Neuropsychiatric Adverse Events and Montelukast: Observational Safety Analyses

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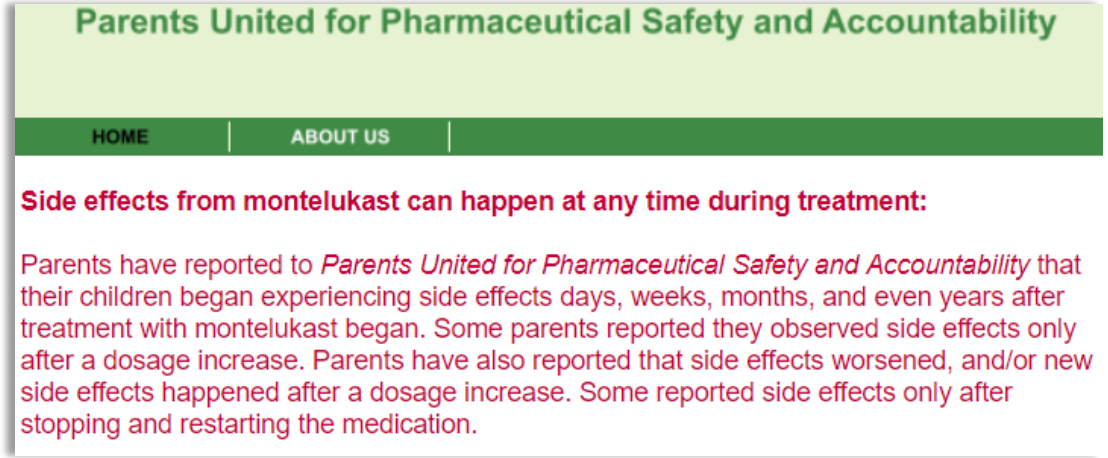
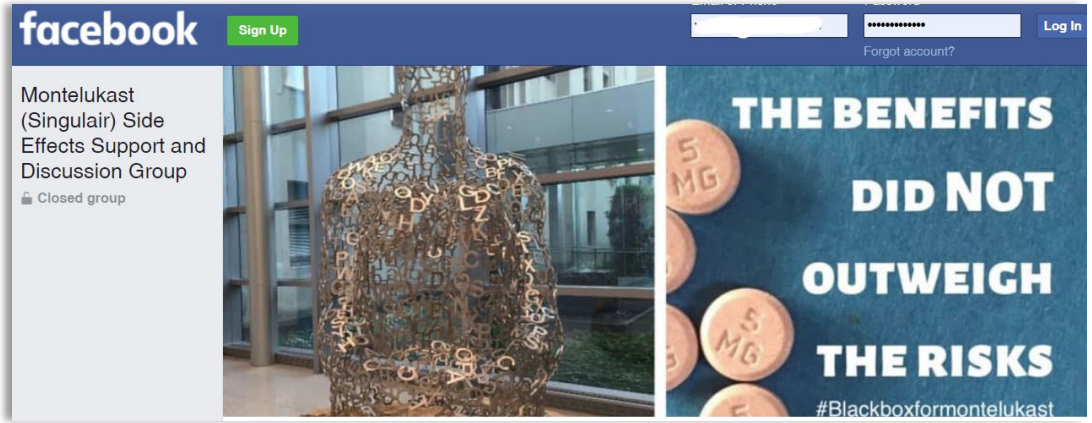
Background

- **November 2017** - FDA received correspondence from patient advocacy groups
  - Incidence of neuropsychiatric adverse events (NAE) is more common than reported, particularly in children
  - A self-sponsored survey of a Facebook Group and a survey study by Bénard et al. (2017)

- **DEPI-II** investigated the association between montelukast (MON) and NAEs
  - Observational literature review
  - Sentinel Distributed Database (SDD) analysis



https://www.parentsforsafety.org/17601/10794.html



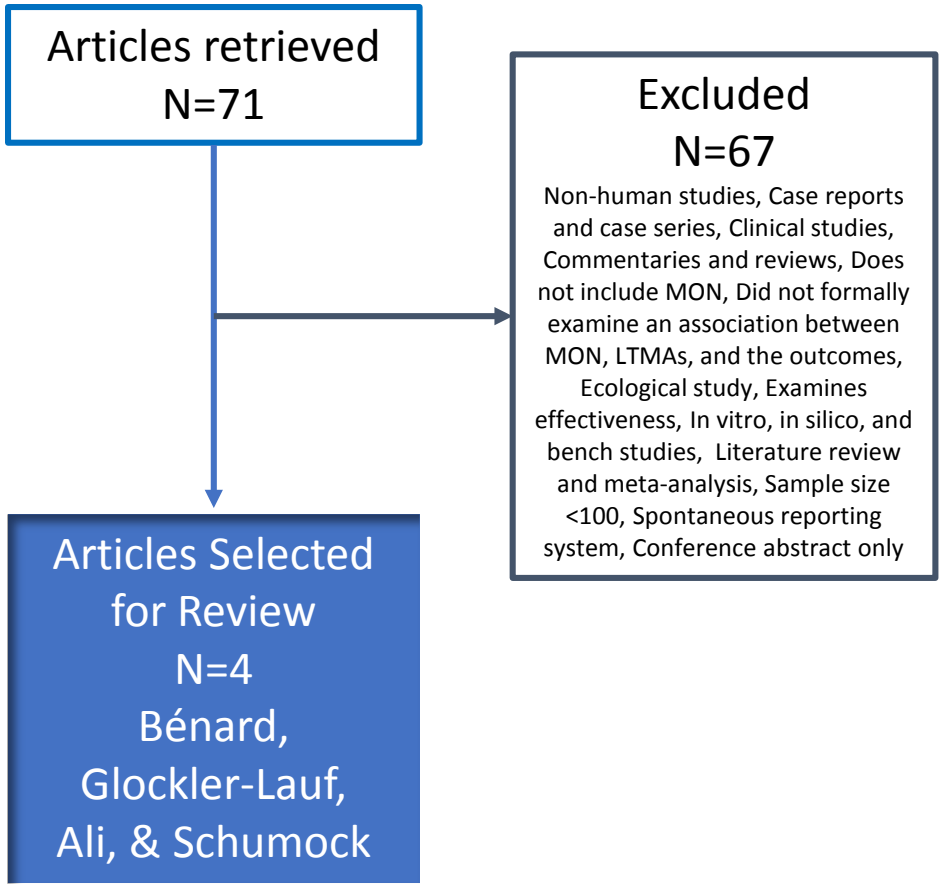
https://www.facebook.com/groups/40378158644/

Observational Literature Review

Four Observational Studies Reviewed

Literature Review Methods

- December 2017, January 2018, July 2019
- National Library of Medicine's Pub Med, Web of Science, EBSCOHost, Google Scholar
  - Asthma
  - Neuropsychia* OR depressi* OR suicid* OR mental OR violen* OR psychiatric or anx* or tremor or behav*
  - Singulair or Montelukast or LTRA or "Leukotriene Receptor Antagonist" or LTMA or "Leukotriene Modifying Agent"
  - Years 2012 – 2019
- Review of references for frequently cited articles



Two Articles Showed No Association

- Schumock et al. (2012) **LTMA and suicide attempt (adjusted odds ratio [adj. OR]: 0.74: CI 0.46-1.20)**
  - Nested case-control study of LifeLink claims data of asthma patients age 5-24 yrs
  - Positive association with montelukast (MON) for pts age 19-24 (adj. OR: 5.15; CI 1.16-22.86)
  - Suicide attempt definition may capture suicidal ideation

- Ali et al. (2019) **MON and neuropsychiatric events, incl. suicide (adj. OR: 1.02; CI 0.82-1.26)**
  - Nested case-control study of LifeLink claims data of asthma patients <18 years old
  - Did not control for multiple comparisons – increased risk for false positives (Type I errors)

Two Articles Reported an Association

- Bénard et al. (2017) **Risk of NAEs for MON vs. ICS (adj. relative risk: 9.00; CI 1.2 – 69.5)**
  - Surveyed parents of 84 children exposed to MON and 84 exposed to ICS
  - Risk probably overestimated since survey was conducted after MON labeling changes and 3 years after drug initiation (recall bias)
  - Results are imprecise due low number of events (n=12) and noted by the wide confidence intervals

- Glockler-Lauf et al. (2019) **MON and NAEs (adj. OR: 1.91; CI 1.15 - 3.18)**
  - Case-control study: Cases may have included psychiatric conditions that existed before asthma medication exposure
  - NAEs ascertained from hospitalization, same day surgery, and emergency room visits regardless of position, and may not always reflect the initial diagnosis

Sentinel Analysis

Sentinel Analysis Objectives

- Compared to ICS, is there an increased risk of depressive disorders, self-harm, and completed suicides associated with MON use?

- Is the risk of NAEs with MON compared to ICS modified by the 2008 Drug Safety Communications (DSC) and MON labeling changes, age, sex, and psychiatric history?

Observational Safety Analysis Methods

- **Data Source**: Sentinel Distributed Database (SDD)
  - January 1, 2000 - September 30, 2015
  - 17 data partner (DP) sites that are large national insurers and integrated delivery care networks
  - Medical and pharmacy data, inpatient and outpatient diagnoses and procedures, and prescription records

- **Exposure:** Incident MON or IC defined as no exposure to ICS, MON, LABA, LTRAs 183 days prior

- **Outcomes:**
  1. Inpatient depressive disorder in primary position
  2. Outpatient depressive disorder in any position, treated with psychotherapy or antidepressant use within 30 days - not validated
  3. Hospitalization due to self-harm - Patrick et. al algorithm
  4. Hospitalization due to self-harm with E-codes
  5. Death by completed suicide – Swain et. al algorithm within six DPs

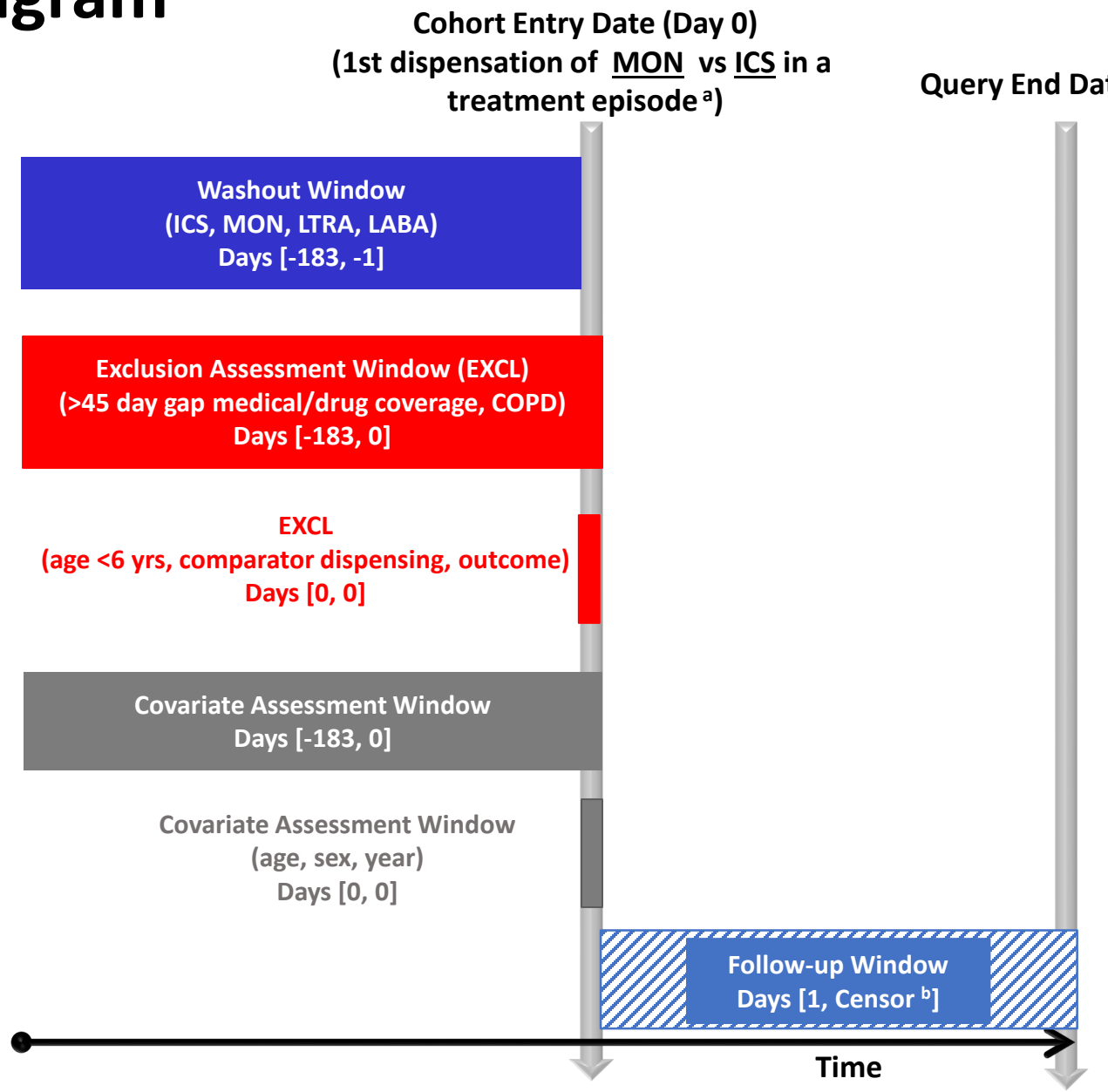
Observational Safety Analysis Methods

Continued

- **Covariates:**
  - Age (continuous)
  - Sex
  - Year
  - Comorbidity score
  - History of psych disorder
  - Psychiatric and psychotropic drugs
  - Self harm (inpatient)
  - Any other psychiatric event
  - 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

Methods Diagram

[a] Treatment episode
- 15-day gap & extension period for inpatient depression and self-harm
- 30-day gap & extension period for outpatient depression



[b] Censoring
- Outcome
- Dispensing of ICS monotherapy, LABAs, ICS combination therapies or LTRAs
- Dispensing of oral corticosteroid
- Asthma related hospitalization: 1° position
- Death
- Data partner end date
- Query end date
- Disenrollment
- End of treatment episode

Statistics

- Standard mean differences for baseline characteristics

- 1:1 Propensity score matching between MON and ICS patients
  - 0.05 calipers within each data partner

- Cox proportional hazards regression to estimate hazard ratios (HRs) and 95% confidence intervals (CIs)
  - Unconditional analysis

Additional Analyses

- Subgroup analyses
  - History of any psychiatric disorder or psychiatric/psychotropic drug use (yes, no)
  - Sex (female, male)
  - Age category (6-11, 12-17, 18+ years)
  - Time before and after MON Drug Safety Communications and labeling changes (years 2000-2007, 2008-2015)

- Sensitivity analyses with inpatient depression
  - Analysis with 0-day episode extension period to examine whether risk attenuated
  - To control for poor adherence to ICS, we compared ICS with a 30-day episode gap and extension period to MON with a 15-day episode gap and extension period

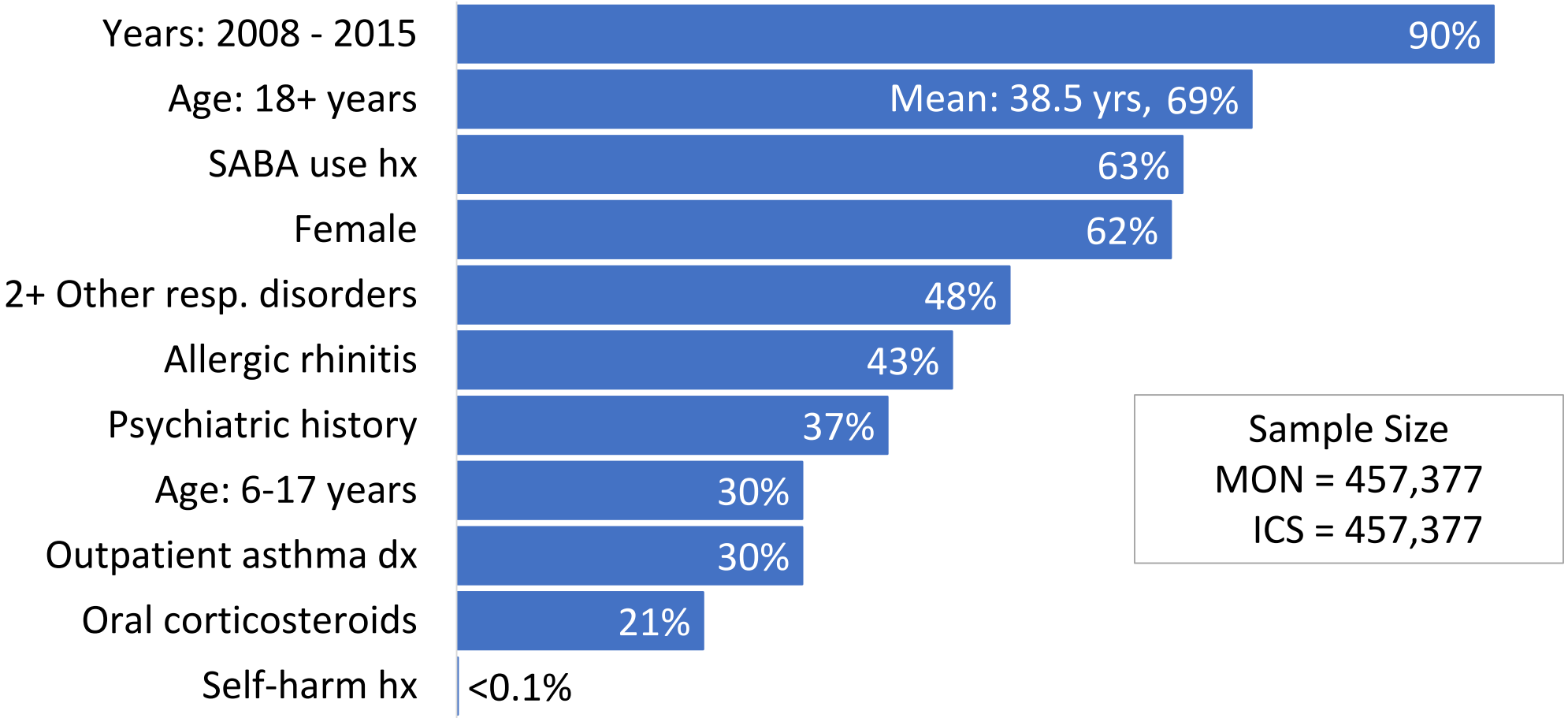
Results

Baseline Covariates

- In **unmatched** cohorts:
  - MON users more likely to have:
    - History of psych disorder
    - Allergic rhinitis
    - Other respiratory disorder (2+ codes)
    - Outpatient asthma dx
    - History of psychiatric/psychotropic drugs
    - History of oral corticosteroids
  - ICS users more likely to have:
    - History of SABA use
- In **1:1 matched** cohorts, all covariates were balanced
  - 89.1% of MON and 34.3% of ICS patients

Baseline Characteristics: Matched MON & ICS Pts

Depression & Self-Harm



Sample Size
MON = 457,377
ICS = 457,377

Values are approximate.

Outpatient Depression is the Most Frequent Outcome

Events are not mutually exclusive

Outcome	Overall N
Outpatient depression	37,740
Inpatient depression	647
Self-harm	219
Self-harm with E-codes	264

Most Events are NAEs with a Previous Psychiatric Diagnosis

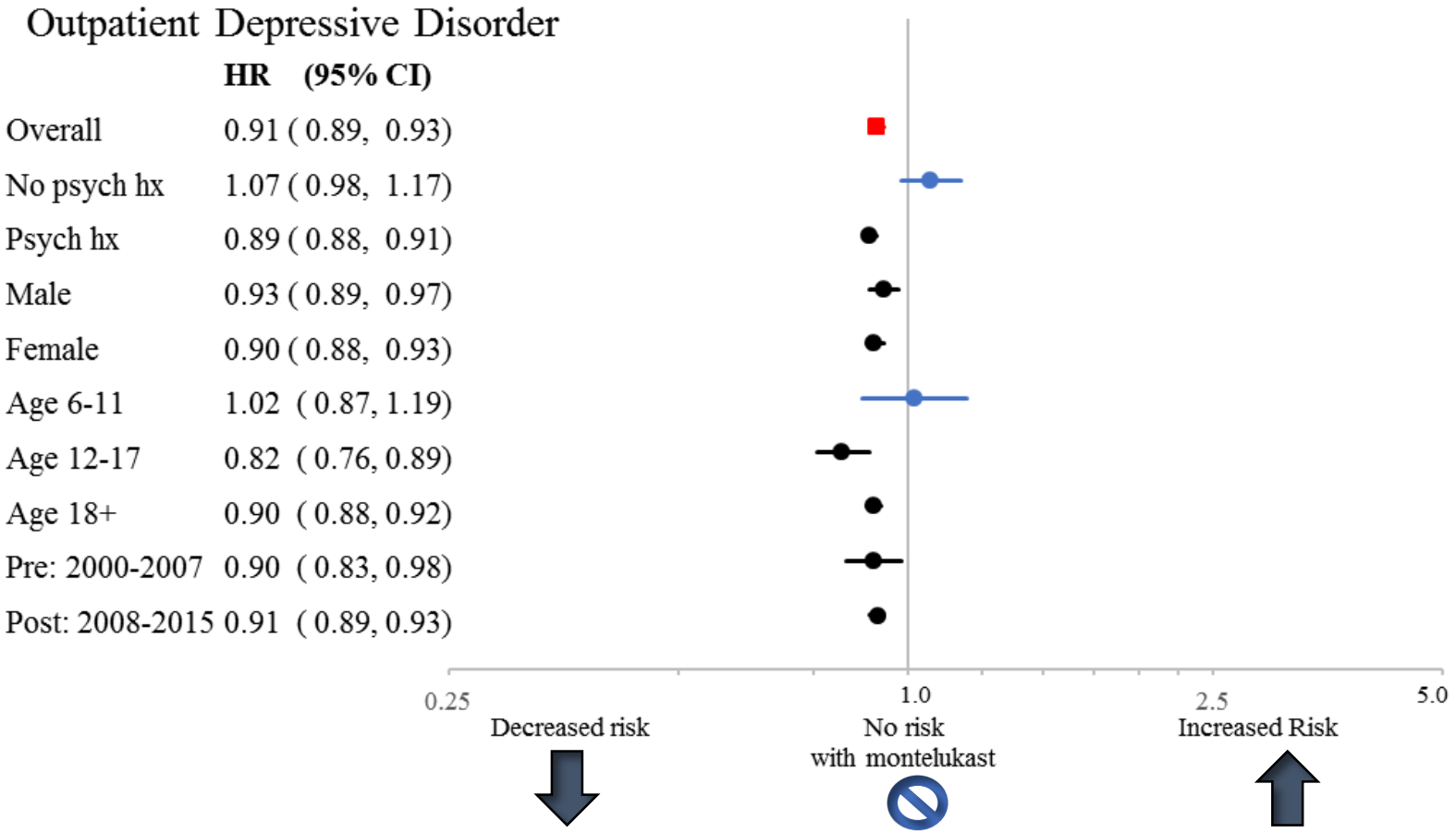
Events are not mutually exclusive

Outcome	Overall N	No Psych Hx N	Psych Hx N
Outpatient depression	37,740	2,178	35,182
Inpatient depression	647	58	581
Self-harm	219	11	205
Self-harm with E-codes	264	19	242

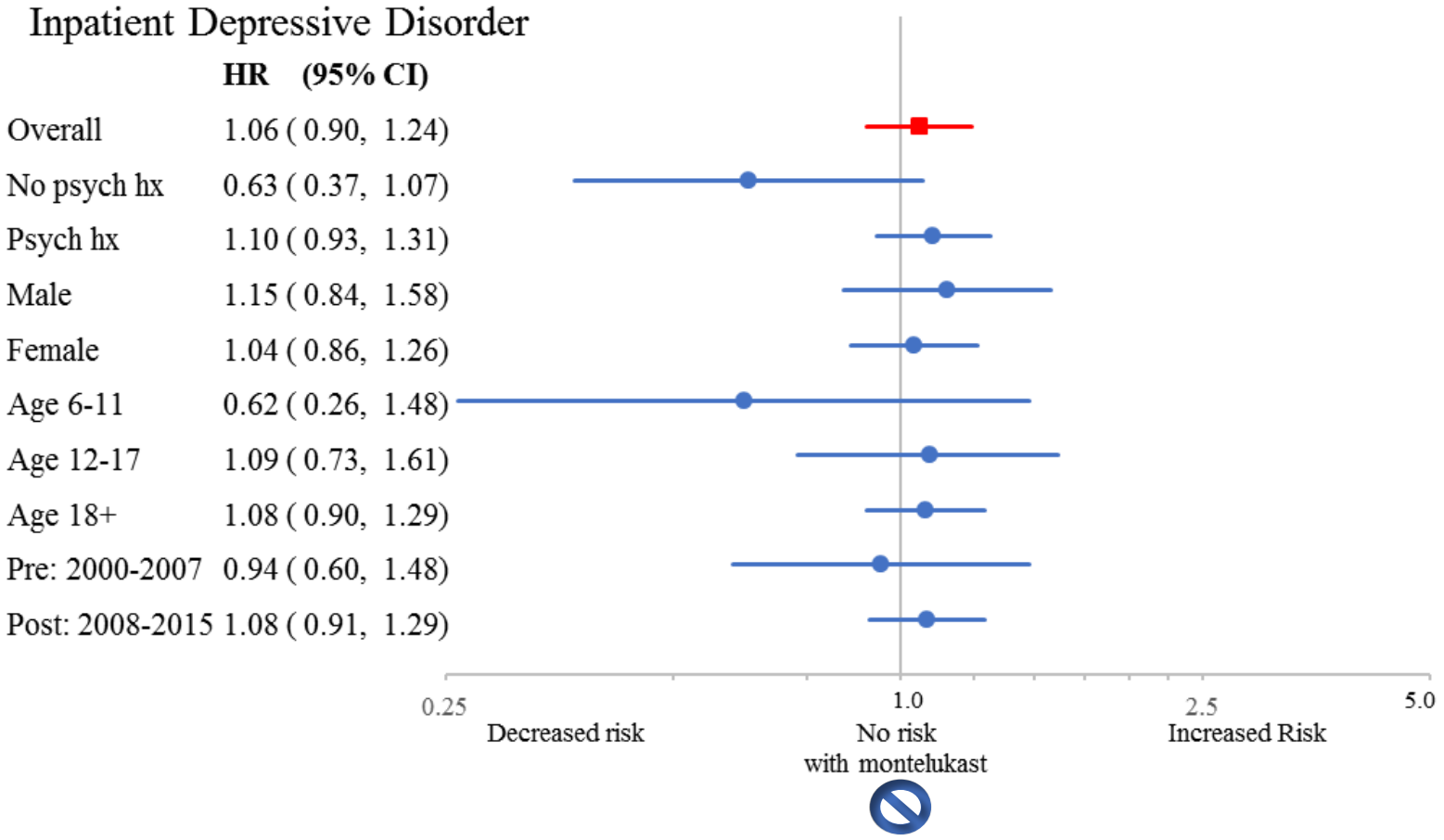
Shorter Average Follow-up (F/U) Days for ICS Pts

Outcome	Overall N	No Psych Hx N	Psych Hx N	ICS F/U Days	MON F/U Days
Outpatient depression	37,740	2,178	35,182	69.7	100.0
Inpatient depression	647	58	581	54.0	81.5
Self-harm	219	11	205	54.1	81.5
Self-harm with E-codes	264	19	242	54.1	81.5

MON: Decreased Risk of Outpatient Depression



MON: No Association with Inpatient Depression

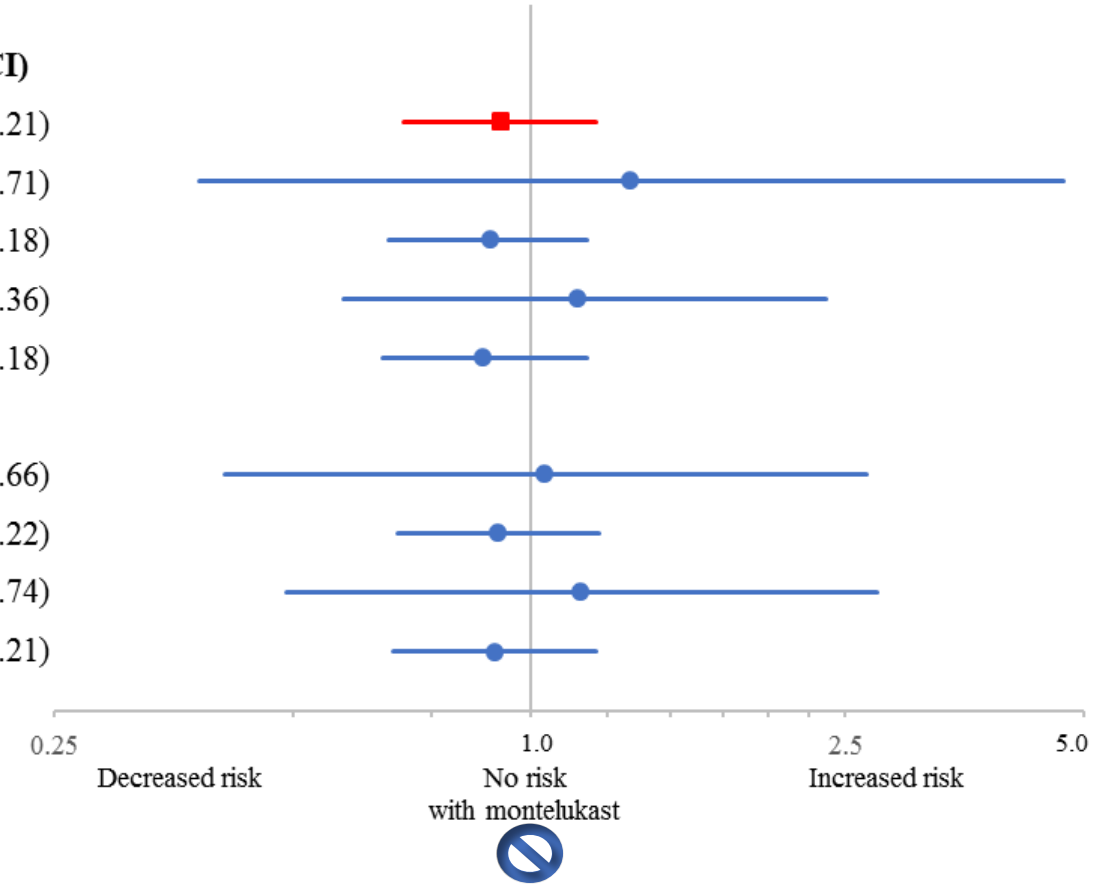


***Sensitivity analysis** 0-day gap/extension period: 1.07 (0.89, 1.28); 30-day gap/extension period: 1.04 (0.90, 1.20)

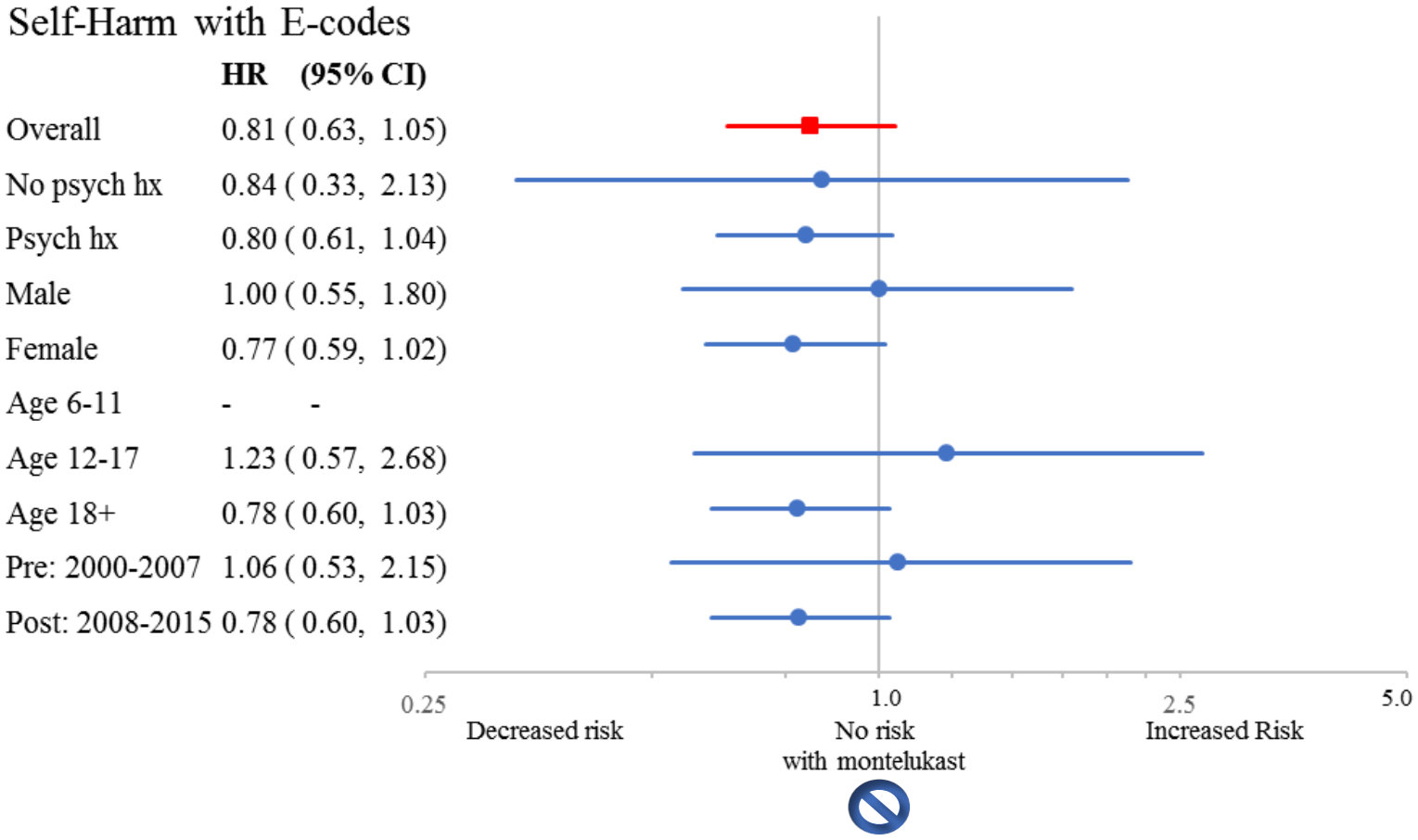
MON: No Association with Self-Harm

Self-Harm

	HR (95% CI)
Overall	0.92 (0.69, 1.21)
No psych hx	1.34 (0.38, 4.71)
Psych hx	0.89 (0.66, 1.18)
Male	1.16 (0.58, 2.36)
Female	0.87 (0.65, 1.18)
Age 6-11	- -
Age 12-17	1.04 (0.41, 2.66)
Age 18+	0.91 (0.68, 1.22)
Pre: 2000-2007	1.16 (0.49, 2.74)
Post: 2008-2015	0.90 (0.67, 1.21)

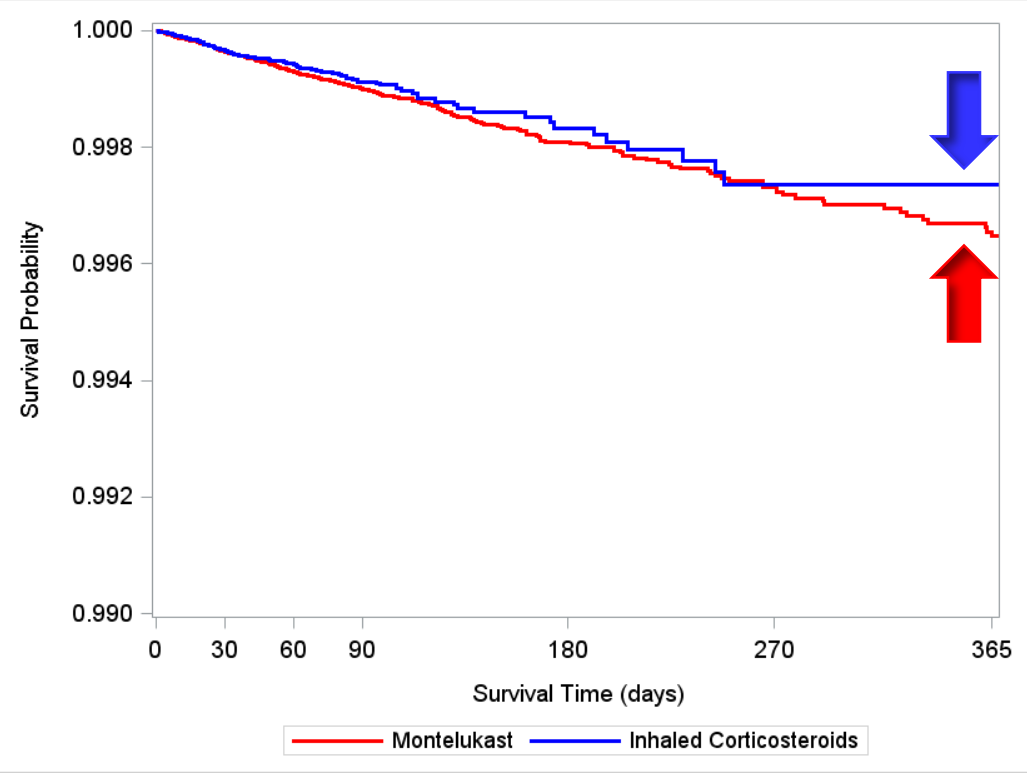


MON: No Association with Modified Self-Harm



1 Year Kaplan-Meier Curves of Event Free Survival

Inpatient Depression



Proportion of ICS patients at risk at 365 days who did not experience inpatient depression

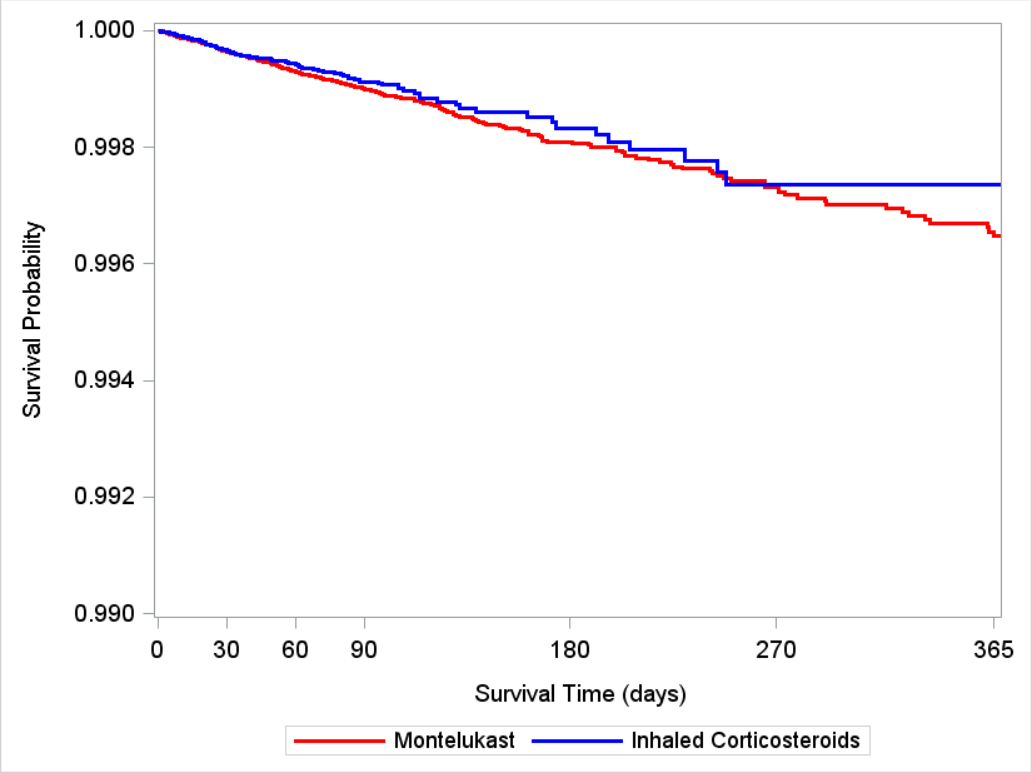
Proportion of MON patients at risk at 365 days who did not experience inpatient depression

MON: Decreased Risk of Outpatient Depression

1 Year Results

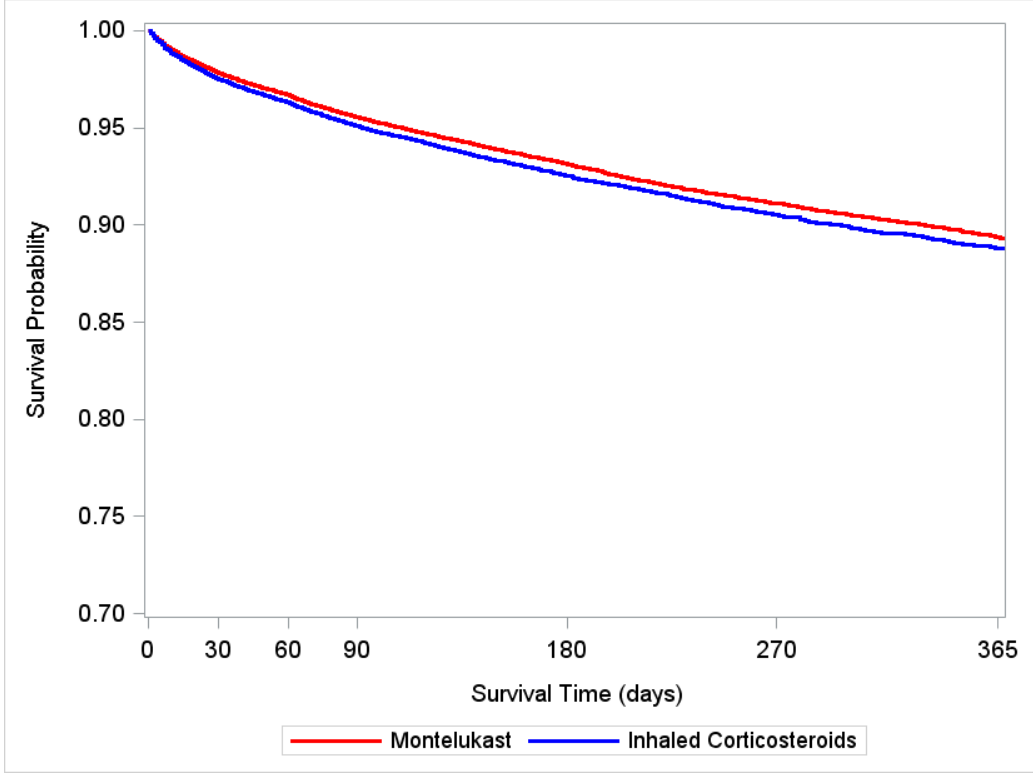
Inpatient Depression

1-yr HR: 1.06; CI: 0.90 – 1.25



Outpatient Depression

1-yr HR: 0.91; CI: 0.89 – 0.93

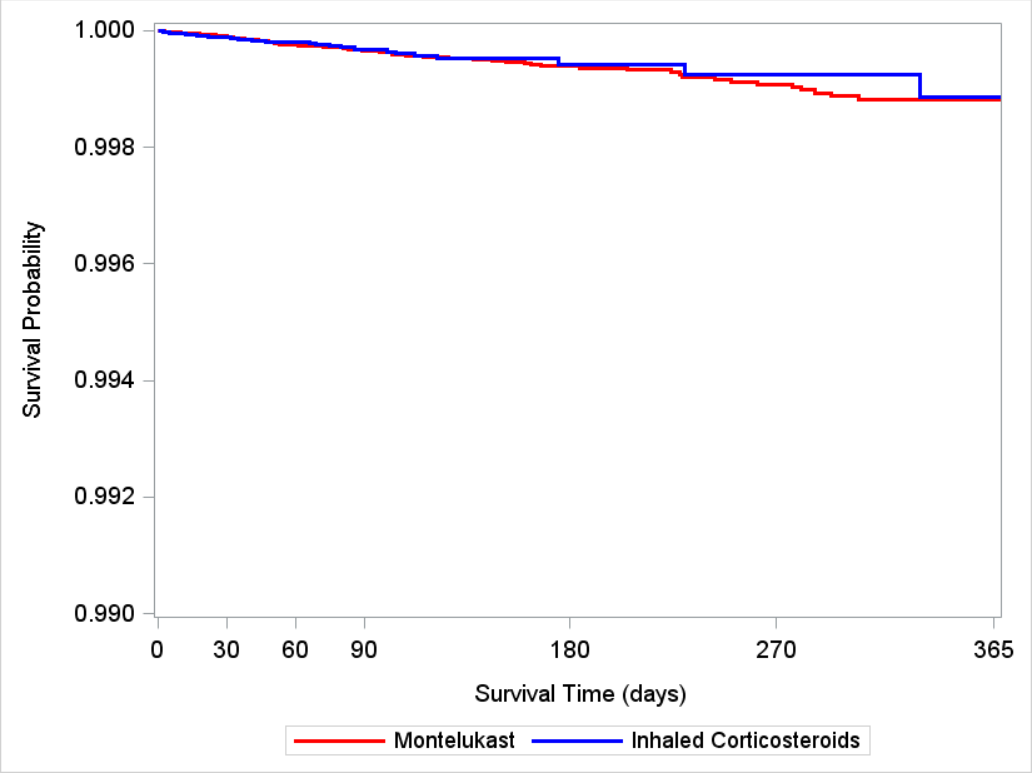


MON: No Association with Self-Harm Outcomes

1 Year Results

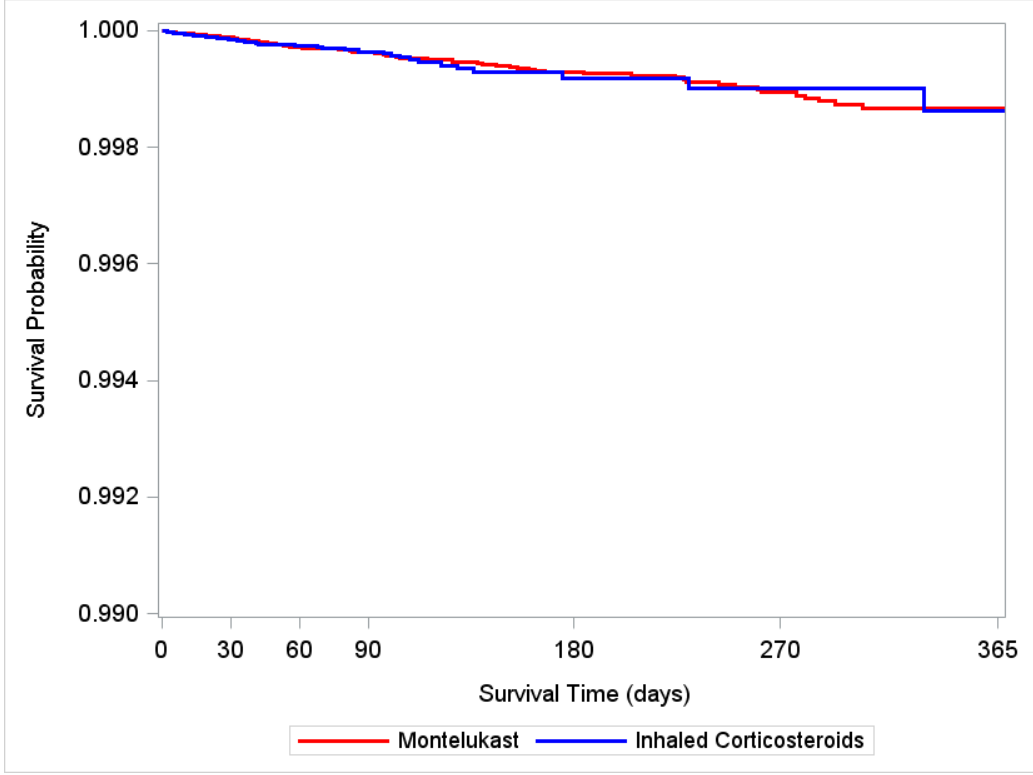
Self-Harm

1-yr HR: 0.96; CI: 0.72 - 1.26



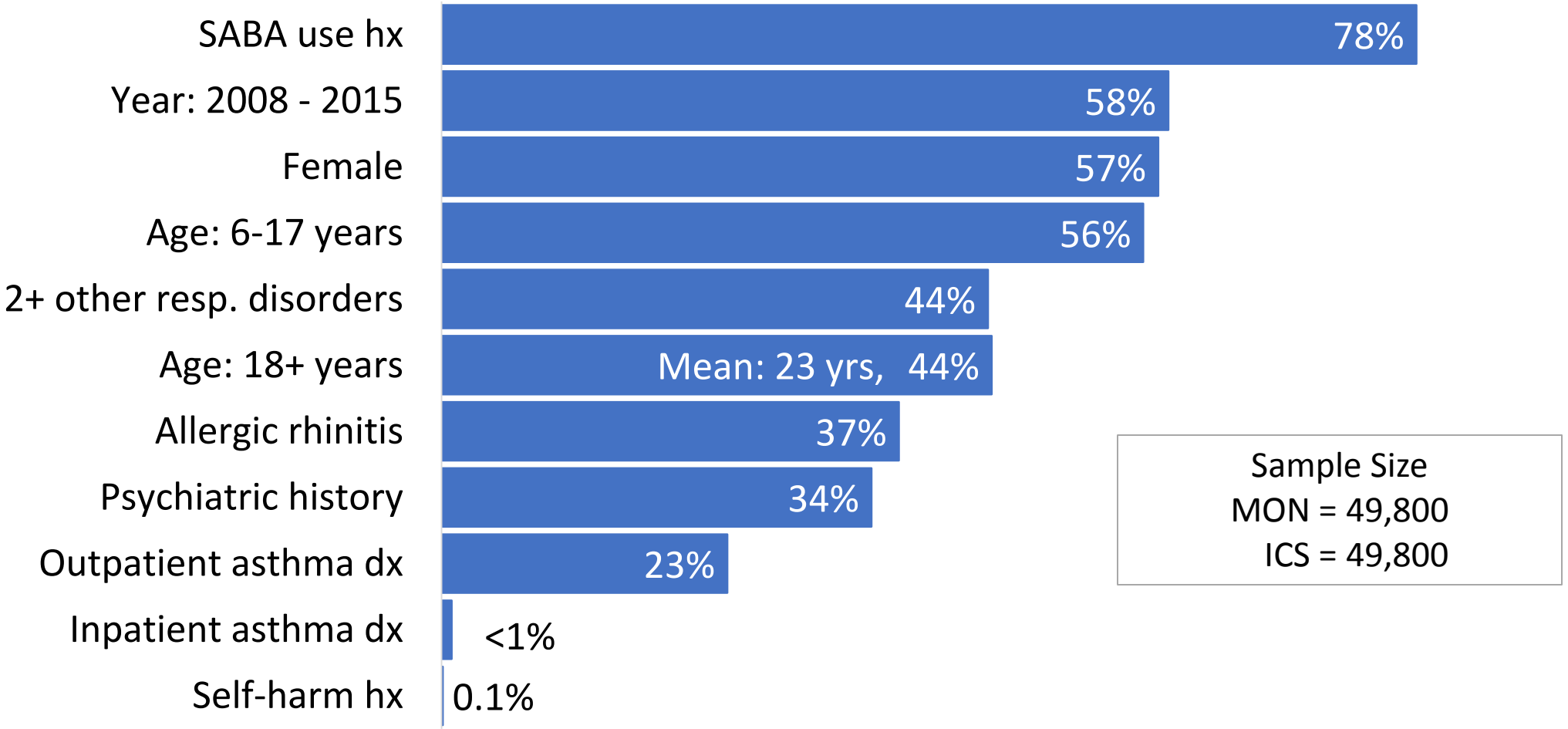
Modified Self-Harm

1-yr HR: 0.86; CI: 0.67 - 1.11



Baseline Characteristics: Matched MON & ICS Pts

Suicide



Values are approximate.

Two Suicides in Adult Female MON users

1:1 Matched population

	No. of New Users	No. of Events	Events per 100,000 Patients
MON	49,800	2	4.02
ICS	49,800	0	0.00

Rate is comparable to CDC age-adjusted suicide rates for females between 1999-2015

	Total		Male		Female	
Year	Number	Deaths per 100,000	Number	Deaths per 100,000	Number	Deaths per 100,000
1999	29,199	10.5	23,458	17.8	5,741	4.0
2000	29,350	10.4	23,618	17.7	5,732	4.0
2001	30,622	10.7	24,672	18.2	5,950	4.1
2002	31,655	10.9	25,409	18.5	6,246	4.2
2003	31,484	10.8	25,203	18.1	6,281	4.2
2004	32,439	11.0	25,566	18.1	6,873	4.5
2005	32,637	10.9	25,907	18.1	6,730	4.4
2006	33,300	11.0	26,308	18.1	6,992	4.5
2007	34,598	11.3	27,269	18.5	7,329	4.6
2008	36,035	11.6	28,450	19.0	7,585	4.8
2009	36,909	11.8	29,089	19.2	7,820	4.9
2010	38,364	12.1	30,277	19.8	8,087	5.0
2011	39,518	12.3	31,003	20.0	8,515	5.2
2012	40,600	12.6	31,780	20.4	8,820	5.4
2013	41,149	12.6	32,055	20.3	9,094	5.5
2014	42,826	13.0	33,162	20.7	9,664	5.8
2015	44,193	13.3	33,994	21.1	10,199	6.0

https://www.cdc.gov/nchs/images/databriefs/301-350/db309_fig1.png

Discussion

Findings

- **No statistical association was observed between montelukast and serious NAEs (inpatient depressive disorder & self-harm) in the overall analyses and across age, sex, & time strata**
  - The absence of risk for these outcomes is consistent with results from clinical trials and well-conducted observational studies (Ali, et al. 2015, Schumock, et al. 2012, Philip et al, 2009)

Findings

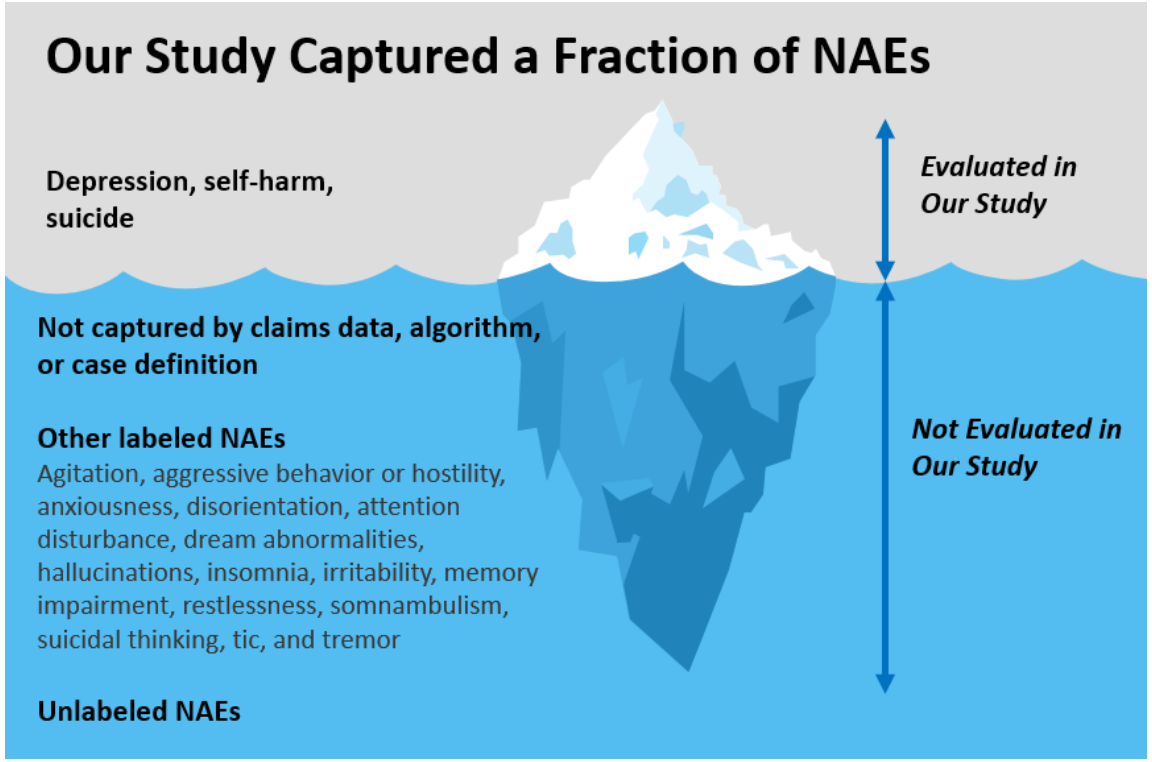
Continued

- **MON patients had decreased risk of outpatient depression compared to ICS patients in those with a psychiatric history**
  - Among those without a psychiatric history, we were unable to conclude that there is an increased risk (HR: 1.07; CI: 0.98 – 1.17)
  - 90% of patients exposed after the 2008 FDA communications; therefore, MON patients may have ceased treatment before depressive symptoms progressed
  - Proportion of patients with ongoing treatment for depression; decreased risk only seen in patients with a psych history

Strengths

- Large patient population from 17 different DPs of varying insured patient populations
- Powered at 80% to detect HR ≥1.25 for inpatient depression and HR ≥1.46 self-harm outcomes, but possibly underpowered for subgroup analyses
- Study patients exposed to MON before and after the 2008 DSC and labeling changes
- Suicide data was extracted from records Sentinel DPs deemed “excellent,” thus ensuring high specificity for this outcome

Limitations



- ICS has poorer adherence relative to MON (Barnes, 2015)
- Did not adjust for socioeconomic status
- Non-proportional hazards for study outcomes
- Channeling bias due to DSC and labeling changes
- Underpowered to rule out an increased risk of 24% (upper bound of CI)
- Potential systemic absorption of ICS may carry a risk of NAEs (Fardet, 2012)

Conclusions

- The Sentinel findings need to be interpreted in light of important limitations
  - We did not find a statistical association between MON and inpatient depression, self-harm, and completed suicide that resulted in medical claims, although a small to modest increase in risk cannot be ruled out
    - Totality of the observational evidence, including well-conducted observational studies, is not suggestive of a risk
  - A decreased risk in treated outpatient depression was observed among patients with psych history of depression
  - Completed suicide was rare and limited to adult, female patients with a psych history

- We welcome discussion from the panel regarding labeling recommendations

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Thank You

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