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
Anti-inflammatory agent that has shown neuroprotection in animal models, with possible cardiovascular benefit, and a good safety profile in adults. But clinical data for non-asthma indications is weak or absent.

**Neuroprotective Benefit:** Preclinical studies suggest neuroprotective potential, but BBB penetration is poor and benefits may be context dependent.

**Aging and related health concerns:** Very little direct data from epidemiology or clinical trials on how montelukast influences health in older individuals. Has anti-inflammatory properties, but data is mixed for cardiovascular health benefit.

**Safety:** Well-tolerated in clinical trials across all age ranges; possible rare risk of psychiatric adverse events, especially in children; only moderate drug interactions based on liver cytochrome P450 activity.
What is it? Montelukast is a generic drug used to treat and prevent asthma symptoms. The drug is marketed by Merck under the brand name Singulair™. The drug inhibits the activity of leukotriene receptors, specifically CysLT1 receptor activation by leukotriene D4 and other molecules, to reduce inflammation and bronchoconstriction. Montelukast has also been shown to inhibit GPR17, another leukotriene receptor.

Montelukast has been on the market since 1998, and is used for long-term treatment or prevention of asthma and exercise-related asthmatic attacks. It can also help with certain allergy symptoms (allergic rhinitis), and possibly for hives (urticaria), for which it is used off-label. (Drugs.com) It targets one component of the inflammatory pathway and is not considered a first-line treatment for asthma. According to the Global Initiative for Asthma, montelukast and other leukotriene inhibitors are less effective for asthma symptoms than other therapies that act through distinct pathways (e.g. inhaled corticosteroids & specific beta-blockers).

Several other asthma drugs also inhibit leukotriene pathways. For example, zafirlukast can also inhibit CysLT1 even though it has a very different chemical structure from montelukast while zileuton inhibits leukotriene synthesis rather than its receptor activity.

Neuroprotective Benefit: Preclinical studies suggest neuroprotective potential, but BBB penetration is poor and benefits may be context dependent.

Types of evidence:
- No meta-analyses, clinical trials, or epidemiology
- Several laboratory studies although on different models/injury paradigms
- Some anatomical data from humans to support the rationale

Human research to suggest prevention of dementia and cognitive aging: There is no direct evidence with respect to dementia risk with montelukast or related drugs. In a small trial in healthy volunteers, montelukast in combination with the antihistamine loratadine had no effect on multitasking ability, vigilance, or sleepiness (Valk Simons 2008).

Human research to suggest benefits to patients with dementia or cognitive aging: None

Mechanisms of action for neuroprotection identified from laboratory and clinical research. 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) (Marshaling Aigner 2015). These studies were performed based on the rationale that other pro-inflammatory cytokines contained in the blood, such as CCL11 (eotaxin-1), are associated with aging and reduced neurogenesis. Cerebroventricular infusion of montelukast (1-2 mg/kg) also protects against the harm induced by brain-infusion of aggregated amyloid-beta 1-42 (Aβ42), resulting in less inflammatory and apoptotic signaling (Lai 2014). Some benefits have also been seen in rodent models of stroke (Zhao 2011), vascular dementia (Singh 2015) and traumatic-brain injury (Biber 2009). In particular, montelukast appears to reduce blood-brain barrier (BBB) permeability, which may lead to secondary protection from some injuries and age-related diseases. Furthermore, Domenico Pratico at Temple University has published results indicating that a different leukotriene inhibitor, zileuton, reduced Alzheimer’s pathology in aged triple transgenic mice (Di Meco 2014 and others).

In summary, montelukast and zileuton have yielded some protective benefits in animal models of neurological disease. Whether the drugs will help humans is not yet clear. Montelukast has poor brain penetration, thus (e.g. Marshaling Aigner 2015) it is uncertain whether it can reliably reach therapeutic concentrations in the brain.

Although a variety of laboratory studies suggest that it may be beneficial, the leukotriene system is somewhat controversial as a target for neurodegenerative disease. 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 2008, Daniele 2010).

**APOE4 interactions:** No data

**Aging and related health concerns:** Very little direct data from epidemiology or clinical trials on how montelukast influences health in older individuals. Has anti-inflammatory properties, but data is mixed for cardiovascular health benefit.

**Types of evidence:**

- No meta-analyses
- 1 population-based cohort study on cardiovascular outcomes
- 3 short trials on relevant blood biomarkers of cardiovascular risk
Leukotrienes are believed to be involved with cardiovascular disease and atherosclerosis (e.g. Riccioni & Back 2012) but montelukast treatment for one month had no effect on biomarkers of cardiovascular health in adults with coronary heart disease (unpublished but results at clinicaltrials.gov). Montelukast did, however, lower some inflammatory biomarkers associated with cardiovascular disease in a trial in asthma patients (Allayee 2007). In Sweden, patients who have used montelukast did not have a decreased risk for stroke or cardiovascular disease, but they may have a lower risk of recurrent stroke (Hazard ratio (HR): 0.62, 95% CI 0.38-0.99) or (in men only) recurrent myocardial infarction (Ingelsson 2012). This suggests potential involvement in the recovery from injury.

Montelukast may also have protective effects in other contexts. 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 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 2011).

**Safety:** Well-tolerated in clinical trials across all age ranges; possible rare risk of psychiatric adverse events, especially in children; only moderate drug interactions based on liver cytochrome P450 activity.

Montelukast has been used from pediatric to elderly populations with asthma with few safety concerns noted (GINA). The most common adverse events reported are headache, influenza, abdominal pain, and cough. Some patients may be hypersensitive to the drug and asthma patients should be aware of safety issues around the treatment of their condition (drugs.com).

Some parents have formed an advocacy organization in the belief that Montelukast (Singulair) has caused suicidal behavior and other severe psychiatric problems in their children. All leukotriene modulators including montelukast are labeled as of 2009 with a warning for a potential risk of depression, suicidal behavior, and other psychiatric events (“agitation, aggressive behavior or hostility, anxiousness, depression, disorientation, disturbance in attention, dream abnormalities, hallucinations, insomnia, irritability, memory impairment, restlessness, somnambulism, suicidal thinking and behavior (including suicide), and tremor” (on the label). This risk is still an ongoing concern (Medscape interview). However, the side effects are reportedly rare, as they were largely undetected in clinical trials (Philip 2009a & 2009b, Holbrook 2008) and a population-based database (Chen 2014). Additionally, asthma itself may have associations with adverse events like suicidality (e.g. Kolves 2015).
Sources and dosing: Montelukast is a generic drug available in the United States. Typical dosing for asthma or allergic rhinitis is 10 mg/day QD. For urticarial, it has been tested at 5-20 mg/day. The dose does not need to be adjusted for geriatric patients or those with hepatic or renal impairment (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).

Zafirlukast has similar pharmacological effects but is structurally different from montelukast. Zileuton inhibits leukotriene synthesis rather than leukotriene receptor activity, and was more effective in asthma patients in a head-to-head trial (Kubavat 2013) and has been shown by the Pratico lab from Temple University to treat mouse models of Alzheimer’s (Joshi Pratico 2014 review). While there have not been any head-to-head comparisons between montelukast and zileuton for non-asthma related outcomes, montelukast is expected to have less risk of drug interactions based on liver cytochrome P450 activity.

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

Research underway: No clinical trials are publicly registered.

Search terms

Pubmed:

- montelukast separately with: aging, mortality, atherosclerosis, telomere, cohort, Alzheimer, cognitive, neurodegenerative, database, incident, apolipoprotein E4,
- leukotriene modifiers, atherosclerosis
- zileuton separately with Alzheimer, cognitive, mortality, aging, apolipoprotein E4,
- leukotriene, apolipoprotein e4

Google:

- montelukast, neurodegenerative
- montelukast, cognitive
- montelukast, side effect
- Clinicaltrials.gov, clinicaltrialsregister.eu, NIH reporter
- montelukast – filtered for arteriosclerosis; scan through for relevant conditions
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