Assessing the risk of intentional self-harm in montelukast users: an observational study in the Sentinel System using ICD-10 coding

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BACKGROUND

- Montelukast is a leukotriene receptor antagonist, approved for treating asthma, bronchoconstriction, and allergic rhinitis.
- Its prescribing information (March 2020) includes a Boxed Warning for neuropsychiatric adverse events.
- A previous study in the Sentinel System in patients with asthma from 2000-2015 showed no increased risk of intentional self-harm (ISH) with montelukast vs. inhaled corticosteroids (ICS).
- ISH in the previous study was measured using ICD-9-CM codes which has variable accuracy.

OBJECTIVE

To determine the risk of intentional self-harm events following montelukast or ICS exposure, using ICD-10-CM codes which may have better accuracy than ICD-9-CM codes for capturing suicide attempts.

METHODS

- Design: Retrospective active comparator new-user cohort study.
- Data source and time period: U.S. FDA Sentinel System from October 1, 2015, to June 30, 2022.
- Cohort: Patients aged 10 years and older, with a diagnosis of asthma, excluding patients with a COPD diagnosis in the 183 days before or on the date of index exposure.
- Exposure: New dispensing of montelukast or ICS.
- Outcome: ISH using ICD-10-CM diagnosis codes.
- Follow-up and censoring: Followed from index dispensing date to occurrence of study outcome, end of exposure episode, initiation or switching to Long-Acting Beta-Agonists (LABA) or comparator treatment, asthma hospitalizations, oral corticosteroid treatment, death, end of study period or end of available data.
- Data analysis: Inverse probability of treatment weighting (IPTW) was used to balance baseline covariates. Hazard ratios (HR) with 95% CI were estimated using case-centered logistic regression. Incidence rate (IR) and time to ISH events were estimated. Subgroup analyses were done by age group, sex, psychiatric history, and pre/post Boxed Warning period. Sensitivity analyses varying care setting and exposure episode gaps were conducted.

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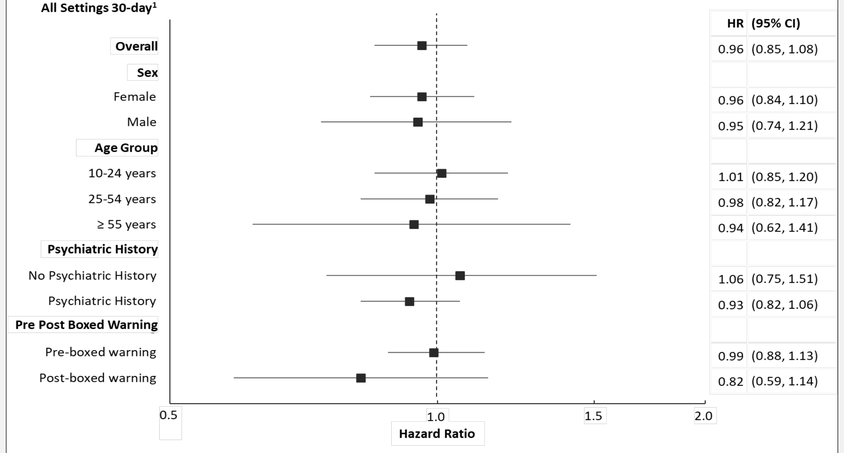
RESULTS

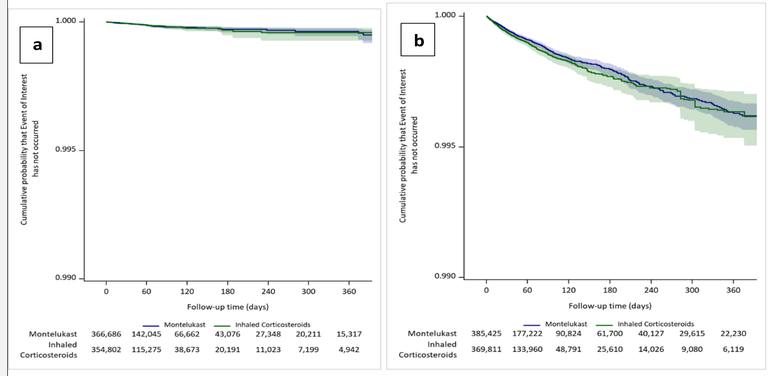
- After weighting, there were 752,230 and 724,855 patients in the montelukast and ICS exposure groups, respectively (Table 1).
- Incidence Rate of ISH per 1000 person-years was higher in the 10–24 years age group [IR (95% CI): 5.3 (4.8, 5.8)] compared to the 25+ years age group [IR (95% CI): 2.0 (1.9, 2.2)].
- Females recorded more ISH events [IR (95% CI): 3.2 (3.0, 3.4)] compared to males [IR (95% CI): 2.0 (1.8, 2.3)].
- No association between montelukast use and ISH compared to ICS use overall [Hazard Ratio (HR) (95% CI): 0.96 (0.85, 1.08)] (Figure 1).
- No association between montelukast use and ISH compared to ICS in the 10–24 years age group [HR (95% CI): 1.01 (0.85, 1.20)] (Figure 1).
- Subgroup and sensitivity analyses showed similar null findings
- ISH was roughly 7-fold more frequent in patients with a psychiatric history compared to patients with no psychiatric history (Figure 2).
- ISH rates were approximately double those observed in the previous study using ICD-9 coding.

Figure 1. Forest Plot of Hazard Ratios (HR) and 95% Confidence Intervals (CI) for Intentional Self-harm in Montelukast Versus Inhaled Corticosteroid Users



[1]*Weighted using Average Treatment Effect in the Treated, (ATT)*

Figure 2: Aggregated Adjusted Kaplan-Meier Estimate and 95% Confidence Interval for Intentional Self-harm in All Care Settings Among Patients With No History of Psychiatric Disorder (a) and Patients With History of Psychiatric Disorder (b)



The shaded region represents the 95% confidence intervals

Table 1: Incidence of Intentional Self-harm Events Among Montelukast Users and Inhaled Corticosteroid Users

	Site-Adjusted Analysis, Unweighted		IPTW Analysis	
	Montelukast	ICS	Montelukast	ICS
Number of New Users	752,280	923,377	752,230	724,855
Person Years at Risk	226,485	199,147	226,474	161,239
Number of Events	580	882	580	501
Incidence Rate per 1,000 Person Years	2.56	4.43	2.56	3.11

LIMITATIONS

- Could not exclude diagnostic codes in outpatient settings that represented past self-harm events.
- Claims data may under ascertain deaths and ISH.
- Data on race and ethnicity were missing in about 50% of the sample.
- Possibility of residual confounding since this was not a randomized controlled trial.

CONCLUSIONS

- No association between montelukast use and ISH was observed.
- Finding cannot rule out occurrence of less common idiosyncratic neuropsychiatric reactions to montelukast.
- Risk of ISH was higher (x7) among patients with a psychiatric history compared to patients with no psychiatric history.
- ICD-10 codes for ISH events appeared to have greater sensitivity than ICD-9 codes.

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