TO: US FDA MONTELUKAST WORKING GROUP
FROM: Administrators of the Montelukast (Singulair) Side Effects Support and Discussion Group
DATE: May 16, 2022

Dear Members of the Science Advisory Board to the National Center for Toxicological Research and the Montelukast Working Group,

The Montelukast (Singulair) Side Effects Support and Discussion group is an international group that consists of montelukast-affected adults and parents/carers of montelukast-affected children. Our membership increases by about 100 members weekly and is currently 16,300+ strong. For the past 10 years, our group, in collaboration with other advocates such as Parents United for Pharmaceutical Safety and Accountability, has advocated for the safer use of montelukast and research into its side effects.

We know from published research that montelukast crosses the blood-brain barrier and accumulates in the brain over time and at levels substantially higher than other body tissues after 24 hours[1]. Montelukast inhibits GPR17[2], a G-protein coupled receptor that is expressed on neurons and glial cells in the human brain. This may contribute to neuropsychiatric events. But the FDA has admitted the exact mechanisms of the medication are not well understood.[3] Neither do we understand why some individuals suffer side effects, while others do not, and why some side effects appear after years of treatment, whereas others appear after a single dose. A 2020 in vitro study showed the capability of montelukast to directly induce toxicity and inflammation in HAPI cells[4], possibly through the involvement of PGE2 and ROS, and toxicity in undifferentiated SH-SY5Y neuroblastoma cells (Tsenge, 2020). Further research on how montelukast works and its effects on the brain, particularly on children's brains, is incredibly important, given the enormous popularity and global distribution of this drug.

WITHDRAWAL SIDE EFFECTS

The FDA currently advises users to stop montelukast immediately if side effects occur. However, our members continue to report an intense and, at times, life-threatening withdrawal upon discontinuation of montelukast. Withdrawal can present as flu-like symptoms and/or severe neuropsychiatric side effects including anxiety, depression, insomnia, and suicidal thoughts and actions. In some severe cases, it presents as psychosis. Few in the medical community acknowledge the medication's side effects, let alone withdrawal effects on discontinuation, and

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[1] FDA, Montelukast. (Singulair, application number 20-829) (Pharmacology Review).
[2] Marschallinger J, Schäffner I, Klein B, et al. Structural and functional rejuvenation of the aged brain by an approved anti-asthmatic drug. *Nat Commun*. 2015;6:8466. Published 2015 Oct 27. doi:10.1038/ncomms9466
[3] September 2019 US FDA Pediatric Advisory Committee Meeting Briefing Document, Page 14
[4] Tseng YT, Cox TM, Grant GD, Arora D, Hall S, McFarland AJ, Ekberg J, Rudrawar S, Anoopkumar-Dukie S. In vitro cytotoxicity of montelukast in HAPI and SH-SY5Y cells. Chem Biol Interact. 2020 Aug 1;326:109134. doi: 10.1016/j.cbi.2020.109134.

offer no treatment options. Els and Webb (2022) document a case study of acute withdrawal from montelukast[5].

Members also report a sudden onset or escalation of side effects after stopping and restarting.

In a small poll conducted in our Facebook group:

- 405 members indicated they have a child/loved one (under 18) who suffered withdrawal symptoms after discontinuing montelukast
- 28 of the 405 respondents indicated that they had a second child impacted by withdrawal after discontinuation
- A further 5 have a third child impacted by withdrawal symptoms
- 136 adult individuals indicated they or an adult loved one experienced withdrawal symptoms after stopping montelukast

We are also concerned with the phenomenon of post acute withdrawal, similar to that experienced by those who abruptly discontinue other psychoactive medications[6]. Given montelukast's actions on the brain and the lived experiences of those who have abruptly stopped taking the drug, we suspect acute withdrawal phenomena are occurring. Our group members report initial improvement after stopping, but then often experience an intense relapse about a month after discontinuation. This is an observation we have seen repeatedly among members of our group.

Other medications that affect the brain, such as antidepressants and anxiolytics, have recommendations to taper off during discontinuation. Research is needed on the best course of action for those who wish to discontinue montelukast. **Should patients discontinue montelukast via tapering, as is done with other medications that affect the brain? Would there be less injury if users tapered off, and if so, by what process?**

Many of the suicide attempts and some completed suicides we know of have been reported after discontinuation of the medication. Treatment options should be available to help ease dangerous withdrawal symptoms. Although anecdotal, a few members have reported relief with azithromycin, which is both an anti-inflammatory and antibiotic. The mechanism here may be that the stress induced by abrupt discontinuation causes immune distress. **A research study on withdrawal relief would save lives. What are the options for treating withdrawal?**

POSSIBLE OVERDOSE

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[5] Els, I. & Wells, S. Neuropsychiatric event on withdrawal of montelukast. J of Paediatrics and Child Health, 2022, 58:721. 2022 https://doi.org/10.1111/jpc.15937.

[6] Haskell, B, Identification and evidence-based treatment of post–acute withdrawal syndrome. The Journal for Nurse Practitioners, 2022, 18: 272-275, doi.org/10.1016/j.nurpra.2021.12.021.

Many medications on the market are based on weight not age. We see often in the support group that side effects appear after a dosage increase. Many children suffer intensely when increased to the 10mg dosage.

Why is montelukast prescribed based on age and not weight? Is it possible that some smaller children or adults are being given too large a dose and are actually experiencing an overdose in addition to side effects?

PROTRACTED RECOVERY

Our members are reporting a protracted period of recovery from side effects after discontinuation of montelukast. This includes long-term mental health injuries and neurological sequelae - complications involving damage to the central nervous system that results in cognitive, sensory, or motor deficits that may also manifest as emotional instability, significant behavioral dysregulation, and seizures in the most severe cases. Our members report that doctors habitually dismiss patients' experience when they report side effects persisting after discontinuing montelukast.

In a small poll conducted in our Facebook group:

- 633 members indicated they have a child/loved one (under 18) who suffered long-term side effects of montelukast
- 33 of the 633 respondents indicated they had a second child impacted by long-term side effects
- A further eight have a third child impacted by long-term side effects
- 159 adult individuals indicated they or an adult loved one experienced long-term side effects

Why is montelukast causing long-term injury? If neuropsychiatric research can show the mechanisms behind these long-term side effects, then treatment options - which should be easily accessible and aligned with specific insurance coding - can be explored and targeted.

DELAYED SIDE EFFECTS

Our members are asking whether negative effects on the brain/neurons from taking this drug may not surface until later in life. Eriksson et al. (2018) found negative effects on the developing brain of a mouse[7]. Both acute and 2-week administrations of montelukast inhibited cellular proliferation and maturation in the hippocampus of the intact juvenile mouse brain. However,

[7] Eriksson Y, Boström M, Sandelius Å, Blennow K, Zetterberg H, Kuhn G, Kalm M. The anti-asthmatic drug, montelukast, modifies the neurogenic potential in the young healthy and irradiated brain. Cell Death Dis. 2018 Jul 10;9(7):775. doi: 10.1038/s41419-018-0783-7.

these mice were sacrificed before sexual and brain maturation. We do not know what a brain treated with montelukast looks like when it reaches adulthood.

Following from this study, is it possible that undiagnosed brain injury suffered by young children who have taken montelukast (many for long periods) will result in further problems later in life? Research needs to look at the long-term implications of taking montelukast.

DOES MONTELUKAST SUBSTANTIALLY ALTER THE MICROBIOME?

Gastrointestinal problems were the first side effect noted by the FDA during pre-clinical trials[8]. Over the years, our members have reported digestive issues both during use and upon discontinuation. These problems range from diarrhea, nausea, vomiting, constipation, acid reflux, IBS, H pylori and newly diagnosed celiac, to name only a few. Could montelukast use substantially impact the microbiome balance to cause a chronic GI illness? Could this explain the chemical sensitivities that are experienced during and after use? A recent study in Nature lists Montelukast as a drug that alters - and is altered by - the bacteria in the microbiome. Montelukast was one of several drugs that were both bioaccumulated by some gut bacteria and degraded by others.[9]

INCREASED SENSITIVITIES

Our members continue to report extreme reactions to other medications, additives, heat, artificial sweeteners, sugar, alcohol, and chemicals as well as a very heightened response to viruses and infections after discontinuing montelukast. Some patients also report the sudden onset of mast cell activation symptoms after stopping.

Could heightened sensitivities experienced after suffering an adverse reaction to montelukast be caused by montelukast-induced microglia dysfunction?

MICROGLIA DYSFUNCTION

As outlined above, affected individuals and families are desperately seeking answers regarding the biological mechanisms that cause the neuropsychiatric side effects of montelukast. For example, we need research to better understand whether and how montelukast impacts the blood brain barrier and plays a part in affecting the immune system by causing microglial dysfunction. Sadly, we don't have the knowledge to answer these questions, but we have the

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[8] FDA, Montelukast. (Singulair, application number 20-829) (Medical Review).

[9] Klünemann, M., Andrejev, S., Blasche, S. *et al.* Bioaccumulation of therapeutic drugs by human gut bacteria. *Nature* 597, 533–538 (2021). https://doi.org/10.1038/s41586-021-03891-8.

collective experience of the devastating damage created by this drug that gives us every right to ask these questions and demand answers.

Our group has concerns that montelukast may initiate a mechanism whereby it impacts microglia and phagocytosis, possibly causing synapse loss. For example, Stevens and colleagues' research on microglia activation and its activity in the brain's hippocampus[10] has prompted many questions for us.

We know that the neuroimmune system is an adaptive system that "learns how to behave." Perhaps when montelukast is present, the body/brain "learns" to reduce proinflammatory microglial activity. If montelukast programs microglia to relax, and stay relaxed in the brain, **what happens when montelukast is withdrawn abruptly? Is it possible that microglia are suddenly activated and enter an overt protective phase to defend against everything, and perhaps no longer be sensitized to a true threat?** If that is the case, it is possible montelukast robs the microglia's ability to distinguish between a true threat in the central nervous system (CNS) versus an innocuous element such as a microbe, resulting in everything provoking a proinflammatory response (e.g., virus, infection, other medications, additives, even heat).

We have many questions about montelukast and microglia:

Does withdrawing montelukast from the brain cause microglia to become locked into a state of perpetual proinflammatory action (pruning synapses, healthy or not)?

Does microglia become dependent on montelukast to keep the neuroimmune system healthy and effective? If so, what happens when an individual stops abruptly?

Does the developmental stage of an individual at the time of discontinuation, impact the severity of problems that present when montelukast is removed from the brain?

Is montelukast use resulting in a process of overactivation of microglial pro-inflammatory action?

Are genetic, pre-existing or environmental triggers impacting the way some individuals recover from an adverse reaction to montelukast and are microglia responding to these triggers?

Is montelukast causing microglia or immune dysfunction?

Does montelukast cause microglia to perceive change, resulting in a stoppage of protective neurochemical emissions, instead producing harmful neuroinflammatory chemicals in the brain?

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[10] Schafer DP, Lehrman EK, Kautzman AG, et al. Microglia sculpt postnatal neural circuits in an activity and complement-dependent manner. *Neuron*. 2012;74(4):691-705. doi:10.1016/j.neuron.2012.03.026

Does withdrawing from montelukast push the brain into a pro-inflammatory state causing synapse loss and runaway inflammation (cytokine storm)? If so, would cytokine storm preventatives for treatment be an option when stopping?

Can we heal affected individuals by modulating the immune/neuroimmune system and if yes, what is the most effective way to achieve this?

If we find an effective treatment option such as IVIG through new and valid research, how can we overcome the tremendous barrier to get these much-needed treatments covered under insurance?

PANS/PANDAS

Some of our members whose children have suffered an adverse reaction to montelukast and have had a very severe and sudden onset of neuropsychiatric symptoms or worsening of side effects within days of discontinuing treatment, have suspected and received clinical diagnoses for PANS or PANDAS (basal ganglia encephalitis, BGE). We have also heard of a member receiving a diagnosis for auto-immune encephalitis. Both the sudden onset and nature of some of the symptoms that start during withdrawal from montelukast (which can look like psychosis) and the remitting and relapsing path of recovery for those who have long term issues are very similar to what occurs in PANS/PANDAS. **Does abruptly stopping montelukast result in PANDAS/ PANS in some individuals? Why is this so? Could this be due to montelukast altering the microbiome? Why do some montelukast users appear to be more susceptible to strep infections? Is montelukast causing the blood brain barrier to become more permeable, and are infections such as strep more likely to cross into the brain when children are using or discontinuing montelukast? Does stopping montelukast abruptly or being on montelukast dysregulate the immune system?**

Montelukast side effects include tonsillitis, which can lead to PANDAS. Those who suffer from PANS or PANDAS often carry an infection that has crossed over into the brain[11]. Mice using montelukast showed increased *Streptococcus pneumoniae* bacterial counts from nasal lavage. Allergic and infected mice experienced higher bacterial counts when compared to control[12]. Increased bacterial *growth* was also identified in infected mice that were using montelukast. This indicates that cysteinyl leukotrienes have an impact on the innate response to bacterial infection. **Could discontinuation or use of montelukast be creating an environment for bacteria and infection to cross into the brain?** If so, we need to notify providers how to look for and treat this - immediately after stopping the drug, as there is a window of time for effective treatment (antibiotics such as azithromycin). If not treated immediately, this immune problem could continue indefinitely.

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[11] Wilbur, C, et al. PANDAS/PANS in childhood: Controversies and evidence, *Paediatrics & Child Health*, May 2019, 24:85–91, https://doi.org/10.1093/pch/pxy145

[12] Khoury P, Baroody FM, Klemens JJ, Thompson K, Naclerio RM. Effect of montelukast on bacterial sinusitis in allergic mice. Ann Allergy Asthma Immunol. 2006 Sep;97(3):329-35. doi: 10.1016/S1081-1206(10)60797-1.

CONCLUSION

Our group has been calling for well-designed studies specifically targeting neuropsychiatric side effects, to better understand how montelukast affects the brain, and in particular, the developing brain, the blood brain barrier and myelination processes. We also want to let you know we are available to assist in any way we can to help if needed. Thank you for your efforts to advance the understanding of our new normal.
Yours sincerely,

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OTHER RECENT RESEARCH

Davis, B.M., Salinas-Navarro, M., Cordeiro, M.F. *et al.* Characterizing microglia activation: a spatial statistics approach to maximize information extraction. *Sci Rep* 7, 1576 (2017). https://doi.org/10.1038/s41598-017-01747-8

Dixon EG, Rugg-Gunn CE, Sellick V*, et al.* Adverse drug reactions of leukotriene receptor antagonists in children with asthma: A systematic review. *BMJ Paediatrics Open* 2021;**5:**e001206. doi:10.1136/bmjpo-2021-001206

Ekhart C, van Hunsel F, Sellick V, de Vries T. Neuropsychiatric reactions with the use of montelukast. BMJ. 2022 Mar 29. doi: 10.1136/bmj-2021-067554.