether the drugs will help humans is not yet clear. Montelukast does penetrate the brain, but it is unclear if the doses used for asthma control in humans lead to therapeutic concentrations of montelukast in the brain (Xiong et al., 2021).

The leukotriene system is somewhat controversial as a target for neurodegenerative disease. A variety of laboratory studies suggest that it can be beneficial. GPR17, a primary target inhibited by montelukast, may be a sensor activated by brain injury that can induce both neuronal death or remodeling and repair, depending on the location of the tissue relative to the injury (e.g. Lecca et al., 2008, Daniele et al., 2010).

APOE4 interactions:

It is not yet known whether there are any differential effects of montelukast based on APOE4 status.

There are hypotheses that chronic peripheral inflammation and APOE4 together increase the risk of AD, such that an individual with both chronic peripheral inflammation and the APOE4 variant has a greater risk of AD than an individual who has only chronic peripheral inflammation or the APOE4 variant. If that is the case, it is theoretically possible that a drug like montelukast that serves to lower chronic peripheral inflammation could have more benefit for an individual who is an APOE4 carrier. However, this remains a theoretical speculation until studies investigate the interaction, if any, of montelukast and APOE4 (Tao et al., 2018).

Aging and related health concerns: Montelukast is used for asthma, and untreated asthma may increase the risk of other health issues that can exacerbate aging or related health concerns. There is little evidence for benefit outside of approved indications.

Types of evidence:

- 2 meta-analyses or systematic reviews
- 2 randomized controlled clinical trials
- 2 observational studies
- 3 short trials on relevant blood biomarkers of cardiovascular risk
- 3 reviews

- 2 laboratory studies

There is very little direct data from epidemiology or trials on how montelukast influences health in older individuals. Some mixed data exists for cardiovascular health and other specific stressors.

Leukotrienes are believed to be involved with cardiovascular disease and atherosclerosis (e.g. Riccioni & Bäck, 2012) but had no effect on biomarkers of cardiovascular health in adults with coronary heart disease treated for one month (unpublished but results at clinicaltrials.gov). Montelukast did, however, lower some inflammatory biomarkers associated with cardiovascular disease in a trial in asthma patients (Allayee et al., 2007). In Sweden, patients who have used montelukast are just as likely to experience stroke or cardiovascular disease, but they may have a lower risk of recurrent stroke (HR 0.62, 95% CI 0.38 to 0.99) or (in men only) recurrent myocardial infarction (Ingelsson et al., 2012). Perhaps this indicates less involvement in aging biology but potential involvement in the recovery from injury. Montelukast may also influence health in other ways. For example, a pilot trial in healthy men reported that it can blunt the effects of air pollution (high particulate matter) on vascular endothelial responses to exercise (Rundel et al., 2010). In patients with COPD (chronic obstructive pulmonary disorder), one pilot study reported that 12 months of montelukast treatment (10 mg/day) reduced hospitalizations, outpatient clinic care, and some inflammatory cytokines (LTB4 & IL-8 but not TNFα) (Gueli et al., 2011).

In theory, leukotriene inhibition may replicate some of the aging-biology effects seen from parabiosis experiments where blood from young mice introduced into older mice seem to rejuvenate their organs and improve health and cognition. Removal of potentially damaging molecules that are elevated in aged blood such as CCL11 (eotaxin-1), a pro-inflammatory chemokine that is associated with aging and reduced neurogenesis, might explain such effects. This observation was part of the rationale for the treatment of aged rats with montelukast by Ludwig Aigner's team (Marschallinger et al., 2015) and the study's focus on brain aging outcomes.

Untreated or uncontrolled asthma can lead to health issues that can exacerbate other aging and health-related conditions. For instance, uncontrolled asthma can contribute to insomnia, anxiety, depression, and obesity – all comorbidities that can contribute to other aging and health-related concerns (Busse & Kraft, 2022; O'Byrne et al., 2013). Montelukast is an approved treatment for asthma and is often used in combination with other medications for symptom management (Wermuth et al., 2023; Global Initiative for Asthma). If montelukast can help to adequately control an individual's asthma or helps prevent exacerbations, then montelukast can indirectly improve health. Moreover, asthma can be life-

threatening; therefore, appropriate treatment such as that with montelukast could contribute to decreased mortality (CDC).

Montelukast has been explored for other potential uses. Montelukast has been suggested to be renoprotective, particularly in early-stage kidney injury (Sarmadian et al., 2024). It has also been explored for use in sleep apnea. A network meta-analysis in pediatric patients found that compared to placebo, montelukast or a combination of mometasone and montelukast appeared particularly promising for treatment of obstructive sleep apnea (Zhang et al., 2024). More research is needed, particularly in adults. Some initial work has also investigated whether montelukast may have efficacy for metabolic dysfunction-associated steatotic liver disease (MASLD) and metabolic dysfunction-associated steatohepatitis (MASH). A network meta-analysis that included several different drugs reported that montelukast was one drug that improved certain markers of MASLD compared to placebo (Kovalic et al., 2023). An RCT tested montelukast compared to placebo in 52 patients with overweight or obesity and MASH for 12 weeks. At the end of the trial, compared to placebo, the patients in the montelukast group had significant improvement in liver stiffness, liver enzymes, several metabolic parameters, and inflammatory and MASH biomarkers (Abdullah et al., 2021).

While some small studies found potential benefit of montelukast in COVID-19 patients, a large RCT in 1,250 patients with mild to moderate COVID-19 found that montelukast did not improve time to sustained recovery compared to placebo or otherwise provide a benefit to patients (Rothman et al., 2024).

Safety: While generally well-tolerated in clinical trials, there is a black box warning on montelukast for serious neuropsychiatric events from post-marketing surveillance data.

Types of evidence:

- 1 meta-analysis or systematic review
- 4 observational studies
- 3 professional resources

Montelukast has been used in a variety of patient populations, from pediatric to elderly groups. Common side effects of montelukast include stomach pain, diarrhea, fever or flu symptoms, ear pain or feeling full or trouble hearing, headache, or cold symptoms like cough or congestion (Drugs.com).

In 2009, the FDA added a warning for potential risk of neuropsychiatric events for leukotriene inhibitors after reports of "agitation, aggression, anxiousness, dream abnormalities and hallucinations, depression, insomnia, irritability, restlessness, suicidal thinking and behavior (including suicide), and tremor". This warning applied to all leukotriene inhibitors, but montelukast was a particular concern given its widespread use (FDA Archive; Medscape interview). After reviewing case reports submitted to the FDA, conducting an observational study using an FDA reporting system, and reviewing the published literature of observational and animal study, the FDA added a black box warning to montelukast in 2020. This warning is for a 'wide variety' of potentially very serious mental health side effects, including agitation, aggression, depression, sleep disturbances, suicidal thoughts and behavior (including suicide). The FDA recommended that montelukast no longer be used as a first-line treatment for allergic rhinitis, especially when the allergic rhinitis is mild, given the risks and availability of other safe and effective options (FDA).

Several studies looked at the relationship between montelukast use and neuropsychiatric events. A 2023 observational study looked at adults in Denmark who had been given treatment for asthma, whether as medication or as a hospital visit. They excluded any patient who had received a neuropsychiatric medication prescription or had a hospital encounter for a neuropsychiatric event in the 6 months before the study period. There were 180,165 patients altogether; 23,355 of those patients had received montelukast in the study period. When they looked at the patients who received montelukast compared to those who hadn't, there were several baseline differences; those who received montelukast tended to have more severe asthma. However, there was no significant difference in use of neuropsychiatric medications over the past 5 years between the two groups. Montelukast use was significantly associated with use of neuropsychiatric medications (HR= 1.14; 95% CI 1.08 to 1.20; $p<0.0001$) in 18- to 44-year-olds; the risk in older adults were not analyzed in this study. When they looked at the all participants in the study, there was no significant association between montelukast prescription and hospital encounter for neuropsychiatric events. When they looked at the association by age, though, they saw a significant association in the youngest age group of 18- to 29-year-olds (HR=1.28; 95% CI 1.12 to 1.47, $p<0.001$) and in 30- to 44-year-olds (HR=1.16; 95% CI 1.02 to 1.31 $p< 0.05$). The hazard ratios decreased with increasing age, with no significant associations in adults over 44 (Jordan et al., 2023).

A study by Paljarvi et al., 2022 used propensity score matching to examine the association between montelukast use and neuropsychiatric events using a large electronic health record database; the

database contains records primarily from the United States. The study included individuals 15 to 64 years of age with asthma or allergic rhinitis who received their first montelukast prescription and matched controls who received a similar medication. The study included a total of 154,946 participants, 77,473 of whom had received montelukast. Patients were followed for 12 months from their index prescription of montelukast or other asthma or allergic rhinitis medication. They found that compared to patients who had not received montelukast, patients who received montelukast had significantly higher frequency of several neuropsychiatric conditions, listed in the table below.

Condition	Patient Population	Odds Ratio and 95% CI
Any sleep disorder	Allergic rhinitis	OR=1.10; 95% CI 1.01 to 1.20
Insomnia	Asthma	OR=1.13; 95% CI 1.01 to 1.27
	Allergic rhinitis	OR=1.15; 95% CI 1.05 to 1.27
Any anxiety disorder	Asthma	OR=1.21; 95% CI 1.05 to 1.20
	Allergic rhinitis	OR=1.12; 95% CI 1.05 to 1.19
Prescription for anti-depressant during follow-up	Asthma	OR=1.16; 95% CI 1.07 to 1.26
	Allergic rhinitis	OR=1.17; 95% CI 1.05 to 1.30
Any neuropsychiatric diagnosis	Asthma	OR=1.11; 95% CI 1.04 to 1.19
	Allergic rhinitis	OR=1.07; 95% CI 1.01 to 1.14

There were no significant differences in other neuropsychiatric conditions, including major depression and nonfatal self-harm.

It should be noted that in at least some of the studies above, the authors note that they cannot exclude the possibility that, as montelukast users tended to have more serious asthma, that the underlying poorer physical health was responsible for the poorer mental health. And, not all studies have found the same associations between montelukast use and neuropsychiatric events.

A 2023 systematic review of all published studies of montelukast and neuropsychiatric events in patients with asthma – including several studies mentioned elsewhere in this report – did not find a significant association between montelukast and suicide-related events or depression. The systematic review included 59 total studies, including 21 pharmacovigilance studies, four reviews of 172 RCTs, 20 observational studies, 10 case reports, and four case series. The conclusion of the systematic review is that as a whole, the data did not suggest a population-wide increase in risk of suicide from montelukast use, but that there could be an increased risk in specific individuals based on their particular medical

profile. The authors stated that current evidence suggested an association between montelukast and anxiety as well as montelukast and sleeping disorders, though they cautioned that the latter was subject to confounding, as montelukast is sometimes prescribed off-label for obstructive sleep apnea. The researchers reported that there may be more neuropsychiatric events such as anxiety and sleeping disorders in elderly patients (Lo et al., 2023).

The systematic review from Lo et al., 2023 included findings from a study from the FDA Sentinel Initiative; this study utilized data from the Sentinel Distributed Database to compare risk of psychiatric events in patients with asthma who received montelukast compared to inhaled corticosteroids (ICS), another asthma treatment. When they looked at the data from the 457,377 montelukast users to the 457,377 ICS users, they did not see any significantly increased frequency of inpatient depressive disorder or self-harm between groups, and they observed a lower frequency of treatment for outpatient depressive disorder in patients who received montelukast compared to those who received ICS (HR=0.91; 95% CI 0.89 to 0.93). This study did not assess the incidence of anxiety disorders or sleeping disorders, and the researchers note that inhaled corticosteroids themselves could be associated with depressive symptoms (Sansing-Foster et al., 2021). Lo et al., 2023 also included reviews of RCTs; the two largest included more than 10,000 patients who received montelukast in an RCT and found no significant increase in frequency of behavioral adverse event or suicidality in participants in these trials compared to placebo and/or active control (Philip et al., 2009 and Philip et al., 2009).

It may be that these events are rare enough that RCTs are not able to identify them, and that observational studies are not able to fully statistically control for residual confounding factors such as severity of underlying illness. It is also possible that there are specific, not yet known underlying risk factors that predispose some but not all patients to neuropsychiatric adverse events. Patients should discuss the potential for neuropsychiatric adverse events with their physician.

Drug interactions:

Montelukast is known to interact with 112 drugs; all drug interactions are moderate (Drugs.com). Some drugs can alter montelukast concentrations by interfering or enhancing its clearance through CYP3A4 or CYP2C9 cytochrome p450 in the liver (Drugs.com interaction checker).

Montelukast has 4 disease interactions. One is major; Montelukast has been associated with neuropsychiatric events and therefore should be used judiciously in patients with history of mental

illness. Montelukast contains phenylalanine, and the phenylalanine content should be considered by anyone who needs to restrict their phenylalanine intake. Finally, montelukast should be used with caution or with careful monitoring in those with liver or pulmonary disorders (Drugs.com).

Genetic variability influences the efficacy of montelukast for asthma (Lima, 2007) and would presumably influence its potential effects/dosing for other conditions.

Research underway:

There are 27 ongoing trials registered at clinicaltrials.gov that involve montelukast. The trials involve a variety of patient populations, from COVID-19 treatment to treatment of sickle cell anemia, to use in cancer, as well as studies examining specific aspects of montelukast in allergies or allergic reactions. Two studies involve neurodegenerative diseases:

NCT05457855 is a non-randomized, non-interventional study under the DREAM (Data Analysis for Drug Repurposing for Effective Alzheimer's Medicines) Study. Overall, DREAM compares the comparative risk of AD or dementia onset between patients prescribed one medication for a specific indication compared to patients with the same indication who were prescribed another medication. The study utilizes healthcare claims data. This specific study is assessing the incidence of dementia in those who received montelukast compared to those who received fluticasone. This study was set to complete in December 2023.

NCT06113640 is a study assessing the efficacy of montelukast in 60 patients with Parkinson's disease (PD). The RCT is randomizing patients to receive either standard of care levo-dopa three times daily, or levo-dopa three times daily plus montelukast once daily. The dosing is set to last for 12 months. The primary outcome of the study is change in Unified Parkinson's Disease Rating Scale (UPDRS) over the 12 months of dosing. This study is estimated to be completed in December of 2025.

Search terms:
Pubmed, Google: montelukast, leukotriene modifiers, zileuton

- Aging, mortality, atherosclerosis, telomere, AD, cognitive, neurodegenerative, APOE4, neurodegenerative, neuropsychiatric events, safety

Websites visited for montelukast:

- Clinicaltrials.gov
- Drugs.com
- WebMD.com
- PubChem
- DrugBank.ca
- Cafepharma