2019 Submission - Royal Commission into Victoria's Mental Health System

Name
Ms Jocelyn Suiter

What are your suggestions to improve the Victorian communitys understanding of mental illness and reduce stigma and discrimination?
n/a

What is already working well and what can be done better to prevent mental illness and to support people to get early treatment and support?
" I would like to recommend a small but significant change which would improve the mental health of many Victorians and prevent suicidal behaviour. I am the parent of a child who suffered the neuropsychiatric side effects of the widely prescribed [redacted] medication [redacted]. The side effects suffered by my child during his two years on [redacted] included severe insomnia, anxiety, emotional outbursts, incontinence and suicidal thoughts. His doctors never warned me of the possibility of side effects and there was no consumer leaflet inside the packaging. It was only by coincidence that I made the link between the [redacted] medication and his severe mental health issues after two years of suffering. I am a member of the [redacted] This group has more than 6580 members from across the globe. Since 2008, this group has been advocating in Australia, the USA and the UK for increased warnings and safeguards around the use of [redacted] Over the years, medical professionals have dismissed the experiences of thousands of affected individuals, including multiple families who have lost loved ones to suicide. However, there is now a growing body of published research confirming the drugs neuropsychiatric side effects, including depression, anxiety and suicidal thoughts and behaviour. These side effects are listed in the drugs Product Information Leaflet, however, I believe more needs to be done to assist those suffering neuropsychiatric side effects to make the link between the mental health struggles experienced and the medication. I want the Australian Therapeutic Goods Administration to create a new and mandated Cautionary Advisory Label (CAL) as part of the Poisons Standard of Australia, for medications that cause severe neuropsychiatric side effects such as suicidal thoughts and actions, and depression and anxiety. Consultation with the state health ministers, including the Victorian health minister, would be required to ensure a national rollout of these CALs. Such a label could have saved my son from two years of suffering, and many others from suicidal behaviour, OCD and other mental health illnesses. A list of medications that cause severe neuropsychiatric side effects were listed in the TGAs recent medical alert (June 2018). They are as follows: antidepressants, particularly selective serotonin reuptake inhibitors (SSRIs) certain smoking cessation medications, including varenicline and buproprion (marketed as Champix and Zyban) certain antiepileptics, including sodium valproate, carbamazepine, levetiracetam, phenytoin, lamotrigine, topiramate, pregabalin and gabapentin isotretinoin (marketed as Roaccutane) atomoxetine (marketed as Strattera and generic brands) montelukast (marketed as Singulair and generic brands) I believe that all of the medications above should have a mandated CAL in all states of Australia. The CAL should read See your doctor immediately if you experience mood changes, such as new or worsening feelings of sadness, depression or fear. This is the wording used for the warning on [redacted] in the

USA. I am asking the royal commission to recommend in its report that the Victorian Health Minister ensures the CAL is placed on the outside of all medications that may cause severe neuropsychiatric side effects, including [redacted] Early intervention is key in reducing the impacts caused by these severe and long-term side effects. In the case of [redacted], many of our groups members have reported that side effects can present at any time during use, even after years of using the medication safely. For this reason, users are lulled into a false sense of security, and making the link between the medication and the side effects can be very difficult. Constant monitoring is required during use, and a CAL on the outside of the packaging acts as a prompt, should the side effects present. [redacted] and as a result, drug companies have been asked to place the Consumer Medicines Leaflet inside the packaging of products in Australia that contain [redacted]. I am are grateful for this improvement but it does not go far enough to reduce the chances of mental health injuries occurring in those who suffer the side effects. While the royal commission is considering the provision of Victorias mental health services, it is also prudent to consider that prevention is better than cure. Please help us to reduce the incidence of mental health injuries in our community. The epidemic of mental health struggles and the increase in suicide requires us to be innovative in our approach. We can no longer accept that mental health injuries are just an accepted part of using any medication. Consumers require increased warnings so they can make informed decisions about their health. The introduction of a CAL that highlights neuropsychiatric side effects will reduce the incidence of mental health injuries. It is a fiscally and ethically responsible answer to a real and devastating problem. I speak on behalf of my child and all of the children who have no voice in this debate. We must help parents to monitor for life-altering or life-threatening side effects. "

What is already working well and what can be done better to prevent suicide?

" I would like to recommend a small but significant change which would improve the mental health of many Victorians and prevent suicidal behaviour. I am the parent of a child who suffered the neuropsychiatric side effects of the widely prescribed [redacted] medication [redacted]. The side effects suffered by my child during his two years on [redacted] included severe insomnia, anxiety, emotional outbursts, incontinence and suicidal thoughts. His doctors never warned me of the possibility of side effects and there was no consumer leaflet inside the packaging. It was only by coincidence that I made the link between the [redacted] medication and his severe mental health issues after two years of suffering. I am a member of the [redacted] This group has more than 6580 members from across the globe. Since 2008, this group has been advocating in Australia, the USA and the UK for increased warnings and safeguards around the use of [redacted]. Over the years, medical professionals have dismissed the experiences of thousands of affected individuals, including multiple families who have lost loved ones to suicide. However, there is now a growing body of published research confirming the drugs neuropsychiatric side effects, including depression, anxiety and suicidal thoughts and behaviour. These side effects are listed in the drugs Product Information Leaflet, however, I believe more needs to be done to assist those suffering neuropsychiatric side effects to make the link between the mental health struggles experienced and the medication. I want the Australian Therapeutic Goods Administration to create a new and mandated Cautionary Advisory Label (CAL) as part of the Poisons Standard of Australia, for medications that cause severe neuropsychiatric side effects such as suicidal thoughts and actions, and depression and anxiety. Consultation with the state health ministers, including the Victorian health minister, would be required to ensure a national rollout of these CALs. Such a label could have saved my son from two years of suffering, and many others from suicidal behaviour, OCD and other mental health

illnesses. A list of medications that cause severe neuropsychiatric side effects were listed in the TGAs recent medical alert (June 2018). They are as follows: antidepressants, particularly selective serotonin reuptake inhibitors (SSRIs) certain smoking cessation medications, including varenicline and buproprion (marketed as Champix and Zyban) certain antiepileptics, including sodium valproate, carbamazepine, levetiracetam, phenytoin, lamotrigine, topiramate, pregabalin and gabapentin isotretinoin (marketed as Roaccutane) atomoxetine (marketed as Strattera and generic brands) montelukast (marketed as Singulair and generic brands) I believe that all of the medications above should have a mandated CAL in all states of Australia. The CAL should read See your doctor immediately if you experience mood changes, such as new or worsening feelings of sadness, depression or fear. This is the wording used for the warning on [redacted] in the USA. I am asking the royal commission to recommend in its report that the Victorian Health Minister ensures the CAL is placed on the outside of all medications that may cause severe neuropsychiatric side effects, including [redacted]. Early intervention is key in reducing the impacts caused by these severe and long-term side effects. In the case of [redacted], many of our groups members have reported that side effects can present at any time during use, even after years of using the medication safely. For this reason, users are lulled into a false sense of security, and making the link between the medication and the side effects can be very difficult. Constant monitoring is required during use, and a CAL on the outside of the packaging acts as a prompt, should the side effects present. [redacted] and as a result, drug companies have been asked to place the Consumer Medicines Leaflet inside the packaging of products in Australia that contain [redacted]. I am are grateful for this improvement but it does not go far enough to reduce the chances of mental health injuries occurring in those who suffer the side effects. While the royal commission is considering the provision of Victorias mental health services, it is also prudent to consider that prevention is better than cure. Please help us to reduce the incidence of mental health injuries in our community. The epidemic of mental health struggles and the increase in suicide requires us to be innovative in our approach. We can no longer accept that mental health injuries are just an accepted part of using any medication. Consumers require increased warnings so they can make informed decisions about their health. The introduction of a CAL that highlights neuropsychiatric side effects will reduce the incidence of mental health injuries. It is a fiscally and ethically responsible answer to a real and devastating problem. I speak on behalf of my child and all of the children who have no voice in this debate. We must help parents to monitor for life-altering or life-threatening side effects. "

What makes it hard for people to experience good mental health and what can be done to improve this? This may include how people find, access and experience mental health treatment and support and how services link with each other.
n/a

What are the drivers behind some communities in Victoria experiencing poorer mental health outcomes and what needs to be done to address this?
n/a

What are the needs of family members and carers and what can be done better to support them?
n/a

What can be done to attract, retain and better support the mental health workforce, including peer support workers?
n/a

What are the opportunities in the Victorian community for people living with mental illness to improve their social and economic participation, and what needs to be done to realise these opportunities?
n/a

Thinking about what Victorias mental health system should ideally look like, tell us what areas and reform ideas you would like the Royal Commission to prioritise for change?
n/a

What can be done now to prepare for changes to Victorias mental health system and support improvements to last?
n/a

Is there anything else you would like to share with the Royal Commission?
n/a

STUDIES/CASE REPORTS AND RESEARCH ARTICLES ON MONTELUKAST NEUROPSCYCHIATRIC (AND OTHER) ADVERSE EVENTS

(FOR REFERENCE ONLY)

Montelukast and Risk of Neuropsychiatric Events in Children with Asthma: A Population-Based, Nested Case-Control Study Dresden Glocker-laufa , Yaron Finkelsteinb , Jingkin Zhub , Laura Feldmanb and Teresa Tob a Western University; b University of Toronto (2018) Published online: 21 Sep 2018

https://www.eapcct.org/publicfile.php?folder=congress&file=Abstracts_Chicago2018.pdf

"Conclusions: Children prescribed montelukast ***were almost twice as likely to experience a new-onset neuropsychiatric event,*** *compared to controls on a different asthma maintenance therapy. Our findings echo the 2014 FDA's Pediatric Advisory Committee recommendations, suggesting increased provider awareness and continued monitoring of neuropsychiatric adverse events in patients administered montelukast. Clinicians should be aware of the potential risks of montelukast, as it may inform their prescribing practices and clinical follow-up visits."*

The Anti-Asthmatic Drug, Montelukast, Modifies the Neurogenic Potential in the Young Healthy and Irradiated Brain Yohanna Eriksson,[1] Martina Boström,[1,2] Åsa Sandelius,[3] Kaj Blennow,[3,4] Henrik Zetterberg,[3,4,5,6] Georg Kuhn,[7,8]and Marie Kalm Cell Death Dis. 2018 Jul; 9(7): 775.
Published online 2018 Jul 10. doi: [10.1038/s41419-018-0783-7]

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6039496/

Interestingly, the animals that received montelukast for 14 days had 50% less proliferating cells in the hippocampus irrespective of receiving CIR or not. Further, the total number of neurons in the granule cell layer was altered during the sub-acute phase. The number of neurons was decreased by montelukast treatment in control animals (15%), but the opposite was seen after CIR, where montelukast treatment increased the number of neurons (15%). The results show beneficial effects by montelukast treatment after CIR in some investigated parameters during both the acute phase and with longer drug treatment. However, it also resulted in lower proliferation in the hippocampus under normal conditions, indicating that the effects of montelukast can be either beneficial or unfavorable, depending on the circumstances."

"In summary, montelukast has negative effects on the maturation of the GCL during normal conditions, whereas during a pathological condition, such as following CIR, the effects can be protective. These findings, with the affected proliferation during normal conditions, in combination with the new profile for psychiatric adverse drug reactions, suggests that prescribing montelukast to young children should be a well thought through decision. However, more studies are needed to investigate if the negative effects are occurring also at lower dose spans and if the effect is chronic if ending the treatment with montelukast."

Neuropsychiatric Adverse Drug Reactions in Children Initiated on Montelukast in Real-Life Practice, Brigitte Benard, Valérie Bastien, Benjamin Vinet, Roger Yang, Maja Krajinovic, Francine M. Ducharme, European Respiratory Journal 2017 50: 1700148; **DOI:** 10.1183/13993003.00148-2017

http://erj.ersjournals.com/content/50/2/1700148

"In the real-life setting, asthmatic children initiated on montelukast experienced a notable risk of neuropsychiatric ADRs leading to drug cessation, that is significantly higher than that associated with ICS."

"The incidence of children on montelukast with drug cessation due to neuropsychiatric adverse events was >10% **http://ow.ly/nCGG30bgjpd"**

Adverse Drug Reactions of Montelukast in Children and Adults (Pharmacology Research and Perspectives) Meindina G. Haarman Florence van Hunsel Tjalling W. de Vries Principal Investigator: Tjalling W de Vries MD PhD 20 September 2017

http://onlinelibrary.wiley.com/doi/10.1002/prp2.341/full
https://doi.org/10.1002/prp2.341

"These data demonstrate that ***montelukast is associated with neuropsychiatric adverse drug reactions such as depression and aggression****. Especially in children nightmares are reported frequently. Allergic granulomatous angiitis is also reported, a causal relationship has not been established."*

"Our data indicate that neuropsychiatric symptoms, such as depression, aggression, suicidal ideation, abnormal behavior, and nightmares, were significantly frequently reported in children and in adults in both the Dutch and the global database. The RORs found in these adverse events were high, pointing to a strong relationship. In addition, although Aldea Perona et al. have argued that more neuropsychiatric symptoms were reported more frequently in children compared to adults (Aldea Perona et al. 2016), we cannot confirm this."

*"The most common adverse events in **adults** according to the summary of product characteristics (SmPC) are upper airway infections (in >10% of all users) fever, rash, nausea, vomiting, diarrhea, and elevated levels of liver enzymes (Dutch Farmacotherapeutic Compass, 2016)."*

*"Most common adverse events in **children** (1–10% of all users) according to the SmPC are headaches, abdominal pain, rash, thirst, hyperkinesia, asthma**,** and eczema (Dutch Children's Formulary, 2016). "*

"The highest RORs were found for aggression (24.99; 95% CI: 23.5–26.6), suicidal ideation (20.4; 95% CI: 19–22), abnormal behavior (34.05; 95% CI: 31.8–36.5), and nightmares (22.46; 95% CI: 20.9–24.2)."

"The ROR compares the rate of reporting a specific adverse effect in a drug with the rate of reporting the same adverse effect in all other drugs."

Neuropsychiatric Adverse Effects of Montelukast in Children European Respiratory Journal 2017 50 1701020 Pierre Ernst, Geneviève Ernst

European Respiratory Journal August 2017

http://erj.ersjournals.com/content/50/2/1701020

*"**Neuropsychiatric ADRs of montelukast are common and difficult to recognise in children** http://ow.ly/wlzW30cQn0f"*

"As for the use of montelukast in children, adverse neuropsychiatric effects are sufficiently common and potentially difficult to recognise in young children to require that parents be informed of these at the initiation of treatment. Notably, the current study included only a small number of adolescents, such that the risk of suicidal behaviour in adolescents reported with montelukast cannot be quantified by the study by Benard et al. [4]. However, it may be prudent to discuss the possibility of mood changes as well as warning signs for suicidality with both adolescents and their parents when initiating treatment. Finally, it would be helpful to have larger studies that would permit the identification of individual predictors of neuro-psychiatric adverse events related to montelukast."

The Effect of Montelukast on Depression Behavior in Rat Forced Swimming Test *Ersöz Gonca,* Journal of Mood Disorders (JMOOD) 2017;7(2):104-9 March 2017

http://pbsciences.org/en/ArticlesDetail.aspx?ID=385&fbclid=IwAR1fPYkmayqJSlN5kOA6sYU0LPa4TSE7JMN4VC_ECYWBt6rpaTHWAl9ymgo

"Conclusion: Montelukast treatment causes depression behavior in both healthy and asthmatic rats"

Seizures as a Rare but Serious Adverse Effect of Leukotriene Receptor Erdem*, Semiha Bahceci et al. Annals of Allergy, Asthma & Immunology, Volume 117 , Issue 1 , 99 – 101* July 2016

http://www.annallergy.org/article/S1081-1206(16)30221-6/pdf

"We report convulsions observed as a rare adverse effect of LTRAs in 3 patients. Two of these patients were being treated for epilepsy, and the seizures were under control. The third patient had no prior history of seizures. Note that seizures were observed in sleep"

Psychiatric Disorders and Montelukast in Children: A Disproportionality Analysis of the VigiBase® Aldea Perona A, et al. Drug Saf. 2016. Authors Aldea Perona A[1], García-Sáiz M[1], Sanz Álvarez E[2]. 20 November 2015

https://www.ncbi.nlm.nih.gov/m/pubmed/26620206/

http://link.springer.com/article/10.1007%2Fs40264-015-0360-2
Please note: The full text of this study is not available from these links but your doctor should be able to easily access the full text.

"Results: *Unexpectedly, completed suicides were reported more frequently for children (IC: 3.15; IC025: 1.98) than for adolescents (IC: 3.11; IC025: 2.61) or the total population (IC 1.95; IC025: 1.73)."*

Onset of side effects: *"Data on duration of treatment, onset of reaction and recovery are presented in annexes 7 and 8 (see ESM 4). Information is limited to approximately one-third of the cases. The median time to onset varies from hours or a few days for sleep disorders and psychotic disorders, to one to several weeks for depression disturbances.* ***For the suicidal category, the median time to onset is much higher, ranging from months to years****."*

"Conclusions: *Neuropsychiatric disorders as side effects of montelukast were more frequently reported for children than for adults. Infants and children seem to be more prone to sleep disturbances, whereas adolescents present symptoms of depression/anxiety and psychotic reactions more often. Suicidal behaviour and*

completed suicide appear to be more frequently reported than previously thought in practice. Risk management plans and epidemiological studies are needed to quantify the risk. Practitioners should be aware of the risk of neuropsychiatric events associated with montelukast use, and should advise the patient and report new cases."

Also see supplementary information – **Annex 8** which shows lingering time frame of side effects in particular for anxiety, anxiety disorder and depression.

https://static-content.springer.com/esm/art%3A10.1007%2Fs40264-015-0360-2/MediaObjects/40264_2015_360_MOESM4_ESM.pdf

Mood and Behavioral Changes Associated with Montelukast Usage in Pediatric Cases Banu Gulcan Oksuz, MD, Mahir Igde, MD, Onur Ozturk, MD* Samsun Education and Research Hospital, Department of General Pediatrics, Samsun, Turkey Samsun Education and Research Hospital, Department of Pediatric Allergy and Immunology, Samsun, Turkey *Atakum Community Health Center, Samsun, Turkey, Samsun, Turkey *Indian Journal of Medical Research and Pharmaceutical Sciences (Vol.2, No. 2)* 2015-02-28

https://www.researchgate.net/publication/271330558

*"**Conclusions**: Patients who are mentally stable before montelukast treatments may have some disturbances in mood and behaviors during treatments so attention should be paid for such reactions. Clinicians should suspect if the patient has unexpected reactions after montelukast. And further studies are needed to evaluate these datas."*

The Effects of Montelukast on Depression and Anxiety behaviors in rats Ersoz Gonca Bulent Ecevit University, Faculty of Arts and Sciences, Zonguldak-Turkey Bulletin of Clinical Psychopharmacology 2015;25(Suppl. 1):S161

https://www.researchgate.net/publication/317800869_The_effect_of_montelukast_on_depression_behaviour_in_rat_forced_swimming_test *(full article could not be accessed)*

"*Conclusion: These results reveal that Montelukast treatment induced depressive behaviors in healthy rats, but it did not cause anxiety behaviors. These findings support the warning with regard to the correlation between suicide, psychiatric symptoms and the use of Montelukast. However, further studies are needed to test the effects of Montelukast on depression and anxiety in rats with experimentally induced asthma, and to elucidate the mechanism of the effects of Montelukast."*

Montelukast-Induced Adverse Drug Reactions: A Review of Case Reports in the Literature –Gioacchino Calapai b Marco Casciaro a Marco Miroddi b Fabrizio Calapai b Michele Navarra c Sebastiano Gangemi a, d a School and Division of Allergology and Clinical Immunology, at b Department of Clinical and Experimental Medicine, and c Department of Drug Sciences and Health Products, University of Messina, and d Institute of Clinical Physiology (IFC), Consiglio Nazionale delle Ricerche (CNR), Messina Unit, Messina, Italy September 2014

http://www.karger.com/Article/FullText/366164

*"**Summary**: The present review analyzed the previous published case reports regarding montelukast-induced adverse drug reactions (ADRs). They included agitation, anxiety, depression, sleep disturbance, hallucinations, suicidal thinking **and** suicidality, tremor, dizziness, drowsiness, neuropathies and seizures. The immune system can be involved, in particular, cases of Churg-Strauss syndrome have been published. Furthermore, it can induce hypersensitivity reactions, including anaphylaxis and eosinophilic infiltration. In addition, hepatobiliary, pancreatic and uropoietic disorders have been observed. Some of these cases are characterized by severe prognosis (i.e. neurological deficit and fatal hepatotoxicity). **Key Message**: The use of montelukast can be burdened by several ADRs, of which physicians should be aware in their clinical practice. A better understanding of the mechanisms causing ADRs after using montelukast could help researchers and clinicians in defining a risk-reduction strategy aimed to lessen montelukast toxicity. More accurate epidemiological studies, in order to discover risk factors favouring montelukast-associated ADRs, are demanded."*

European Respiratory Journal -- Side Effects of the Leukotriene Receptor Antagonists in Asthmatic Children Semiha Bahceci Erdem, Hikmet Tekin Nacaroglu, Canan Sule Unsal Karkiner, Ilker Gunay, Demet Can, European Respiratory Journal 2014 44 September 2014

http://erj.ersjournals.com/content/44/Suppl_58/P916.short

*"**Conclusion**: The side effects of LTRAs were common in children. Therefore, patients must be informed at the beginning of the treatment and they must be evaluated at certain intervals."*

Alice in Wonderland syndrome: A rare neurological manifestation with microscopy in a 6-year-old child, Anne Weissenstein, Elisabeth Luchter, and M.A. Stefan Bittmann, J Pediatr Neurosci. Sep-Dec 2014

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4302569/

Cases of AIWS with the use of montelukast,[10] a mast cell stabilizer, are described.

Case Report - Sleeptalking! Sleepwalking! Side Effects of Montelukast 5 August 2013. *Samer Alkhuja, Natalya Gazizov, and Mary Ellen Alexander, Case Reports in Pulmonology, vol. 2013, Article ID 813786, 3 pages, 2013. https://doi.org/10.1155/2013/813786.*

https://www.hindawi.com/journals/cripu/2013/813786/?fbclid=IwAR3AeZXkxaJW68JRfKVpVUVdwEYadoXAf3spkmN9PR3L0Lfb2fdPsMjqzjU

"Although montelukast reduces AHI in patients with OSA by treating upper airway ARS [6], its use may result in the development of parasomnias. In such an event, the discontinuation of montelukast is usually sufficient to relieve this adverse effect."

STOP - Suicidality Treatment Occurring in Pediatrics - *Report of drugs associated with suicidality.* Ms Noha Iessa, Dr Macey L Murray, Professor Ian Wong. 14/05/2012

https://www.kcl.ac.uk/ioppn/depts/cap/research/cipprt/projects/stop/d02.1.pdf

"There were a total of 40 drug-SRAE combinations in 2-11 year olds. …..Atomoxetine (n=119), montelukast (n=113) and methylphenidate (n=60) were also the three medications with highest number of reports for depression as well as for suicidal ideation in this age group."

See Page 13 – Table of Psychiatric adverse events co-reported with suicide-related adverse events

Adverse Drug Events in Children under Age 18 Institute for Safe Medication Practices Special Report on Children - QuarterWatch **-** January 2014 https://www.ismp.org/sites/default/files/attachments/2018-01/2013Q1-Kids-Special.pdf

"Suspect Drugs Psychiatric disorders were reported for 25% or more of all adverse events for 10 of the 15 drugs on the QuarterWatch ranking of the most frequent suspects. The total included two drugs without intended psychotropic effects, montelukast (SINGULAIR for asthma and allergies) and isotretinoin (CLARAVIS for acne)."

"Psychiatric adverse drug events, notably suicidal behaviors, represent the major adverse effects reported in children under age 18. Dechallenge—or careful, tapered discontinuation—is often a viable strategy for testing whether a drug is responsible for changes in behavior or mood."

Effect of Concomitant use of Montelukast and Efavirenz on Neuropsychiatric Adverse Events. Ibarra-Barrueta O[1], Palacios-Zabalza I, Mora-Atorrasagasti O, Mayo-Suarez J. Ann Pharmacother. 2014 Jan;48(1):145-8. doi: 10.1177/1060028013510396. Epub 2013 Nov 5

https://www.ncbi.nlm.nih.gov/m/pubmed/24259633/?fbclid=IwAR0GWQSd2GWcDJzHU92SmaC9z1nhOg2SHbkn-EfrfcKcupaySrnw85wOHEI

"In November 2011, montelukast was started for asthma and shortly thereafter neuropsychiatric symptoms appeared, consisting of disturbed sleep, vivid dreams, irritability, confusion, and concentration difficulties. In January 2012, 2 months after the introduction of montelukast, she continued to report unbearable symptoms without any improvement; so, montelukast was withdrawn and the psychiatric symptoms completely disappeared."

Psychiatric disorders associated with montelukast: data from the National Pharmacovigilance Database]. [Article in French] Marchand MS[1], Jonville-Béra AP, Autret-Leca E; Association française des centres régionaux de pharmacovigilance. Arch Pediatr. 2013 Mar;20(3):269-73. doi: 10.1016/j.arcped.2012.12.006. Epub 2013 Feb 1.

https://www.ncbi.nlm.nih.gov/pubmed/23375423

"Abstract Montelukast (Singulair(®)) has been the subject of post-marketing warnings about psychiatric events occurring that had not been identified during clinical trials. The objective of this study was to take stock of the adverse events (AEs) related to montelukast reported in France. Cases of psychiatric disorders reported to regional pharmacovigilance centers (CRPV) and the literature data were analyzed. The 56psychiatric AEs account for 20% of all AEs reported in the montelukast CRPV: essentially sleep disorders, behavioral disorders and depression. This risk is also found in pharmacovigilance databases in other countries, especially in the North American database, which recorded a significant number of cases of "suicidality", including suicidal ideation, suicide attempts, and suicides. Analysis of clinical efficacy studies have failed to confirm these AEs. The potential severity of these events prompts physicians to seek the existence of psychiatric disorders before prescribing the drug and to carefully monitor the occurrence of AEs during treatment."

A Case of Alice-In-Wonderland Syndrome Probably Associated with the use of Montelukast. Bernal Vañó E, López Andrés N., An Pediatr (Barc). February 2013

https://www.ncbi.nlm.nih.gov/pubmed/22857942
http://www.analesdepediatria.org/es/un-caso-sindrome-alicia-el/articulo/S1695403312003165/ [Article in Spanish]

Hallucination Development with Montelukast in a Child with Asthma: Case Presentation. Kocyigit, Aysen & Gulcan Oksuz, Banu & Yarar, Fulya & Uzun, Funda & Igde, Mahir & Islek, Ismail. Iranian Journal of Allergy, Asthma, and Immunology. (2013). 12. 397-399.

https://www.researchgate.net/publication/256332973_Hallucination_Development_with_Montelukast_in_a_Child_with_Asthma_Case_Presentation

"Leukotriene receptor antagonists(montelukast) have been used for many years in the treatment of asthma both acute and chronic stages. They are accepted commonly as safe but mostly possible side effects are ignored. However, montelukast also could lead to important adverse reactions like hallucinations. In literature only 2 reports have been found about hallucinations with it. One is a study which reports 3 patients from 48 children and the other is a 29 year-old case report. In our case, psychiatric adverse reactions of montelukast,especially hallucinations are reported similarly. We are presenting a child who had visual

hallucinations after starting to use montekulast and after stopping the medicine these complaints disappeared in 48 hours. Although it is a safe drug, it should not be forgotten that it has psychiatric side effects which may be missed easily especially in children."

Nightmares Induced by Montelukast in Children and Adults
Gloria Cereza, Núria Garcia Doladé, Joan-Ramon Laporte, European Respiratory Journal 2012 40: 1574-575; DOI: 10.1183/09031936.00092812 (2012)

http://erj.ersjournals.com/content/40/6/1574.full

"Factors predisposing to this adverse effect and its mechanism remain to be elucidated. Meanwhile, it is important to bear in mind that montelukast may be a cause of nightmares, particularly in children. Usually nightmares disappear after withdrawal of the drug. Unexplained nightmares can lead to unjustified psychiatric consultation and possibly to additional treatments, which can add more morbidity. Doctors, patients and their families should be fully informed about this risk."

Delayed Onset of Neuropsychiatric Effects Associated with Montelukast. Byrne F[1], Oluwole B[2], Whyte V[3], Fahy S[4], McGuinness D[5]., Ir J Psychol Med. 2012 Jan;29(2):125-127. doi: 10.1017/S0790966700017432.

https://www.ncbi.nlm.nih.gov/pubmed/30199961

"Montelukast (a leukotriene receptor antagonist) is a commonly prescribed medication used in the management of asthma in both children and adults. It has been associated with a possible increased risk of various neuropsychiatric events in post-marketing analyses of clinical trial data and surveillance studies. When establishing a link between a medication and side effects, it is usual to establish and enquire whether there is a chronological relationship between the commencement of the medication and the onset of the symptoms. We report a case where a number of unusual neuropsychiatric events were reported several years after commencement of montelukast in a young boy who may have a genetic predisposition and a likely psychological trigger. There was complete resolution of these symptoms upon the withdrawal of montelukast."

Psychiatric adverse drug reactions reported during a 10-year period in the Swedish pediatric population. Bygdell M1, Brunlöf G, Wallerstedt SM, Kindblom JM. Pharmacoepidemiol Drug Saf. 2012 Jan;21(1):79-86. doi: 10.1002/pds.2265. Epub 2011 Nov 10.

https://www.ncbi.nlm.nih.gov/pubmed/22076661 *(Full text available in Files section)*

"After exclusion of vaccines, the three most frequently suspected drugs were montelukast, centrally working sympathomimetic drugs, and inhaled glucocorticoids. Serious adverse reactions were reported more frequently for drugs used off-label than for drugs used according to the Swedish Physician's Desk Reference. Aggressiveness was reported more frequently for boys than for girls as were suicidal conditions."

Association Between Leukotriene-Modifying Agents and Suicide: What is the Evidence? Schumock GT[1], Lee TA, Joo MJ, Valuck RJ, Stayner LT, Gibbons RD. Drug Saf. 2011 Jul 1;34(7):533-44. doi: 10.2165/11587260-000000000-00000.

https://www.ncbi.nlm.nih.gov/pubmed/21663330

"From 1998 to 2009 there were 838 suicide-related adverse events associated with leukotrienes reported to the FDA, of which all but five involved montelukast. Nearly all cases were reported in 2008 and 2009 (96.1%) after the FDA warnings. LTMAs are approved for use in asthma and allergic rhinitis, and are effective drugs. Both of these diseases are also associated with suicide, making confirmation of the association more difficult. Given the lack of good evidence, we recommend that a large observational cohort or case-control study be conducted to quantify the association between LTMAs and suicide. Until then, when prescribing LTMAs, clinicians should consider the potential for suicide and monitor patients who may be at elevated risk carefully for suicidal ideation or psychiatric symptoms associated with suicidal behaviour."

QuarterWatch: 2008 Quarter 2 - Institute for Safe Medication Practices Special Report on Children - January 2009

https://www.ismp.org/sites/default/files/attachments/2018-01/2008Q2.pdf

"The discovery of hundreds of possible cases of serious psychiatric side effects of montelukast 10 years after its original approval—combined with previous reporting on varenicline (Chantix) —suggest that current clinical testing standards may be inadequate to detect psychiatric side effects prior to approval. Furthermore, in both

cases, modest public notices issued by the FDA triggered an outpouring of adverse event reports, once patients and doctors started to make the connection between the symptoms and the drug. This response suggests the extent to which patient injury associated with prescription drug therapy is being routinely underreported."

Montelukast and Psychiatric Disorders in Children Pharmacoepidemiol Drug Saf. Wallerstedt SM[1], Brunlöf G, Sundström A, Eriksson AL. 2009 Sep;18(9):858-64. doi: 10.1002/pds.1794.

https://www.ncbi.nlm.nih.gov/pubmed/19551697

"Conclusions*: Psychiatric ADRs can occur during montelukast treatment in children, indicating that attention to this is essential. Further studies are needed to establish the magnitude of the problem."*
"The fact that the patients (except for one) did not suffer from depressive symptoms before they started montelukast, the short latency, and recovery after withdrawal of the drug all strengthen our hypothesis that depressive symptoms are an ADR related to the use of montelukast. According to the Marketing Authorisation Holder of montelukast, depression will be added to the product information."

Montelukast and Worsening of Hallucinations in Paranoid Schizophrenia. Anandan, N & Ibitoye, Francis. (2008). Psychiatric Bulletin. 32. 276-276. 10.1192/pb.32.7.276.

https://www.cambridge.org/core/journals/psychiatric-bulletin/article/montelukast-and-worsening-of-hallucinations-in-paranoid-schizophrenia/34749583F786347172AA4801DACDF8E3

"We thought it possible that montelukast was aggravating the somatic and visual hallucinations and the medication was stopped. After 2 days the new symptoms subsided completely. Though some of the previously present psychotic symptoms were still there, the patient was less agitated than when on montelukast."

Montelukast and Depressive Symptoms (2007)

The Netherlands Pharmacovigilance Centre Lareb identifies risks associated with the use of medicines in daily practice and is the Knowledge Centre for adverse drugs reactions (ADRs).

https://databankws.lareb.nl/Downloads/kwb_2006_4_montel.pdf

"The fact that the patients (except for one) did not suffer from depressive symptoms before they started montelukast, the short latency, and recovery after withdrawal of the drug all strengthen our hypothesis that depressive symptoms are

an ADR related to the use of montelukast. According to the Marketing Authorisation Holder of montelukast, depression will be added to the product information."

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OTHER REPORTED ADVERSE EVENTS

Fetal Exposure to Montelukast and Congenital Anomalies: A Population Based Study in Denmark, Clara Cavero-Carbonell, Anne Vinkel-Hansen, Mª José Rabanque-Hernández, Carmen Martos, Ester Garne Birth Defects Research, The Teratology Society First published: 01 March 2017

http://onlinelibrary.wiley.com/doi/10.1002/bdra.23621/full

"Risk of preterm birth, maternal preeclampsia and gestational diabetes was increased for pregnancies exposed to montelukast. No significant differences were found for the risk of major congenital anomalies (CA)."

"Pregnant women with prescriptions for montelukast had a higher risk of preterm birth and maternal complications. These risks are known to be associated with maternal asthma, no increased risk of CA was found. Further analysis including more exposed pregnancies will be needed to determine the risk of specific CA. "

Montelukast Sodium Risk of Thrombocytopenia Japan.

https://www.who.int/medicines/publications/Pharm_Newsletter2_2015.pdf?fbclid=IwAR1Z-tABf9TDuueEkDNLcktbhi0fu3ZGZq7GdMRvRus2LV5MGGRF_PLFkKs

"The MHLW/PMDA informed that cases of thrombocytopenia have been reported in patients treated with montelukast sodium (Singulair® and Kipres®) in Japan. Montelukast sodium is indicated for bronchial asthma and allergic rhinitis. Based on expert advice and available evidence, the MHLW/PMDA have recommended the following texts should be added in the "Clinically significant adverse reactions" subsection of the "Adverse reactions" section for montelukast. Thrombocytopenia: Thrombocytopenia may occur (initial signs and symptoms are: bleeding tendencies including purpura, epistaxis, and gingival bleeding). If these symptoms are observed, administration of this drug should be discontinued and appropriate measures should be taken.

Reference: Revision of Precautions, 17 February 2015, MHLW/PMDA (www.pmda.go.jp/english/)"

Hepatotoxicity Caused by Montelukast in A Paediatric Patient.
Lebensztejn DM[1], Bobrus-Chociej A[1], Kłusek M[1], Uscinowicz M[1], Lotowska J[2], Sobaniec-Lotowska M[2], Kaczmarski M[1]. Lebensztejn DM, et al. Prz Gastroenterol. 2014.

https://www.ncbi.nlm.nih.gov/m/pubmed/25061494

"Recently, hepatotoxicity has been reported with this drug in adult patients, but only one letter to the editor has reported a case of probable montelukast-induced hepatotoxicity in a child. We present a case of a 3.5-year-old boy, receiving treatment with montelukast, who developed hepatocellular injury. The exclusion of other causes of increased activity of aminotransferases (viral, metabolic, autoimmune), improvement after dechallenge, the morphological findings and previous reports of comparable cases support the diagnosis of montelukast-induced liver injury in this boy. Physicians should strictly analyse indications for this drug and be aware of potential drug-induced liver disease caused by this agent. Therefore, the periodical assessment of aminotransferases should be recommended during treatment with this leukotriene modifier."

A Case of Montelukast-Induced Hepatotoxicity. Sass DA, Chopra KB, Wu T. Am J Gastroenterol. 2003 Mar;98(3):704-5. (full text not available but please see info from NIH Liver Tox belew)

Case 1. Cholestatic hepatitis due to montelukast.
[Modified from: Sass DA, Chopra KB, Wu T. A case of montelukast-induced hepatotoxicity. Am J Gastroenterol 2003; 98: 704-5. PubMed Citation]

https://livertox.nih.gov/Montelukast.htm#other_refs

A Rare Adverse Effect of Montelukast Treatment: Ecchymosis.
Aypak C[1], Türedi Ö, Solmaz N, Yıkılkan H, Görpelioğlu S. Respir Care. 2013 Sep;58(9):e104-6. doi: 10.4187/respcare.02298. Epub 2013 Jan 15.

https://www.ncbi.nlm.nih.gov/pubmed/23322887

http://m.rc.rcjournal.com/content/respcare/58/9/e104.full.pdf?fbclid=IwAR3b_uaRKlORTl19vs9bFTXpo2GLwqKNoh9yy-KTYTfPfXYi2D5FE5VWw3o

"Montelukast is a leukotriene receptor antagonist that is effective in the treatment of allergic rhinitis and asthma. We report a rare case of a 31-year-old woman with a history of allergic rhinitis and moderate persistent asthma, who experienced severe bruising on her lower extremities after starting montelukast treatment. Clinicians should be aware of the possibility of unusual bruising during montelukast therapy, and in those patients montelukast should be discontinued."

Montelukast sodium-induced hematuria: a case report and literature review of 19 cases in mainland China. Xie JX, Wei JF, Meng L. Int J Clin Pharmacol Ther. 2013 Dec;51(12):958-62. doi: 10.5414/CP201952.

https://www.ncbi.nlm.nih.gov/pubmed/24131737?fbclid=IwAR1SgPFiCNlDQfX3gpPtLUAeX9LxhKtwQjT6FQTg-i2IPE8SjRzxtUwmRK4

"We report a rare case of montelukast sodium-induced hematuria in a 58-year-old female patient with allergic rhinitis. Renal function returned to normal after drug withdrawal. We reviewed 19 case reports of adverse reactions associated with montelukast sodium in mainland China and found that (1) 37% of patients were pediatric patients, (2) psychiatric disorders, rashes and uropoietic organs symptom were common, (3) uropoietic organ symptoms reported in mainland China were very rare abroad. The clinician in China should be vigilant about the adverse reaction of montelukast sodium and further studies are needed to explore the pathogenesis of montelukast-induced uropoietic organ symptoms."

**Please note that hematuria is the presence of blood in urine.*

Important elements for the diagnosis of drug-induced liver injury. Agarwal VK, McHutchison JG, Hoofnagle JH, Drug-Induced Liver Injury Network. *Clin Gastroenterol Hepatol*. 2010;8(5):463-70.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3901223/?fbclid=IwAR1mhG9CNun2wjzW2lZNs9qvdaoCWrgS3nL5SgsdL6sT0iPkucp84xmTAb4

Churg-Strauss Syndrome Associated with Montelukast Therapy. Kaliterna DM[1], Perković D, Radić M. J Asthma. 2009 Aug;46(6):604-5. doi: 10.1080/02770900903006273.

"Churg-Strauss syndrome is a rare form of eosinophilic vasculitis associated with asthma. Several cases of eosinophilic conditions including Churg-Strauss syndrome have recently been reported in asthmatic patients being treated with antileukotriene receptor antagonists. However, whether these drugs have a direct pathogenic role remains controversial. We describe two patients who developed Churg-Strauss syndrome after starting treatment with montelukast."

Fatal Liver Failure Following Food Supplements During Chronic Treatment with Montelukast. Actis GC[1], Bugianesi E, Ottobrelli A, Rizzetto M. Dig Liver Dis. 2007 Oct;39(10):953-5. Epub 2006 Dec 6. Division of Gastroenterology, Ospedale San Giovanni Battista, Torino 10126, Italy. actis_g@libero.it

https://www.ncbi.nlm.nih.gov/pubmed/17157086

"We speculate on a causal relationship between the assumption of the additives and the fatal hepatitis and envisage a synergy between the additives and montelukast, which per se has well been studied as a hepatotoxic drug.

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FDA - SAFETY OF SINGULAIR

IMPORTANT: FDA ISSUES REMINDER LETTER TO HEALTH PROFESSIONALS ABOUT THE RISK OF NEUROPSYCHIATRIC EVENTS WITH LEUKOTRIENE INHIBITORS, MONTELUKAST [SINGULAIR], ZAFIRLUKAST [ACCOLATE], ZILEUTON [ZYFLO, ZYFLO CR] (Copy is shared with *Parents United for Pharmaceutical Safety and Accountability)*

To obtain a copy of the email please contact http://www.parentsforsafety.org/

INTERVIEW - Montelukast's Underrecognized Adverse Drug Events. Medscape article. Mar 02, 2015

http://www.medscape.com/viewarticle/840302?src=smo_tw_aimm%3Fsrc%3Dsttwit#vp_1

"Continued concerns about suicidality and neuropsychiatric events with montelukast were again raised at a recent FDA Pediatric Advisory Committee (PAC) meeting in September 2014. Medscape spoke with Sally Seymour, MD, and Erika Torjusen, MD, MHS, both at the Center for Drug Evaluation and Research in the Division of Pulmonary, Allergy, and Rheumatology at the FDA, about the advisory committee meeting, concerns with these agents, and the implications for HCPs."

TRANSCRIPT – FDA PEDIATRIC ADVISORY COMMITTEE MEETING Washington, D.C. Tuesday, September 23, 2014
https://www.fda.gov/downloads/ScienceResearch/SpecialTopics/PediatricTherapeuticsResearch/UCM434618.pdf

Pediatric Postmarketing Pharmacovigilance and Drug Utilization Review – September 2, 2014
https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/PediatricAdvisoryCommittee/UCM519868.pdf

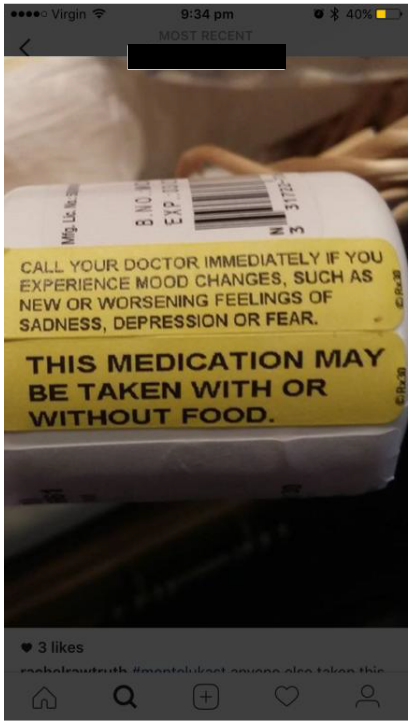
TRANSCRIPT – FDA PEDIATRIC ADVISORY COMMITTEE MEETING, Washington DC, May 2, 2014 (Over the Counter request)
https://wayback.archive-it.org/7993/20170404152755/https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/NonprescriptionDrugsAdvisoryCommittee/UCM402352.pdf

Food and Drug Administration Center for Drug Evaluation and Research Summary Minutes of the Nonprescription Drugs Advisory Committee (NDAC) Meeting May 2, 2014
https://wayback.archive-it.org/7993/20170404152757/https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/NonprescriptionDrugsAdvisoryCommittee/UCM404353.pdf

A list of medications that cause severe neuropsychiatric side effects were listed in the TGA's recent medical alert (June 2018). They are as follows:

- antidepressants, particularly selective serotonin reuptake inhibitors (SSRIs)
- certain smoking cessation medications, including varenicline and buproprion (marketed as Champix and Zyban)
- certain antiepileptics, including sodium valproate, carbamazepine, levetiracetam, phenytoin, lamotrigine, topiramate, pregabalin and gabapentin
- isotretinoin (marketed as Roaccutane)
- atomoxetine (marketed as Strattera and generic brands)
- montelukast (marketed as Singulair and generic brands)

I believe that all of the medications above should have a mandated CAL in all states of Australia. The CAL should read – '*See your doctor immediately if you experience mood changes, such as new or worsening feelings of sadness, depression or fear'*. This is the wording used for the warning on [redacted] in the USA.



I am asking the royal commission to recommend in its report that the Victorian Health Minister ensures the CAL is placed on the outside of all medications that may cause severe neuropsychiatric side effects, including [redacted].