

Supplementary Material

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

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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 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

R44.8 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
- F98.8 onset usually occurring in
childhood and adolescence
- Unspecified behavioural and emotional disorders with onset
- F98.9 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
- F62 Enduring personality changes, not attributable to brain damage 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
- F66 Psychological and behavioural disorders associated with sexual development and orientation
- 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
- F68.1 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

- F94 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
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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)												

1-3	8	64.06	0.31 (0.14, 0.59)	0.001	18	59.39	0.79 (0.48, 1.23)	0.335	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	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	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	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	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	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 Person	IRR (95% CI)	P-value	No of Person	IRR (95% CI)	P-value	No of Person	IRR (95% CI)	P-value	No of Person	IRR (95% CI)	P-value	No of Person	IRR (95% CI)	P-value	No of Person	IRR (95% CI)	P-value	No of Person	IRR (95% CI)	P-value
Observation period 1																					
Unexposed	97	211.09	1	1,277	2752.8	3	3,057	6804.5	0	1,916	4177.9	1	745	1811.5	8	106	216.11	1	78	170.05	1
Exposed	2	7.76	(0.09, 0.440)	34	80.23	(0.69, 0.944)	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)
		1.90)			1.44)			1.24)			0.91)			1.02)			3.78)			2.10)	
Time since initiation of LTRA (days)																					
1-3	0	1.87	NA	6	21.59	(0.25, 0.285)	13	53.48	(0.33, 0.071)	12	31.56	(0.48, 0.701)	8	26.37	(0.31, 0.307)	1	1.86	(0.20, 0.697)	0	1.76	NA
		1.81			1.78			1.55			1.51)			1.03			2.57			2.05	
4-7	1	1.22	(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)
		13.28)			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	1.34	NA	11	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)	

			1.38			0.61			0.88			0.36			0.64			1.83						
15-30	1	1.64	(0.18, 0.752	4	15.40	(0.19, 0.332	11	32.07	(0.45, 0.666	3	19.56	(0.09, 0.076	6	20.59	(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	0	1.57	NA NA	3	13.23	(0.13, 0.298	9	27.08	(0.40, 0.635	5	17.42	(0.22, 0.313	5	13.61	(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	0.12	NA NA	1	5.71	(0.02, 0.436	5	14.58	(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	369	757.61	1	4,021	8367.3	1	10,051	22319.	1	7,057	15805.	1	621	1393.5	1	692	1440.2	1	173	331.17	1			
				5				33			4			5			1							
			1.40			1.20			1.01			0.99			0.79			1.15					1.33	
Exposed	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)

			0.74			0.78			0.52			0.87			0.47			0.48					1.39	
0-3	2	7.23	(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			1.13			2.50						
4-7	1	4.52	(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)						

			3.43			2.19			1.58			1.34			1.13			1.65			3.60
8-14	6	5.1	(1.33, 0.004	38	43.47	(1.55, <0.001	53	85.20	(1.19, 0.001	40	77.23	(0.96, 0.070	5	10.81	(0.40, 0.792	5	7.32	(0.59, 0.270	3	2.06	(1.11, 0.032
			7.21)			2.99)			2.06)			1.81)			2.46)			3.61)			11.6)
			0.47			1.08			0.77			0.52			0.19			1.05			1.30
15-30	1	6.34	(0.03, 0.450	22	51.71	(0.69, 0.708	29	95.46	(0.52, 0.161	17	83.59	(0.31, 0.007	1	12.85	(0.01, 0.097	4	9.22	(0.32, 0.923	1	1.92	(0.18, 0.797
			2.11)			1.62)			1.09)			0.81)			0.84)			2.49)			9.50)
			2.47			0.71			0.47			0.54			1.27			0.75			1.04
31-90	5	6.97	(0.85, 0.059	15	54.72	(0.41, 0.200	16	87.13	(0.27, 0.003	16	76.24	(0.31, 0.014	7	13.57	(0.53, 0.546	3	10.73	(0.18, 0.632	1	2.41	(0.14, 0.971
			5.72)			1.15)			0.74)			0.85)			2.56)			2.03)			7.82)
			0.92			0.49			0.57			0.55			1.16			1.30			
>90	1	4.42	(0.05, 0.935	5	28.79	(0.17, 0.123	9	43.06	(0.26, 0.107	7	30.20	(0.23, 0.130	2	4.47	(0.19, 0.839	3	7.04	(0.30, 0.681	0	1.94	NA NA
			4.78)			1.1)			1.07)			1.11)			3.98)			3.97)			

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)								
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 events	Person-year	IRR (95% CI)	P-value	No of events	Person-year	IRR (95% CI)	P-value
Unexposed	16,114	37889.88	1		2,730	6599.50	1	
Exposed	416	1077.87	1.07 (0.96, 1.18)	0.210	57	95.22	1.81 (1.36, 2.36)	<0.001
Time since initiation of LTRA (days)								
1-3	83	313.00	0.72 (0.58, 0.89)	0.003	12	38.69	0.91 (0.51, 1.60)	0.735
4-7	122	164.19	2.03 (1.68, 2.42)	<0.001	22	16.83	3.92 (2.56, 6.02)	<0.001
8-14	91	162.92	1.54 (1.24, 1.88)	<0.001	16	14.68	3.34 (2.02, 5.52)	<0.001
15-30	53	185.87	0.78 (0.59, 1.02)	0.077	5	12.93	1.18 (0.48, 2.86)	0.720
31-90	45	171.67	0.72 (0.53, 0.96)	0.034	2	9.05	0.68 (0.17, 2.79)	0.592
>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		5,294	12519.69	1		15,734	37027.20	1	
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)												
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	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

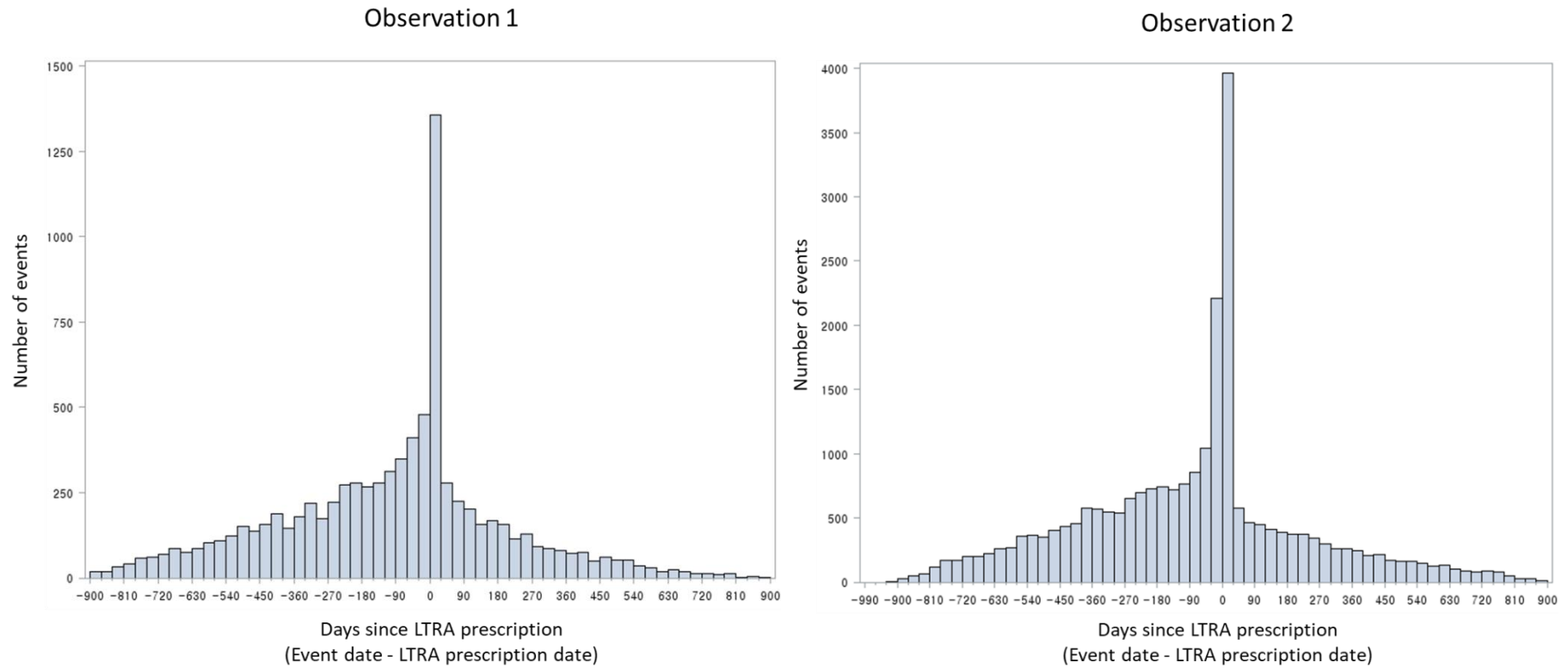
No, number; IRR, incidence rate ratio; CI, confidence interval; LTRA, leukotriene receptor antagonist

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



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