Risk of Neuropsychiatric Adverse Events among Montelukast Users

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Disclosures

- No external funding to disclose

- The views expressed in this presentation are those of the presenter and do not necessarily reflect those of the FDA

Background

- November 2017 - FDA received correspondence from the Parents United for Pharmaceutical Safety and Accountability and The Montelukast (Singulair) Side Effects Support and Discussion Group
  - Incidence of neuropsychiatric adverse events (NAE) is more common than reported, particularly in children
  - A self-sponsored survey of a Facebook Group
  - A survey study by Bénard et al. (2017) which showed a 9 – 12 fold risk of NAEs with Montelukast vs. Inhaled Corticosteroids
- Two well conducted observational studies showed no association
  - Schmock et al (2012): Adjusted OR: 0.74 (0.46 – 1.20)
  - Ali et al (2015): Adjusted OR: 1.01 (0.88 – 1.44)

Objectives

- Compared to Inhaled Corticosteroid (ICS) use, is there an increased risk of depressive disorders, self-harm, and suicides associated with montelukast use?

- Is the risk of Neuropsychiatric Adverse Events (NAEs) with Montelukast (MON) compared to ICS modified by the 2008 montelukast labeling changes, age, sex, and psychiatric history?

Methods

- **Data Source**: Sentinel Distributed Database (SDD)
  - January 1, 2000 to September 30, 2015
  - 16 data partner (DP) sites, primarily large national insurers and integrated delivery care networks
  - Medical and pharmacy data, including inpatient and outpatient diagnoses and procedures, and retail and mail order prescription records.

- **Exposure:** MON or ICS with no exposure to ICS, MON, LABA, LTRAs 183 days prior

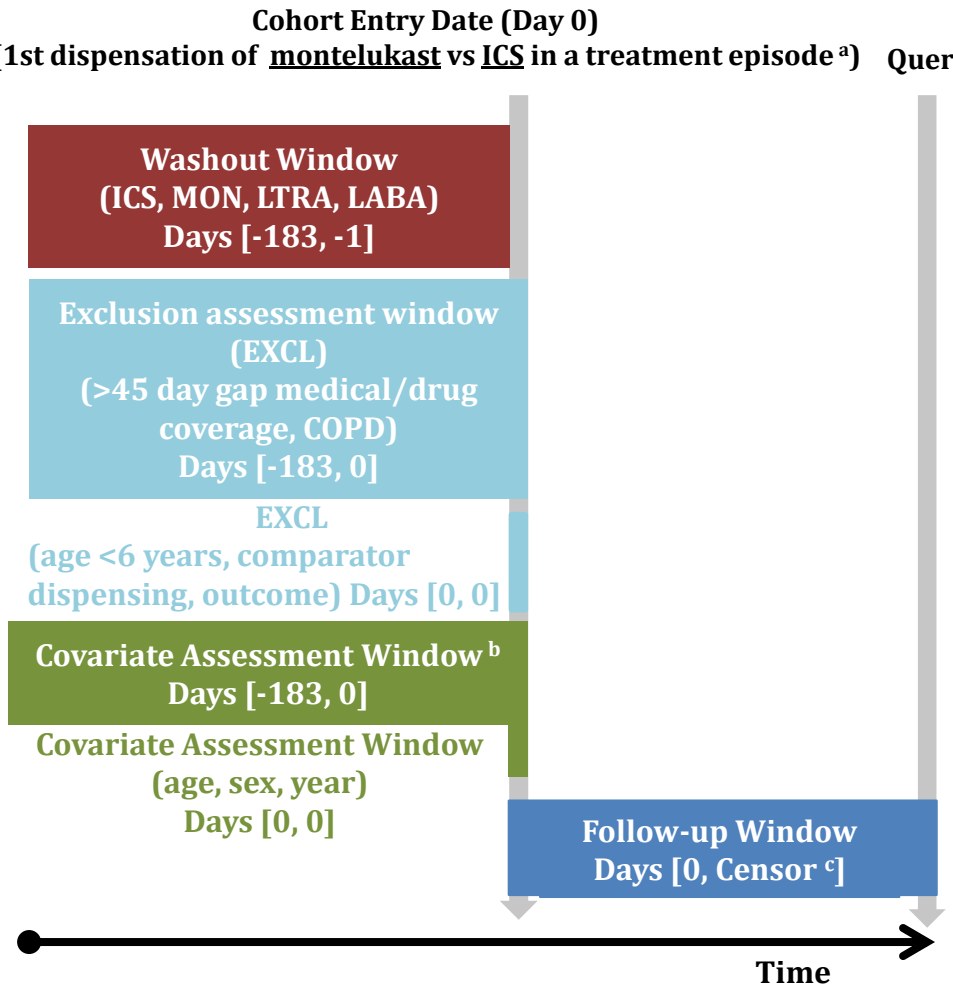
- **Outcomes and Validity:**
  - inpatient depressive disorder in primary position on an inpatient claim – more severe cases
  - outpatient depressive disorder requiring psychotherapy or antidepressant use within 30 days in any position - not validated
  - hospitalization due to self-harm - Patrick et. al algorithm[1] 73% PPV
  - hospitalization due to self-harm with E-codes

[1]Patrick AR, Miller M, Barber CW, Wang PS, Canning CF, Schneeweiss S. Identification of hospitalizations for intentional self-harm when E-codes are incompletely recorded. *Pharmacoepidemiol Drug Saf.* 2010;19(12):1263-1275.

Methods

[a] Treatment episode
Date of dispensing and days supply with a stockpiling algorithm if a new dispensation occurs before the end of days supply. Gaps <15 days between end of days supply and next dispensation were bridged. 15 days was added to the last dispensation's days supply in an exposure episode. 30 day gap & extension for outpatient depression.

[b] Covariates for Adjustment [-183, 0]
- Comorbidity score
- History of psych disorder
- Psychiatric and psychotropic drugs
- Substance abuse
- Allergic rhinitis
- Respiratory disorder (≥ 2 codes)
- Asthma (emergency department)
- Asthma (inpatient primary position)
- Asthma (outpatient)
- Asthma exacerbations/status asthmaticus
- Oral corticosteroids
- Short acting beta-agonists
- Anticholinergic agents
- Phosphodiesterase inhibitors

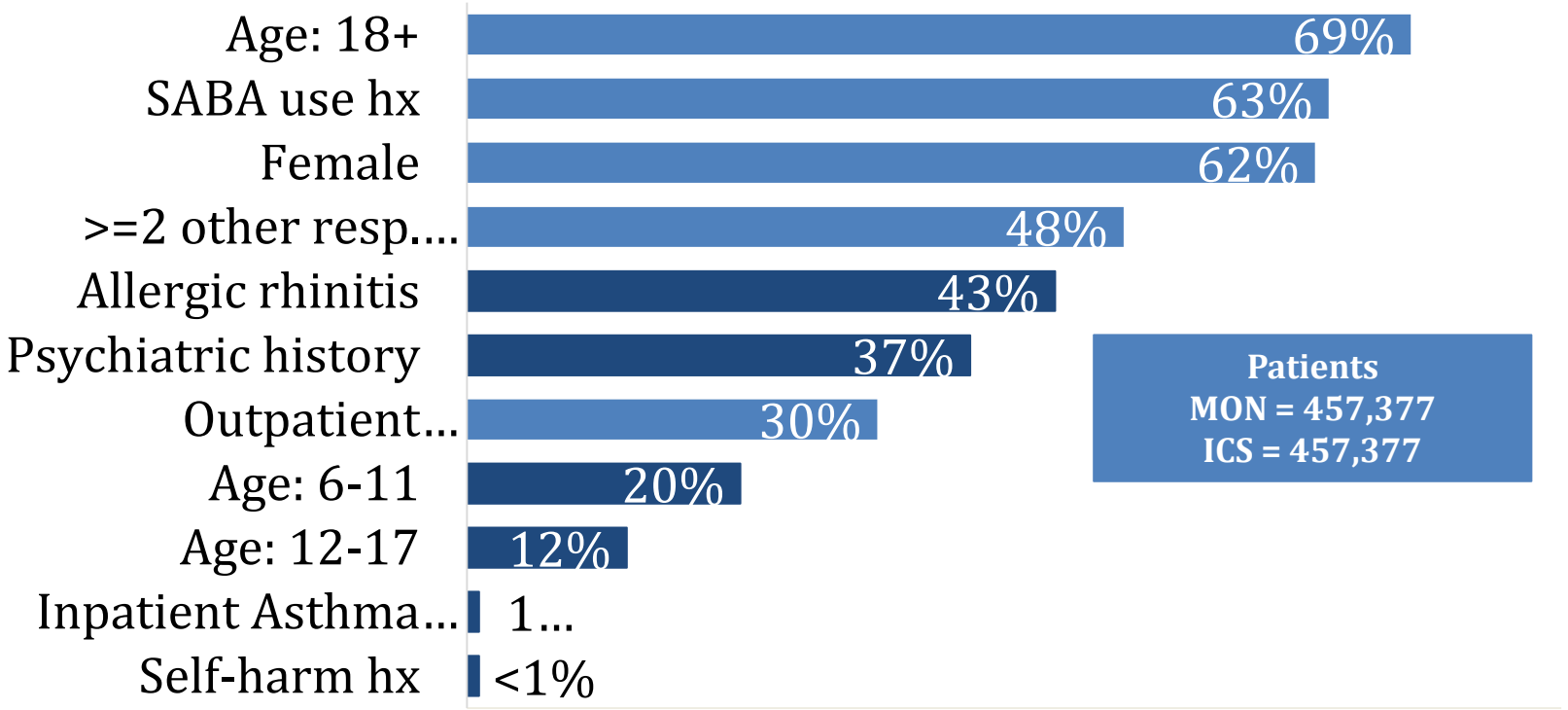


[c] Censoring
- Dispensing of ICS monotherapy, LABAs, ICS combination therapies or LTRAs
- Dispensing of oral corticosteroid
- Asthma related hospitalization in the primary position
- Death
- Data partner end date
- Query end date
- Disenrollment
- Outcome
- End of treatment episode

Statistics

- Standardized mean differences (SMD) for baseline characteristics
- 1:1 Propensity score matching between MON and ICS patients
  - Matching (0.05 calipers w/in each data partner)
- Cox proportional hazards regression to estimate hazard ratios (HRs) and 95% confidence intervals (CIs)
  - Unconditional Modeling: not stratified by matched pairs
  - Subgroup analyses
    - sex (female, male)
    - age category (6-11, 12-17, 18+ years)
    - history of any psychiatric disorder (yes, no)
    - time before and after MON labeling changes (years 2000-2007, 2008-2015)
- Post-hoc Analysis: Due to non-proportionality for hazard after 1 year
  - Evaluated all study outcomes for a maximum follow-up of 1 year

Baseline Characteristics of Matched MON and ICS pts



Values are approximate.

Outpatient Depression is the Most Frequent Outcome

Outcome	%	N
Inpatient depression	1.6	647
Outpatient depression	97.12	37,740
Self-harm	0.57	219
Self-harm with E-codes	0.69	264
Grand Total	100	38,870

94% of NAEs in Patients with Prior Psychiatric Diagnosis

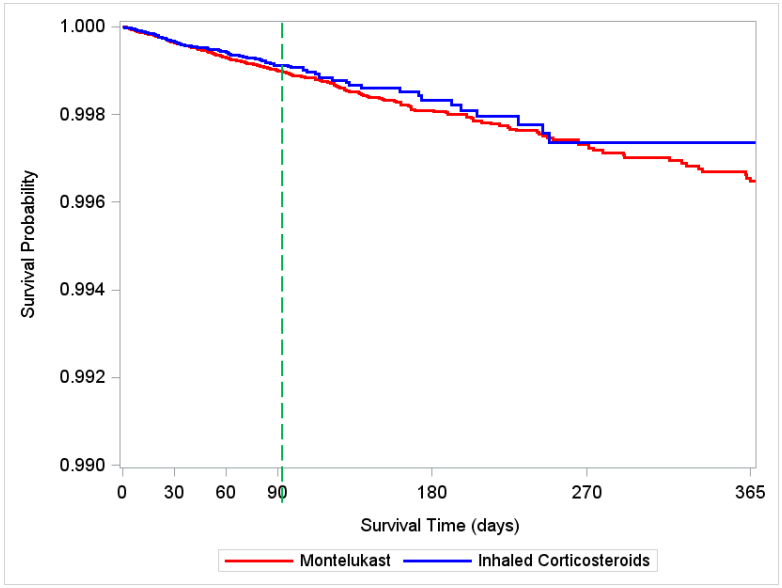
Outcome	%	N	No Psych Hx*	Psych Hx*
Inpatient depression	**1.6**	**647**	58	581
Outpatient depression	**97.12**	**37,740**	**2,178**	**35,182**
Self-harm	**0.57**	**219**	--	--
Self-harm with E-codes	**0.69**	**264**	--	--
Grand Total	**100**	**38,870**	**2292 (6%)**	**36,022 (94%)**

Prior psychiatric diagnosis: at least one psychiatric diagnosis in the baseline period

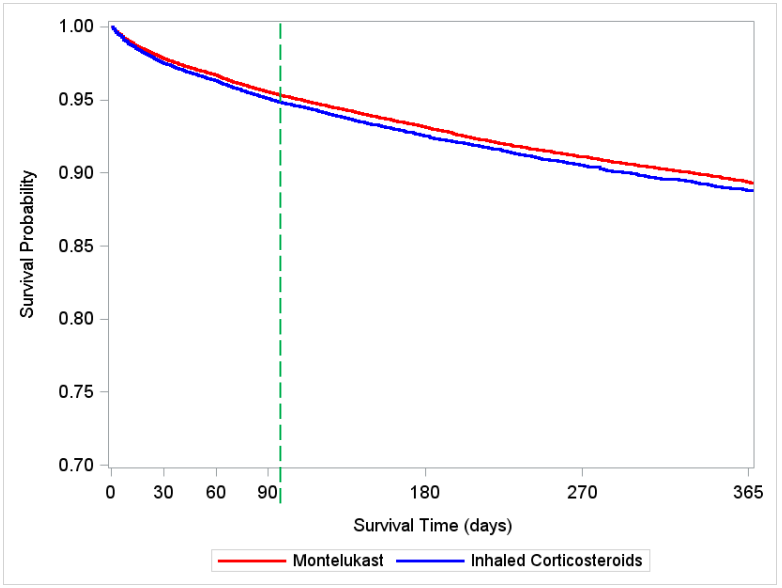
*Data are not presented due to a small cell size or to assure a small cell cannot be recalculated from the cells presented.

One-year Event-free Survival Curves

Inpatient Depression

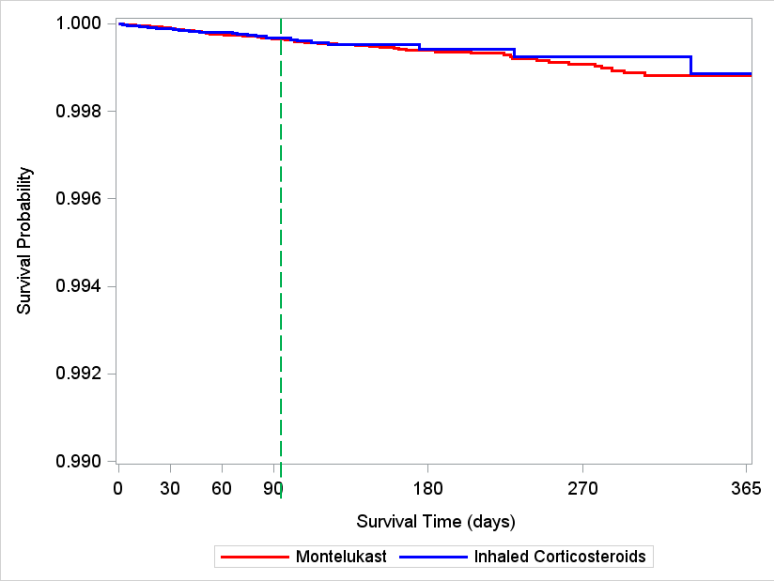


Outpatient Depression

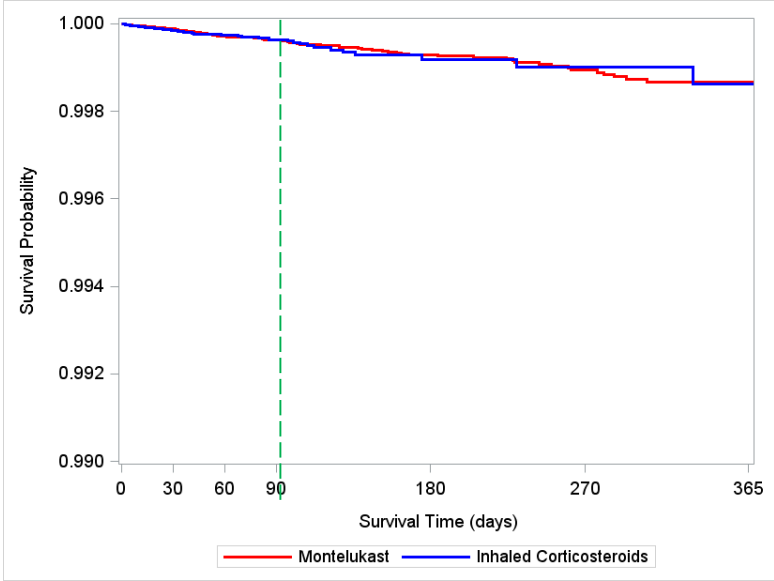


One-year Event-free Survival Curves

Self-Harm



Self-Harm with E-codes



Decreased risk of Outpatient Depression w/ MON vs ICS

Overall HR (95% CI) (Unconditional Matched Cohort)

Outcome	Exposure	1-Year HR (95% CI)	HR (95% CI)
Inpatient Depression	MON	1.06 (0.90, 1.25)	1.06 (0.90, 1.24)
	ICS	1.07 (0.89, 1.28)[a] 1.04 (0.90, 1.20)[b]	1.07 (0.89, 1.28)[a] 1.04 (0.90, 1.20)[b]
Outpatient Depression	MON	**0.91 (0.90, 0.93)**	**0.91 (0.89, 0.93)**
	ICS		
Self- harm	MON	0.96 (0.72, 1.26)	0.92 (0.69, 1.21)
	ICS		
Self-Harm E-codes	MON	0.86 (0.67, 1.11)	0.81 (0.63, 1.05)
	ICS		

P<.001

Sensitivity analyses: [a] 0 day extension period, [b] 30 day extension period for ICS

Age Groups

Subgroup HR (95% CI) (Unconditional Matched Cohort)

Age	Inpatient Depression	Outpatient Depression	Self-harm	Self-harm E codes
Age 6-11	0.62 (0.26, 1.48)	1.02 (0.87, 1.19)	--	--
Age 12 – 17	1.09 (0.73, 1.61)	**0.82 (0.76, 0.89)**	1.04 (0.41, 2.66)	1.23 (0.57, 2.68)
Age 18+	1.08 (0.90, 1.29)	**0.90 (0.88, 0.92)**	0.91 (0.68, 1.22)	0.78 (0.60, 1.03)

P<.001

No significant increase in risk observed for all study outcomes
Trend toward increased risk for inpatient depression among older patients

Age Groups: 1 Year

Subgroup HR (95% CI) (Unconditional Matched Cohort)

Age	Inpatient Depression	Outpatient Depression	Self-harm	Self-harm E codes
Age 6-11	0.60 (0.25, 1.45)	1.02 (0.87, 1.19)	--	--
Age 12 – 17	1.09 (0.73, 1.61)	**0.82 (0.76, 0.89)**	1.04 (0.41, 2.66)	1.23 (0.57, 2.68)
Age 18+	1.08 (0.90, 1.30)	**0.90 (0.88, 0.92)**	0.95 (0.71, 1.28)	0.83 (0.63, 1.09)

P<.001

Outpatient depression values remain the same.

Gender

Subgroup HR (95% CI) (Unconditional Matched Cohort)

	Inpatient Depression	Outpatient Depression	Self-harm	Self-harm E codes
Male	1.15 (0.84, 1.58)	**0.93 (0.89, 0.97)**	1.16 (0.58, 2.36)	1.00 (0.55, 1.80)
Female	1.04 (0.86, 1.26)	**0.90 (0.88, 0.93)**	0.87 (0.65, 1.18)	0.77 (0.59, 1.02)

P<.001

No difference in risk by gender

Gender: 1 Year

Subgroup HR (95% CI) (Unconditional Matched Cohort)

	Inpatient Depression	Outpatient Depression	Self-harm	Self-harm E codes
Male	1.14 (0.83, 1.56)	**0.93 (0.89, 0.97)**	1.32 (0.64, 2.70)	1.17 (0.64, 2.15)
Female	1.05 (0.87, 1.27)	**0.90 (0.88, 0.92)**	0.90 (0.66, 1.22)	0.80 (0.61, 1.07)

P<.001

Labeling Change

Subgroup HR (95% CI) (Unconditional Matched Cohort)

	Inpatient Depression	Outpatient Depression	Self-harm	Self-harm E codes
Pre: 2000 - 2007	0.94 (0.60, 1.48)	**0.90 (0.83, 0.98)**	1.16 (0.49, 2.74)	1.06 (0.53, 2.15)
Post: 2008 - 2015	1.08 (0.91, 1.29)	**0.91 (0.89, 0.93)**	0.90 (0.67, 1.21)	0.78 (0.60, 1.03)

P<.001

Labeling Change: 1 Year

Subgroup HR (95% CI) (Unconditional Matched Cohort)

	Inpatient Depression	Outpatient Depression	Self-harm	Self-harm E codes
Pre: 2000- 2007	0.94 (0.59, 1.48)	**0.90 (0.83, 0.98)**	1.16 (0.49, 2.74)	1.06 (0.52, 2.14)
Post: 2008 - 2015	1.09 (0.91, 1.30)	**0.91 (0.89, 0.93)**	0.95 (0.70, 1.28)	0.84 (0.64, 1.10)

P<.001

Psych History

Subgroup HR (95% CI) (Unconditional Matched Cohort)

	Inpatient Depression	Outpatient Depression	Self-harm	Self-harm E codes
Psych Hx.	1.10 (0.93, 1.31)	**0.89 (0.88, 0.91)**	0.89 (0.66, 1.18)	0.80 (0.61, 1.04)
No psych Hx.	0.63 (0.37, 1.07)	1.07 (0.98, 1.17)	1.34 (0.38, 4.71)	0.84 (0.33, 2.13)

P<.001

- 93% (36,210/38,870) of patients with an NAE outcome had a psychiatric history.
- No significant associations observed although there was a trend toward increased risk for outpatient depression and self-harm outcomes

Psych History: 1 Year

Subgroup HR (95% CI) (Unconditional Matched Cohort)

	Inpatient Depression	Outpatient Depression	Self-harm	Self-harm E codes
Psych Hx.	1.11 (0.93, 1.32)	**0.89 (0.87, 0.91)**	0.93 (0.70, 1.24)	0.86 (0.66, 1.12)
No psych Hx.	0.61 (0.36, 1.05)	1.07 (0.98, 1.18)	1.29 (0.36, 4.62)	0.79 (0.30, 2.06)

P<.001

- 93% (36,210/38,870) of patients with an NAE outcome had a psychiatric history.
- Previous trends observed

Discussion

- Majority of subjects with psychiatric outcomes had a psychiatric history
- No association between montelukast and inpatient depression, self-harm compared to ICS
  - Retrospective analysis of 46 placebo controlled trial showed no difference in risk (OR: 1.12 CI: 0.93-1.36)[1]
  - Nested case-control study[2] designed to examine the association between asthma and NAEs found no association (OR: 1.02, CI: 0.8201.26)
  - Nested case-control study[3] designed to examined the association between LTMAs and attempted suicides (self-harm) showed no association (OR: 0.70, CI: 0.36-1.39)

[1] Philip G, Hustad CM, Malice MP, Noonan G, Ezekowitz A, Reiss TF, et al. Analysis of behavior-related adverse experiences in clinical trials of montelukast. J Allergy Clin Immunol. 2009;124(4):699-706.e8.
[2] Ali MM, O'Brien CE, Cleves MA, Martin BC. Exploring the possible association between montelukast and neuropsychiatric events among children with asthma: a matched nested case-control study. Pharmacoepidemiol Drug Saf. 2015;24(4):435-45.
[3] Schumock GT, Stayner LT, Valuck RJ, Joo MJ, Gibbons RD, Lee TA. Risk of suicide attempt in asthmatic children and young adults prescribed leukotriene-modifying agents: a nested case-control study. J Allergy Clin Immunol. 2012;130(2):368-75.

Discussion

- Decreased risk of treated outpatient depression among montelukast
  - 90% of montelukast exposure occurred after a 2009 label change which instructs prescribers to be alert for neuropsychiatric events and to evaluate risk benefits of continuing montelukast should events occur
  - Patients treated for depression likely channeled to ICS
  - Outcome definition required diagnosis and psychotherapy or treatment, thus may have captured more patients with pre-existing depression

Study Strengths/Limitations

- Study Strengths
  - Large sample size
  - Able to study the effects in populations with and without psych history and before and after labeling changes
  - Control for concomitant use of asthma medications with increased risk of NAEs

- Study Limitations
  - Did not adjust for socioeconomic status (SES): Lower SES associated with worsen asthma severity
    - Our study used other variables to control for asthma severity.
    - No evidence that MON and ICS are prescribed disproportionally to patients of varying SES.
  - Only study outcomes that included diagnoses that resulted in healthcare claims, which are likely to be more severe NAEs
  - No adjustment for multiple comparisons; chance of false positive (Type I error)
    - 1 cohort per analysis
    - Direction and magnitude of estimates for outpatient depression outcome consistent

Conclusion

- No association between montelukast use and hospitalizations for depression or self-harm events.
- Our findings should be interpreted considering the study's limitations.
- Subsequent FDA action was based on the totality of available evidence.

https://www.fda.gov/drugs/drug-safety-and-availability/fda-requires-boxed-warning-about-serious-mental-health-side-effects-asthma-and-allergy-drug

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