Supplementary Material

Leukotriene-receptor antagonist and risk of neuropsychiatric events in children, adolescents, and young adults: A self-controlled case series

Ji Soo Park, Yoo Jung Cho, Je-Yeon Yun, Hye Jin Lee, Jinho Yu, Hyeon-Jong Yang, Dong In Suh, on behalf of the Korean childhood Asthma REsearch team

Contents

Supplementary Text ............................................................... 2
Supplementary Table S1 ......................................................... 3
Supplementary Table S2 ......................................................... 16
Supplementary Table S3 ......................................................... 18
Supplementary Table S4 ......................................................... 21
Supplementary Table S5 ......................................................... 22
Supplementary Table S6 ......................................................... 23
Supplementary Table S7 ......................................................... 24
Supplementary Table S9 ......................................................... 26
Supplementary Figure S1 ......................................................... 27
Reference ............................................................................. 28
Supplementary Text

MATERIALS AND METHODS

Assessment of exposure

One of the main assumptions that the SCCS method relies on is that events do not influence subsequent exposures. To test for this assumption, we drew a histogram of the time interval between the first event of each patient (t) and the starting date of exposures (u) before and after the first event was plotted. [1] In this case, the first event (t) is the first NPE of each participant, and the starting date of exposures (u) is the date of LTRA prescription. The x-axis is the number of days from start of LTRA prescription to an NPE (t-u). The events on the negative x-axis are events that occurred before the start of exposure, meaning the LTRA was prescribed after the NPE. The events on the positive x-axis are events that occurred after the start of exposure, meaning the LTRA was prescribed before the NPE. If events were sparse in the negative intervals compared to the positive intervals, this would indicate that exposures were delayed after an event (i.e., the event influenced the exposure). If LTRAs were less frequently prescribed due to an NPE, than the events on the negative x-axis would be fewer than those on the positive x-axis. A peak of events on the short x-axis is expected, as these are the events of interest to our study hypothesis. The NPEs that are expected shortly after prescription of LTRA would form a peak on the short positive x-axis.
### Supplementary Table S1. International Statistical Classification of Diseases and Related Health Problems, 10th edition (ICD-10) codes for neuropsychiatric diagnoses

| Type of neuropsychiatric diagnosis | ICD-10 code | Diagnosis                                      |
|------------------------------------|-------------|-----------------------------------------------|
| Psychotic disorder                 |             |                                               |
|                                    | F20         | Schizophrenia                                 |
|                                    | F20.0       | Paranoid schizophrenia                        |
|                                    | F20.1       | Hebephrenic schizophrenia                     |
|                                    | F20.2       | Catatonic schizophrenia                       |
|                                    | F20.3       | Undifferentiated schizophrenia                |
|                                    | F20.4       | Post-schizophrenic depression                 |
|                                    | F20.5       | Residual schizophrenia                        |
|                                    | F20.6       | Simple schizophrenia                          |
|                                    | F20.8       | Other schizophrenia                           |
|                                    | F20.9       | Schizophrenia, unspecified                    |
|                                    | F21         | Schizotypal disorder                          |
|                                    | F22         | Persistent delusional disorders               |
|                                    | F22.0       | Delusional disorder                           |
|                                    | F22.8       | Other persistent delusional disorders         |
|                                    | F22.9       | Persistent delusional disorder, unspecified   |
|                                    | F23         | Acute and transient psychotic disorders       |
F23.0 Acute polymorphic psychotic disorder without symptoms of schizophrenia

F23.1 Acute polymorphic psychotic disorder with symptoms of schizophrenia

F23.2 Acute schizophrenia-like psychotic disorder

F23.3 Other acute predominantly delusional psychotic disorders

F23.8 Other acute and transient psychotic disorders

F23.9 Acute and transient psychotic disorder, unspecified

F24 Induced delusional disorder

F25 Schizoaffective disorders

F25.0 Schizoaffective disorder, manic type

F25.1 Schizoaffective disorder, depressive type

F25.2 Schizoaffective disorder, mixed type

F25.8 Other schizoaffective disorders

F25.9 Schizoaffective disorder, unspecified

F28 Other nonorganic psychotic disorders

F29 Unspecified nonorganic psychosis

R41.0 Disorientation, unspecified

R44 Other symptoms and signs involving general sensations and perceptions

R44.0 Auditory hallucinations

R44.1 Visual hallucinations

R44.2 Other hallucinations

R44.3 Hallucinations, unspecified
Other and unspecified symptoms and signs involving general sensations and perceptions

Mood disorder

F30 Manic episode
F30.0 Hypomania
F30.1 Mania without psychotic symptoms
F30.2 Mania with psychotic symptoms
F30.8 Other manic episodes
F30.9 Manic episode, unspecified
F31 Bipolar affective disorder
F31.0 Bipolar affective disorder, current episode hypomanic
F31.1 Bipolar affective disorder, current episode manic without psychotic symptoms
F31.2 Bipolar affective disorder, current episode manic with psychotic symptoms
F31.3 Bipolar affective disorder, current episode mild or moderate depression
F31.4 Bipolar affective disorder, current episode severe depression without psychotic symptoms
F31.5 Bipolar affective disorder, current episode severe depression with psychotic symptoms
F31.6 Bipolar affective disorder, current episode mixed
F31.7 Bipolar affective disorder, currently in remission
F31.8 Other bipolar affective disorders
F31.9  Bipolar affective disorder, unspecified
F32  Depressive episode
F32.0  Mild depressive episode
F32.1  Moderate depressive episode
F32.2  Severe depressive episode without psychotic symptoms
F32.3  Severe depressive episode with psychotic symptoms
F32.8  Other depressive episodes
F32.9  Depressive episode, unspecified
F33  Recurrent depressive disorder
F33.0  Recurrent depressive disorder, current episode mild
F33.1  Recurrent depressive disorder, current episode moderate
F33.2  Recurrent depressive disorder, current episode severe without psychotic symptoms
F33.3  Recurrent depressive disorder, current episode severe with psychotic symptoms
F33.4  Recurrent depressive disorder, currently in remission
F33.8  Other recurrent depressive disorders
F33.9  Recurrent depressive disorder, unspecified
F34  Persistent mood [affective] disorders
F34.0  Cyclothymia
F34.1  Dysthymia
F34.8  Other persistent mood [affective] disorders
F34.9  Persistent mood [affective] disorder, unspecified
F38  Other mood [affective] disorders
F38.0 Other single mood [affective] disorders
F38.1 Other recurrent mood [affective] disorders
F38.8 Other specified mood [affective] disorders
F39 Unspecified mood [affective] disorder

Anxiety disorder

F40 Phobic anxiety disorders
F40.0 Agoraphobia
F40.1 Social phobias
F40.2 Specific (isolated) phobias
F40.8 Other phobic anxiety disorders
F40.9 Phobic anxiety disorder, unspecified
F41 Other anxiety disorders
F41.0 Panic disorder [episodic paroxysmal anxiety]
F41.1 Generalized anxiety disorder
F41.2 Mixed anxiety and depressive disorder
F41.3 Other mixed anxiety disorders
F41.8 Other specified anxiety disorders
F41.9 Anxiety disorder, unspecified
F42 Obsessive-compulsive disorder
F42.0 Predominantly obsessional thoughts or ruminations
F42.1 Predominantly compulsive acts [obsessional rituals]
F42.2 Mixed obsessional thoughts and acts
F42.8 Other obsessive-compulsive disorders
F42.9  Obsessive-compulsive disorder, unspecified
F43  Reaction to severe stress, and adjustment disorders
F43.0  Acute stress reaction
F43.1  Post-traumatic stress disorder
F43.2  Adjustment disorders
F43.8  Other reactions to severe stress
F43.9  Reaction to severe stress, unspecified
F44  Dissociative [conversion] disorders
F44.0  Dissociative amnesia
F44.1  Dissociative fugue
F44.2  Dissociative stupor
F44.3  Trance and possession disorders
F44.4  Dissociative motor disorders
F44.5  Dissociative convulsions
F44.6  Dissociative anaesthesia and sensory loss
F44.7  Mixed dissociative [conversion] disorders
F44.8  Other dissociative [conversion] disorders
F44.9  Dissociative [conversion] disorder, unspecified
F45  Somatoform disorders
F45.0  Somatization disorder
F45.1  Undifferentiated somatoform disorder
F45.2  Hypochondriacal disorder
F45.3  Somatoform autonomic dysfunction
F45.4  Persistent somatoform pain disorder
F45.8  Other somatoform disorders
F45.9  Somatoform disorder, unspecified
F48   Other neurotic disorders
F48.0  Neurasthenia
F48.1  Depersonalization-derealization syndrome
F48.8  Other specified neurotic disorders
F48.9  Neurotic disorder, unspecified
R45.1  Restlessness and agitation

Sleep-related disorder

F51    Nonorganic sleep disorders
F51.0  Nonorganic insomnia
F51.1  Nonorganic hypersomnia
F51.2  Nonorganic disorder of the sleep-wake schedule
F51.3  Sleepwalking [somnambulism]
F51.4  Sleep terrors [night terrors]
F51.5  Nightmares
F51.8  Other nonorganic sleep disorders
F51.9  Nonorganic sleep disorder, unspecified
G47    Sleep disorders
G47.0  Disorders of initiating and maintaining sleep [insomnias]
G47.1  Disorders of excessive somnolence [hypersomnias]
G47.2  Disorders of the sleep-wake schedule
G47.3  Sleep apnoea
G47.30 Obstructive sleep apnoea
G47.31 Central sleep apnoea
G47.32 Mixed sleep apnoea
G47.38 Other sleep apnoea
G47.4 Narcolepsy and cataplexy
G47.8 Other sleep disorders
G47.9 Sleep disorder, unspecified

Cognitive disorder

R41.1 Anterograde amnesia
R41.2 Retrograde amnesia
R41.3 Other amnesia
F90 Hyperkinetic disorders
F90.0 Disturbance of activity and attention
F90.1 Hyperkinetic conduct disorder
F90.8 Other hyperkinetic disorders
F90.9 Hyperkinetic disorder, unspecified

Other behavioural and emotional disorders with onset usually occurring in childhood and adolescence

F98 Nonorganic enuresis
F98.0 Nonorganic enuresis
F98.1 Nonorganic encopresis
F98.2 Feeding disorder of infancy and childhood
F98.3 Pica of infancy and childhood
F98.4  Stereotyped movement disorders
F98.5  Stuttering [stammering]
F98.6  Cluttering

Other specified behavioural and emotional disorders with onset usually occurring in childhood and adolescence

Unspecified behavioural and emotional disorders with onset usually occurring in childhood and adolescence

Movement disorder

G20  Parkinson's disease
G21  Secondary parkinsonism
G21.0  Malignant neuroleptic syndrome
G21.1  Other drug-induced secondary parkinsonism
G21.2  Secondary parkinsonism due to other external agents
G21.3  Postencephalitic parkinsonism
G21.4  Vascular parkinsonism
G21.8  Other secondary parkinsonism
G21.9  Secondary parkinsonism, unspecified
G24  Dystonia
G24.0  Drug-induced dystonia
G24.1  Idiopathic familial dystonia
G24.2  Idiopathic nonfamilial dystonia
G24.3 Spasmodic torticollis
G24.4 Idiopathic orofacial dystonia
G24.5 Blepharospasm
G24.8 Other dystonia
G24.9 Dystonia, unspecified
G25 Other extrapyramidal and movement disorders
G25.0 Essential tremor
G25.1 Drug-induced tremor
G25.2 Other specified forms of tremor
G25.3 Myoclonus
G25.4 Drug-induced chorea
G25.5 Other chorea
G25.6 Drug-induced tics and other tics of organic origin
G25.8 Other specified extrapyramidal and movement disorders
G25.9 Extrapyramidal and movement disorder, unspecified

Personality disorder

F60 Specific personality disorders
F60.0 Paranoid personality disorder
F60.1 Schizoid personality disorder
F60.2 Dissocial personality disorder
F60.3 Emotionally unstable personality disorder
F60.4 Histrionic personality disorder
F60.5 Anankastic personality disorder
F60.6  Anxious[avoidant] personality disorder
F60.7  Dependent personality disorder
F60.8  Other specific personality disorders
F60.9  Personality disorder, unspecified
F61    Mixed and other personality disorders
       Enduring personality changes, not attributable to brain damage
F62    and disease
F62.0  Enduring personality change after catastrophic experience
F62.1  Enduring personality change after psychiatric illness
F62.8  Other enduring personality changes
F62.9  Enduring personality change, unspecified
F63    Habit and impulse disorders
F63.0  Pathological gambling
F63.1  Pathological fire-setting[pyromania]
F63.2  Pathological stealing[kleptomania]
F63.3  Trichotillomania
F63.8  Other habit and impulse disorders
F63.9  Habit and impulse disorder, unspecified
F64    Gender identity disorders
F64.0  Transsexualism
F64.1  Dual-role transvestism
F64.2  Gender identity disorder of childhood
F64.8  Other gender identity disorders
F64.9  Gender identity disorder, unspecified
F65 Disorders of sexual preference
F65.0 Fetishism
F65.1 Fetishistic transvestism
F65.2 Exhibitionism
F65.3 Voyeurism
F65.4 Paedophilia
F65.5 Sadomasochism
F65.6 Multiple disorders of sexual preference
F65.8 Other disorders of sexual preference
F65.9 Disorder of sexual preference, unspecified

Psychological and behavioural disorders associated with
sexual development and orientation

F66
F66.0 Sexual maturation disorder
F66.1 Egodystonic sexual orientation
F66.2 Sexual relationship disorder
F66.8 Other psychosexual development disorders
F66.9 Psychosexual development disorder, unspecified

F68 Other disorders of adult personality and behaviour
F68.0 Elaboration of physical symptoms for psychological reasons
Intentional production or feigning of symptoms or disabilities,
either physical or psychological [factitious disorder]
F68.8 Other specified disorders of adult personality and behaviour
F69 Unspecified disorder of adult personality and behaviour
Disorders of social functioning with onset specific to childhood and adolescence

F94.0 Elective mutism

F94.1 Reactive attachment disorder of childhood

F94.2 Disinhibited attachment disorder of childhood

F94.8 Other childhood disorders of social functioning

F94.9 Childhood disorder of social functioning, unspecified
**Supplementary Table S2. Risk of neuropsychiatric events in relation to leukotriene receptor antagonist use in patients with asthma or allergic rhinitis according to age group and observation period**

| Variable                      | Children (3–11 years) | Adolescent (12–18 years) | Young adult (19–30 years) |
|-------------------------------|-----------------------|--------------------------|---------------------------|
|                               | No of events | Person-year | IRR (95% CI) | P-value | No of events | Person-year | IRR (95% CI) | P-value | No of events | Person-year | IRR (95% CI) | P-value |
| **Observation period 1**      |             |             |              |         |             |             |              |         |             |             |              |         |
| Unexposed                     | 1,193       | 3062.25     | 1            |          | 684         | 1707.66     | 1            |          | 3,417       | 7749.78     | 1            |          |
| Exposed                       | 48          | 154.55      | 0.72 (0.53, 0.97) | 0.036   | 19          | 46.14       | 1.10 (0.65, 1.75) | 0.707   | 63          | 170.80      | 0.94 (0.72, 1.22) | 0.675   |
| **Time since initiation of LTRA (days)** |
| 1-3                           | 7           | 43.67       | 0.38 (0.16, 0.74) | 0.011   | 5           | 12.57       | 1.03 (0.37, 2.24) | 0.950   | 16          | 51.62       | 0.79 (0.46, 1.26) | 0.359   |
| 4-7                           | 14          | 24.28       | 1.36 (0.76, 2.23) | 0.255   | 4           | 7.16        | 1.44 (0.44, 3.42) | 0.469   | 13          | 26.48       | 1.25 (0.69, 2.08) | 0.421   |
| 8-14                          | 7           | 27.95       | 0.59 (0.25, 1.16) | 0.170   | 3           | 7.47        | 1.05 (0.26, 2.78) | 0.939   | 17          | 26.25       | 1.64 (0.97, 2.58) | 0.047   |
| 15-30                         | 9           | 30.05       | 0.69 (0.33, 1.26) | 0.275   | 4           | 8.38        | 1.25 (0.38, 3.04) | 0.661   | 7           | 29.71       | 0.60 (0.26, 1.17) | 0.181   |
| 31-90                         | 8           | 21.37       | 0.85 (0.38, 1.63) | 0.664   | 2           | 7.04        | 0.78 (0.13, 2.57) | 0.739   | 6           | 25.20       | 0.59 (0.23, 1.23) | 0.208   |
| >90                           | 3           | 7.24        | 1.02 (0.24, 2.95) | 0.981   | 1           | 3.52        | 0.86 (0.05, 4.47) | 0.888   | 4           | 11.55       | 0.92 (0.27, 2.34) | 0.874   |
| **Observation period 2**      |             |             |              |         |             |             |              |         |             |             |              |         |
| Unexposed                     | 1,274       | 3331.54     | 1            |          | 2661        | 6393.54     | 1            |          | 11,799      | 27302.12    | 1            |          |
| Exposed                       | 57          | 224.27      | 0.61 (0.46, 0.80) | <0.001  | 99          | 204.97      | 1.32 (1.06, 1.62) | 0.012   | 285         | 655.26      | 1.20 (1.05, 1.35) | 0.005   |
| **Time since initiation of LTRA (days)** |

16
| No | IRR   | CI               | P-value | No | IRR   | CI               | P-value |
|----|-------|------------------|---------|----|-------|------------------|---------|
| 1-3| 8     | 64.06            | 0.31 (0.14, 0.59) | 0.001 | 18 | 59.39 | 0.79 (0.48, 1.23) | 0.335 |
|    |       |                  |         | 7  | 61    | 213.4           | 0.77 (0.59, 0.99) | 0.047 |
| 4-7| 10    | 34.56            | 0.72 (0.36, 1.27) | 0.299 | 28 | 30.52 | 2.46 (1.65, 3.52) | <0.001 |
|    |       |                  |         | 5  | 111   | 105.38          | 2.85 (2.35, 3.43) | <0.001 |
| 8-14| 16   | 34.41            | 1.13 (0.66, 1.80) | 0.625 | 26 | 29.36 | 2.40 (1.58, 3.47) | <0.001 |
|     |       |                  |         | 3  | 64    | 96.55           | 1.79 (1.38, 2.28) | <0.001 |
| 15-30| 10 | 38.32            | 0.62 (0.31, 1.09) | 0.131 | 11 | 33.30 | 0.89 (0.46, 1.54) | 0.707 |
|     |       |                  |         | 2  | 25    | 105.01          | 0.64 (0.42, 0.93) | 0.026 |
| 31-90| 8    | 39.21            | 0.48 (0.21, 0.90) | 0.039 | 12 | 33.90 | 0.97 (0.51, 1.66) | 0.911 |
|      |       |                  |         | 1  | 15    | 92.43           | 0.43 (0.25, 0.69) | 0.001 |
| >90 | 5     | 13.71            | 0.85 (0.29, 1.96) | 0.733 | 4  | 18.50 | 0.58 (0.17, 1.45) | 0.300 |
|     |       |                  |         | 3  | 9     | 42.48           | 0.59 (0.27, 1.10) | 0.126 |

No, number; IRR, incidence rate ratio; CI, confidence interval; LTRA, leukotriene receptor antagonist
## Supplementary Table S3. Risk of neuropsychiatric events in relation to leukotriene receptor antagonist use in patients with asthma or allergic rhinitis according to type of neuropsychiatric event and observation period.

| Variable | Psychotic disorder | Mood disorder | Anxiety disorder | Sleep-related disorder | Cognitive | Movement | Personality disorder |
|----------|--------------------|---------------|------------------|-----------------------|-----------|----------|----------------------|
| No of events | IRR (95% CI) | No of events | IRR (95% CI) | No of events | IRR (95% CI) | No of events | IRR (95% CI) | No of events | IRR (95% CI) | No of events | IRR (95% CI) | No of events | IRR (95% CI) |
| Observation period 1 | | | | | | | | | | | | | |
| Unexposed | 97 | 211.09 | 1 | 1,277 | 1 | 3,057 | 1 | 1,277 | 1 | 3,057 | 1 | 1,277 | 1 | 3,057 |
| | | 2752.8 | | 6804.5 | | 4177.9 | | 1811.5 | | 345 | | 106 | | 31 |
| | | 0.07 | | 0.07 | | 0.07 | | 0.07 | | 0.07 | | 0.07 | | 0.07 |
| Exposed | 2 | 7.76 | (0.09, 0.44) | 34 | 80.23 | (0.69, 0.94) | 71 | 186.71 | (0.75, 0.808) | 30 | 109.15 | (0.42, 0.018) | 31 | 98.11 | (0.48, 0.078) | 4 | 8.73 | (0.41, 0.521) | 2 | 6.83 | (0.09, 0.498) |
| | | 1.44 | | 1.24 | | 0.91 | | 1.02 | | 3.78 | | 2.10 | | 1.90 |

| Time since initiation of LTRA (days) | | | | | | | | | | | | |
| 1-3 | 0.64 | 0.6 | 0.89 | 0.69 | 1.49 |
| | 1.32 | 1.00 | 1.51 | 1.31 | 10.91 |
| | 1.81 | 1.78 | 1.55 | 0.42 | 1.03 | 2.57 | 2.05 |
| 4-7 | 0.25 | 0.25 | 0.561 | 9 | 11.72 | (0.85, 0.090) | 18 | 29.28 | (0.94, 0.066) | 3 | 16.67 | (0.10, 0.134) | 7 | 15.45 | (0.44, 0.939) | 1 | 1.13 | (0.35, 0.356) | 1 | 1.02 | (0.27, 0.485) |
| | 3.25 | 2.41 | 1.09 | 2.02 | 18.97 | 15.31 |
| | 2.03 | 1.27 | 0.53 | 0.50 | 2.06 | 1.92 |
| 8-14 | 0.14 | 0.12 | 0.22 | 15 | 12.57 | (1.04, 0.022) | 15 | 30.23 | (0.72, 0.364) | 4 | 17.25 | (0.16, 0.211) | 4 | 18.29 | (0.15, 0.165) | 1 | 1.40 | (0.28, 0.479) | 1 | 1.11 | (0.26, 0.527) |
| | 3.57 | 2.05 | 1.25 | 1.17 | 15.35 | 14.37 | | | | | | | | | | | | | |
| Time since initiation of LTRA (days) | Unexposed | Exposed |
|-------------------------------------|-----------|---------|
|observation period | | 2 | | 2 |
| 15-30 | 1.64 (0.18, 0.752) | 4.15 (0.19, 0.332) | 11.32 (0.45, 0.666) | 19.19 (0.09, 0.076) | 6.20 (0.25, 0.291) | 1.1.72 (0.24, 0.559) | 0.1.45 NA NA |
| 10.40 | 1.45 | 1.52 | 0.94 | 1.33 | 13.88 |
| 0.54 | 0.85 | 0.63 | 0.80 |
| 31-90 | 1.57 NA NA | 3.13 (0.13, 0.298) | 9.27 (0.40, 0.635) | 5.17 (0.22, 0.313) | 5.13 (0.28, 0.634) | 0.1.71 NA NA | 0.1.19 NA NA |
| 1.45 | 1.57 | 1.40 | 1.79 |
| 0.44 | 0.99 | 1.03 | 0.62 |
| >90 | 0.12 NA NA | 1.5.71 (0.02, 0.436) | 5.14 (0.34, 0.984) | 3.6.69 (0.24, 0.959) | 1.3.80 (0.03, 0.635) | 0.0.92 NA NA | 0.0.30 NA NA |
| 2.22 | 2.33 | 2.96 | 3.07 |

Observation period 2

| Unexposed | Exposed |
|-----------|---------|
| 369 757.61 | 1 4,021 |
| 1 | 22319 |
| 5 | 1 10,051 |
| 33 | 1 7,057 |
| 4 | 1 621 |
| 5 | 1 692 |
| 1 | 1 173 |
| 1 | 1 331.17 |
| 1.40 | 1.20 |
| 1.01 | 0.99 |
| 0.79 | 1.15 |
| 1.33 |
| 16 | 34.57 (0.79, 0.223) | 138 295.63 (1.00, 0.045) | 236 599.90 (0.88, 0.834) | 189 494.35 (0.85, 0.897) | 24 73.79 (0.51, 0.290) | 26 57.13 (0.74, 0.516) | 7 13.91 (0.54, 0.489) |
| 2.33 | 1.44 | 1.16 | 1.15 | 1.19 | 1.71 | 2.79 |

| Time since initiation of LTRA (days) | Unexposed | Exposed |
|-------------------------------------|-----------|---------|
| 0.74 | 0.78 | 0.52 | 0.87 | 0.47 | 0.48 | 1.39 |
| 0.3 | 2.72 (0.12, 0.666) | 24 75.08 (0.51, 0.234) | 40 194.68 (0.37, <0.001) | 50 147.85 (0.65, 0.317) | 4 21.18 (0.14, 0.130) | 3 15.10 (0.12, 0.204) | 2 3.47 (0.34, 0.650) |
| 2.31 | 1.13 | 0.70 | 1.13 | 1.09 | 1.25 | 5.70 |
| 0.61 | 2.01 | 2.40 | 1.92 | 1.13 | 2.50 |
| 4-7 | 1.45 (0.03, 0.626) | 34 41.85 (1.40, <0.001) | 89 94.39 (1.92, <0.001) | 59 79.25 (1.46, <0.001) | 5 10.92 (0.40, 0.790) | 8 7.72 (1.13, 0.011) | 0 2.11 NA NA |
| 2.74 | 2.78 | 2.94 | 2.46 | 2.46 | 4.74 |
| Age Group | No. | Number | IRR   | 95% CI | 95% CI, <0.001 | 95% CI, <0.001 | 95% CI, <0.001 | 95% CI, <0.001 | 95% CI, <0.001 | 95% CI, <0.001 | 95% CI, <0.001 |
|-----------|-----|--------|-------|--------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|
| 8-14      | 6   | 51.2   | 4.42  | (0.05, 0.93) | 0.17, 0.123 | 0.17, 0.123 | 0.17, 0.123 | 0.17, 0.123 | 0.17, 0.123 | 0.17, 0.123 | 0.17, 0.123 |
| 15-30     | 1   | 31.4   | 4.47  | (0.19, 0.83) | 0.19, 0.83 | 0.19, 0.83 | 0.19, 0.83 | 0.19, 0.83 | 0.19, 0.83 | 0.19, 0.83 | 0.19, 0.83 |
| 31-90     | 5   | 54.7   | 28.79 | (0.17, 0.123) | 0.17, 0.123 | 0.17, 0.123 | 0.17, 0.123 | 0.17, 0.123 | 0.17, 0.123 | 0.17, 0.123 | 0.17, 0.123 |
| >90       | 1   | 43.0   | 30.2  | (0.19, 0.83) | 0.19, 0.83 | 0.19, 0.83 | 0.19, 0.83 | 0.19, 0.83 | 0.19, 0.83 | 0.19, 0.83 | 0.19, 0.83 |

No, number; IRR, incidence rate ratio; CI, confidence interval; LTRA, leukotriene receptor antagonist
Supplementary Table S4. Risk of neuropsychiatric events in relation to leukotriene receptor antagonist use in patients with asthma or allergic rhinitis according to indication of leukotriene receptor antagonist

| Variable | Asthma | | | | Allergic rhinitis only | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | No of events | Person-year | IRR (95% CI) | P-value | No of events | Person-year | IRR (95% CI) | P-value |
| Unexposed | 12,950 | 30489.35 | 1 |  | 8,078 | 19057.54 | 1 |  |
| Exposed | 409 | 1059.03 | 1.00 (0.90, 1.10) | 0.938 | 162 | 396.95 | 1.19 (1.01, 1.39) | 0.038 |

**Time since initiation of LTRA (days)**

|  | No | Person-year | IRR (95% CI) | P-value | No | Person-year | IRR (95% CI) | P-value |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| 1-3 | 86 | 310.60 | 0.71 (0.57, 0.87) | 0.002 | 29 | 134.10 | 0.75 (0.42, 0.87) | 0.010 |
| 4-7 | 118 | 161.45 | 1.87 (1.55, 2.24) | <0.001 | 62 | 66.93 | 2.14 (2.06, 3.42) | <0.001 |
| 8-14 | 90 | 160.14 | 1.44 (1.16, 1.77) | 0.001 | 43 | 61.86 | 1.63 (1.47, 2.70) | <0.001 |
| 15-30 | 48 | 182.12 | 0.67 (0.50, 0.88) | 0.006 | 18 | 62.64 | 0.67 (0.50, 1.28) | 0.426 |
| 31-90 | 43 | 166.93 | 0.65 (0.47, 0.87) | 0.006 | 8 | 52.21 | 0.60 (0.20, 0.83) | 0.022 |
| >90 | 24 | 77.79 | 0.81 (0.52, 1.22) | 0.347 | 2 | 19.20 | 0.76 (0.05, 0.92) | 0.082 |

No, number; IRR, incidence rate ratio; CI, confidence interval; LTRA, leukotriene receptor antagonist
Supplementary Table S5. Risk of neuropsychiatric events in relation to leukotriene receptor antagonist use in patients with asthma or allergic rhinitis according to type of leukotriene receptor antagonist

| Variable                        | Montelukast          | Pranlukast           |
|---------------------------------|----------------------|----------------------|
|                                 | No of | Person-year | IRR (95% CI) | P-value | No of | Person-year | IRR (95% CI) | P-value |
| 16,114                          | 37,889.88          | 1                    | 2,730      | 65,995.5 | 1     |
| Unexposed                       | 16,114  | 37,889.88 | 1.07 (0.96, 1.18) | 0.210  | 57    | 95.22      | 1.81 (1.36, 2.36) | <0.001 |
| Exposed 1-3                     | 83     | 313.00   | 0.72 (0.58, 0.89) | 0.003  | 12    | 38.69      | 0.91 (0.51, 1.60) | 0.735  |
| Exposed 4-7                     | 122    | 164.19   | 2.03 (1.68, 2.42) | <0.001 | 22    | 16.83      | 3.92 (2.56, 6.02) | <0.001 |
| Exposed 8-14                    | 91     | 162.92   | 1.54 (1.24, 1.88) | <0.001 | 16    | 14.68      | 3.34 (2.02, 5.52) | <0.001 |
| Exposed 15-30                   | 53     | 185.87   | 0.78 (0.59, 1.02) | 0.077  | 5     | 12.93      | 1.18 (0.48, 2.86) | 0.720  |
| Exposed 31-90                   | 45     | 171.67   | 0.72 (0.53, 0.96) | 0.034  | 2     | 9.05       | 0.68 (0.17, 2.79) | 0.592  |
| Exposed >90                     | 22     | 80.23    | 0.79 (0.49, 1.20) | 0.296  | 0     | 3.05       | NA         | NA     |

No, number; IRR, incidence rate ratio; CI, confidence interval; LTRA, leukotriene receptor antagonist
Supplementary Table S6. Risk of neuropsychiatric events in relation to leukotriene receptor antagonist use in patients with asthma or allergic rhinitis according to sex

| Variable                     | Male                  |                   | Female                |                   |
|------------------------------|-----------------------|-------------------|-----------------------|-------------------|
|                              | No of events | Person-year | IRR (95% CI) | P-value | No of events | Person-year | IRR (95% CI) | P-value |
| Unexposed                    | 8,560       | 20806.96    | 1             |         | 12,468       | 28739.93    | 1             |         |
| Exposed                      | 280         | 730.54      | 1.07 (0.94, 1.22) | 0.266    | 291         | 725.44      | 1.04 (0.91, 1.17) | 0.567   |
| Time since initiation of LTRA (days) |          |              |               |         |              |              |               |         |
| 1-3                          | 61          | 197.31      | 0.86 (0.66, 1.10) | 0.257    | 54          | 247.39      | 0.56 (0.42, 0.72) | <0.001 |
| 4-7                          | 70          | 111.79      | 1.75 (1.37, 2.21) | <0.001   | 110         | 116.59      | 2.41 (1.98, 2.90) | <0.001 |
| 8-14                         | 71          | 116.31      | 1.69 (1.32, 2.13) | <0.001   | 62          | 105.68      | 1.51 (1.16, 1.93) | 0.001   |
| 15-30                        | 34          | 130.64      | 0.71 (0.50, 0.98) | 0.051    | 32          | 114.12      | 0.72 (0.50, 1.01) | 0.068   |
| 31-90                        | 27          | 122.05      | 0.60 (0.40, 0.87) | 0.010    | 24          | 97.10       | 0.63 (0.41, 0.93) | 0.029   |
| >90                          | 17          | 52.43       | 0.95 (0.55, 1.54) | 0.851    | 9           | 44.56       | 0.51 (0.24, 0.96) | 0.057   |

No, number; IRR, incidence rate ratio; CI, confidence interval; LTRA, leukotriene receptor antagonist
**Supplementary Table S7. Risk of neuropsychiatric events in relation to leukotriene receptor antagonist use in patients with severe asthma according to type of observation period**

| Variable | Total period | Obs period 1 | Obs period 2 |
|----------|--------------|--------------|--------------|
|          | No of events | Person-year  | IRR (95% CI) | P-value | No of events | Person-year | IRR (95% CI) | P-value | No of events | Person-year | IRR (95% CI) | P-value |
| Unexposed| 21028        | 49546.89     | 1            |          | 5294        | 12519.69     | 1            |          | 15734        | 37027.20     | 1            |          | 0.047   |
| Exposed  | 571          | 1455.98      | 1.05 (0.96, 1.15) | 0.266   | 130         | 371.49       | 0.88 (0.73, 1.06) | 0.185   | 441         | 1084.50      | 1.11 (1.00, 1.22) | 0.047   |

**Time since initiation of LTRA (days)**

|          | No of events | Person-year  | IRR (95% CI) | P-value | No of events | Person-year | IRR (95% CI) | P-value | No of events | Person-year | IRR (95% CI) | P-value |
|----------|--------------|--------------|--------------|---------|--------------|--------------|--------------|---------|--------------|--------------|--------------|---------|
| 1-3      | 6            | 21.77        | 0.63 (0.25, 1.3) | 0.269   | 5            | 13.93        | 0.80 (0.28, 1.74) | 0.616   | 1            | 7.85         | 0.30 (0.02, 1.36) | 0.236   |
| 4-7      | 10           | 15.41        | 1.48 (0.73, 2.63) | 0.228   | 5            | 9.98         | 1.09 (0.39, 2.4)  | 0.843   | 5            | 5.43         | 2.19 (0.77, 4.83) | 0.087   |
| 8-14     | 10           | 19.54        | 1.18 (0.59, 2.11) | 0.604   | 7            | 12.44        | 1.24 (0.52, 2.45) | 0.584   | 3            | 7.10         | 1.04 (0.26, 2.76) | 0.944   |
| 15-30    | 8            | 26.98        | 0.69 (0.31, 1.31) | 0.304   | 5            | 15.96        | 0.69 (0.24, 1.53) | 0.424   | 3            | 11.03        | 0.68 (0.17, 1.80) | 0.505   |
| 31-90    | 9            | 31.49        | 0.66 (0.31, 1.23) | 0.231   | 6            | 16.73        | 0.77 (0.30, 1.63) | 0.535   | 3            | 14.77        | 0.52 (0.13, 1.40) | 0.267   |
| >90      | 5            | 18.00        | 0.65 (0.22, 1.52) | 0.377   | 2            | 7.50         | 0.60 (0.09, 2.07) | 0.494   | 3            | 10.51        | 0.78 (0.18, 2.31) | 0.697   |

No, number; IRR, incidence rate ratio; CI, confidence interval; LTRA, leukotriene receptor antagonist
Supplementary Table S8. Risk of neuropsychiatric events in relation to leukotriene receptor antagonist use in patients with asthma or allergic rhinitis, allowing for a 3-month interval between events.

| Variable                  | Total period | Obs period 1 | Obs period 2 |
|---------------------------|--------------|--------------|--------------|
|                           | No of events | Person-year  | IRR (95% CI) | P-value | No of events | Person-year  | IRR (95% CI) | P-value |
| Unexposed                 | 24240        | 49546.89     | 1            |         | 6,079        | 12519.69     | 1            |         | 18,161      | 37027.20 | 1 |
| Exposed                   | 680          | 1455.98      | 0.92 (0.85, 0.99) | 0.038   | 148          | 371.49       | 0.81 (0.68, 0.96) | 0.015   | 532          | 1084.50  | 1.02 (0.93, 1.12) | 0.663 |
| Time since initiation of LTRA (days) |             |              |              |         |              |              |              |         |              |          |               |    |
| 1-3                       | 139          | 444.70       | 0.62 (0.53, 0.73) | <0.001  | 32           | 107.86       | 0.60 (0.42, 0.84) | 0.004   | 107          | 336.85  | 0.67 (0.55, 0.81) | <0.001 |
| 4-7                       | 193          | 228.38       | 1.68 (1.45, 1.93) | <0.001  | 32           | 57.92        | 1.12 (0.77, 1.56) | 0.540   | 161          | 170.46  | 1.99 (1.69, 2.32) | <0.001 |
| 8-14                      | 147          | 221.99       | 1.31 (1.11, 1.54) | 0.001   | 31           | 61.66        | 1.03 (0.70, 1.44) | 0.892   | 116          | 160.33  | 1.51 (1.25, 1.81) | <0.001 |
| 15-30                     | 81           | 244.77       | 0.64 (0.51, 0.80) | <0.001  | 25           | 68.13        | 0.74 (0.48, 1.08) | 0.144   | 56           | 176.64  | 0.65 (0.49, 0.83) | 0.001 |
| 31-90                     | 69           | 219.15       | 0.59 (0.46, 0.75) | <0.001  | 18           | 53.61        | 0.66 (0.40, 1.03) | 0.088   | 51           | 165.54  | 0.61 (0.46, 0.80) | 0.001 |
| >90                       | 51           | 96.99        | 1.00 (0.73, 1.33) | 0.99    | 10           | 22.30        | 0.99 (0.48, 1.04) | 0.975   | 41           | 74.69   | 1.11 (0.79, 1.54) | 0.528 |

No, number; IRR, incidence rate ratio; CI, confidence interval; LTRA, leukotriene receptor antagonist.
Supplementary Table S9. Risk of neuropsychiatric events in relation to leukotriene receptor antagonist use in patients with asthma or allergic rhinitis according to age groups, allowing for a 3-month interval between events

| Variable                        | Children (3–11 years) | Adolescent (12–18 years) | Young adult (19–30 years) |
|--------------------------------|-----------------------|--------------------------|---------------------------|
|                                 | No of events | Person-year | IRR (95% CI) | P-value | No of events | Person-year | IRR (95% CI) | P-value | No of events | Person-year | IRR (95% CI) | P-value |
| Unexposed                       | 2,759       | 6393.79     | 1            |         | 3872        | 8101.20     | 1            |         | 17,609       | 35051.90     | 1            |         |
| Exposed                         | 122         | 378.82      | 0.63 (0.52, 0.76) | <0.001 | 138         | 251.11      | 1.13 (0.94, 1.36) | 0.172 | 420         | 826.05       | 1.02 (0.92, 1.12) | 0.768 |
| Time since initiation of LTRA (days) |           |                  |                     |         |              |                     |             |         |              |                     |             |
| 1-3                             | 15          | 107.73       | 0.29 (0.17, 0.47) | <0.001 | 32          | 71.96       | 0.90 (0.62, 1.26) | 0.557 | 92          | 265.02       | 0.70 (0.57, 0.86) | 0.001 |
| 4-7                             | 25          | 58.84        | 0.88 (0.57, 1.27) | 0.510  | 33          | 37.69       | 1.81 (1.26, 2.52) | 0.001 | 135         | 131.86       | 2.05 (1.72, 2.42) | <0.001 |
| 8-14                            | 28          | 62.37        | 0.90 (0.61, 1.29) | 0.601  | 32          | 36.83       | 1.81 (1.25, 2.53) | 0.001 | 87          | 122.80       | 1.41 (1.13, 1.73) | 0.002 |
| 15-30                           | 22          | 68.37        | 0.62 (0.39, 0.93) | 0.028  | 17          | 41.68       | 0.83 (0.49, 1.30) | 0.441 | 42          | 134.72       | 0.61 (0.44, 0.82) | 0.002 |
| 31-90                           | 18          | 60.57        | 0.55 (0.33, 0.85) | 0.013  | 16          | 40.94       | 0.76 (0.44, 1.22) | 0.296 | 35          | 117.63       | 0.57 (0.40, 0.79) | 0.001 |
| >90                             | 14          | 20.94        | 1.24 (0.67, 2.13) | 0.460  | 8           | 22.01       | 0.78 (0.34, 1.56) | 0.518 | 29          | 54.03        | 1.03 (0.68, 1.51) | 0.871 |

No, number; IRR, incidence rate ratio; CI, confidence interval; LTRA, leukotriene receptor antagonist
Supplementary Figure S1. Histogram of time intervals from leukotriene receptor antagonist prescription date to neuropsychiatric event

Observation 1

Observation 2
REFERENCE

1. Farrington, P., Whitaker, H., & Weldeselassie, Y.G. (2018). Self-Controlled Case Series Studies: A Modelling Guide with R (2nd ed.). Chapman and Hall/CRC