Neuropsychiatric events associated with montelukast in patients with asthma: a systematic review

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SUPPLEMENTARY MATERIAL 1. Search strategy and outcome definitions

Studies included in this systematic review were searched and identified on 7 September 2022. Literature search was conducted using databases including Pubmed, EMBASE and Cochrane Library.

Search terms included in PubMed

((“Montelukast” [Supplementary Concept] OR “Montelukast” [All Fields] OR “singulair” [All Fields]) OR (“leukotriene-modifying agents” [All Fields]) OR ((leukotrienes [MeSH Terms] OR leukotriene [All Fields]) AND “modifying” [All Fields] AND “agents” [All Fields]) OR (“leukotriene antagonist” [All Fields]) OR ((“leukotrienes” [MeSH Terms] OR “leukotriene” [All Fields]) AND “antagonist” [All Fields]) OR (“leukotriene antagonists” [All Fields]) OR ((“leukotrienes” [MeSH Terms] OR “leukotriene” [All Fields]) AND “antagonists” [All Fields]) OR (“leukotriene antagonists” [Pharmacological Action]) OR (“leukotriene” [All Fields] AND “receptor” [All Fields] AND “antagonist” [All Fields]) OR (“Receptors, Leukotriene” [MeSH Terms] AND “antagonist” [All Fields]) OR (((“Receptors, Leukotriene” [MeSH Terms]) OR (“receptor” [All Fields] AND “leukotriene” [All Fields]) OR “leukotriene receptor” [All Fields]) AND “blocker” [All Fields])) AND (“neuropsychiatric” [All Fields] OR “psychiatry” [MeSH Terms] OR “psychiatry” [All Fields] OR “psychiatric” [All Fields] OR “mental” [All Fields] OR “mental disorders” [All Fields] OR (“mental” [All Fields] AND “disorders” [All Fields]) OR “mental disorders” [MeSH Terms] OR “psychiatric disease” [All Fields] OR (psychiatric [All Fields] AND disease [All Fields]) OR “psychiatric illness” [All Fields] OR (psychiatric [All Fields] AND illness [All Fields]) OR “psychiatric diagnosis” [All Fields] OR (psychiatric [All Fields] AND diagnosis [All Fields]) OR adverse [All Fields] OR schizophrenia [MeSH Terms] OR schizophrenia [All Fields] OR (“schizophrenic” [All Fields] AND “disorder” [All Fields]) OR “bipolar disorder” [MeSH Terms] OR “bipolar disorder” [All Fields] OR (bipolar [All Fields] AND disorder [All Fields]) OR “bipolar disorders” [All Fields] OR (bipolar [All Fields] AND disorders [All Fields]) OR mania [All Fields] OR depression [MeSH Terms] OR depression [All Fields] OR “depressive disorder” [MeSH Terms] OR “depressive disorder” [All Fields] OR (depressive [All Fields] AND disorder [All Fields]) OR “depressive disorders” [All Fields] OR (depressive [All Fields] AND disorders [All Fields]) OR “mood disorders” [MeSH Terms] OR “mood disorders” [All Fields] OR “mood disorder” [All Fields] OR (mood [All Fields] AND disorder [All Fields]) OR (mood [All Fields] AND disorders [All Fields]) OR “psychotic disorders” [MeSH Terms] OR (“psychotic disorders” [All Fields]) OR (“psychotic” [All Fields] AND “disorders” [All Fields]) OR (“psychotic disorder” [All Fields]) OR (“psychotic” [All Fields] AND “disorder” [All Fields]) OR psychosis [All Fields] OR confusion [MeSH Terms] OR confusion [All Fields] OR anxiety [MeSH Terms] OR anxiety [All Fields] OR “anxiety disorders” [MeSH Terms] OR “anxiety disorders” [All Fields] OR (anxiety [All Fields] AND disorders [All Fields]) OR “anxiety disorder” [All Fields] OR (anxiety [All Fields] AND disorder [All Fields]) OR nervousness [All Fields] OR (“Stress” [Journal] OR “stress” [All Fields]) OR “personality disorders” [MeSH Terms] OR “personality disorders” [All Fields] OR (personality [All Fields] AND disorders [All Fields]) OR “personality disorder” [All Fields] OR (personality [All Fields] AND disorder [All Fields]) OR sleep [MeSH Terms] OR sleep [All Fields] OR “sleep-wake transition disorders” [MeSH Terms] OR “sleep-wake transition disorders” [All Fields] OR “sleep arousal disorders” [MeSH Terms] OR “sleep arousal disorders” [All Fields] OR “sleep stages” [MeSH Terms] OR “sleep stages” [All Fields] OR (sleep [All Fields] AND stage [All Fields]) OR “sleep wake disorders” [MeSH Terms] OR “sleep wake disorders” [All Fields] OR (sleep [All Fields] AND wake [All Fields] AND disorders [All Fields]) OR “sleep initiation and maintenance disorders” [MeSH Terms] OR (sleep [All Fields] AND initiation [All Fields] AND maintenance [All Fields] AND disorders [All Fields]) OR insomnia [All Fields] OR somnolence [All Fields] OR parasomnia [All Fields] OR “night terrors” [MeSH Terms] OR “night terrors” [All Fields] OR nightmare [All Fields] OR dreams [MeSH Terms] OR dreams [All Fields] OR aggression [MeSH Terms] OR aggression [All Fields] OR aggressiveness [All Fields] OR hostility [MeSH Terms] OR hostility [All Fields] OR hostile [All Fields] OR “psychomotor agitation” [MeSH Terms] OR “psychomotor agitation” [All Fields] OR (psychomotor [All Fields] AND agitation [All Fields]) OR agitation [All Fields] OR restlessness [All Fields] OR disorientation [All Fields] OR hyperkinesis [MeSH Terms] OR hyperkinesis [All Fields] OR hyperactivity [All Fields] OR “problem behavior” [MeSH Terms] OR “problem behavior” [All Fields] OR (problem [All Fields] AND behavior [All Fields]) OR behavior [MeSH Terms] OR behaviour [All Fields] OR “behavioural disorders” [All Fields] OR (behavioural [All Fields] AND disorder [All Fields]) OR “irritable mood” [MeSH Terms] OR “irritable mood” [All Fields] OR (irritable [All Fields] AND mood

[All Fields]) OR “irritability” [All Fields] OR suicide [MeSH Terms] OR suicide [All Fields] OR “suicidal ideation” [MeSH Terms] OR “suicidal ideation” [All Fields] OR (suicidal [All Fields] AND ideation [All Fields]) OR “suicidal behaviour” [All Fields] OR (suicidal [All Fields] AND behaviour [All Fields]) OR self-harm [All Fields] OR self-injury [All Fields] OR hallucinations [MeSH Terms] OR hallucinations [All Fields] OR hallucination [All Fields] OR delusions [MeSH Terms] OR delusions [All Fields] OR delusion [All Fields] OR vertigo [MeSH Terms] OR vertigo [All Fields] OR “speech disorders” [MeSH Terms] OR “speech disorders” [All Fields] OR (speech [All Fields] AND disorders [All Fields]) OR “disruptive, impulse control, and conduct disorders” [MeSH Terms] OR “disruptive, impulse control, and conduct disorders” [All Fields] OR (disruptive [All Fields] AND impulse [All Fields] AND control [All Fields] AND conduct [All Fields] AND disorders [All Fields]) OR “impulse control disorders” [All Fields] OR (impulse [All Fields] AND control [All Fields] AND disorders [All Fields]) OR violence [MeSH Terms] OR violence [All Fields] OR “attention deficit disorder with hyperactivity” [MeSH Terms] OR “attention deficit disorder with hyperactivity” [All Fields] OR adhd [All Fields] OR “attention deficit disorder” [All Fields] OR (attention [All Fields] AND deficit [All Fields] AND disorder [All Fields]) OR “cognitive dysfunction” [MeSH Terms] OR “cognitive dysfunction” [All Fields] OR (cognitive [All Fields] AND dysfunction [All Fields]) OR “cognitive impairment” [All Fields] OR (cognitive [All Fields] AND impairment [All Fields]) OR “memory disorders” [MeSH Terms] OR “memory disorders” [All Fields] OR (memory [All Fields] AND disorders [All Fields]) OR “memory loss” [All Fields] OR (memory [All Fields] AND loss [All Fields]) OR “memory disorder” [All Fields] OR (memory [All Fields] AND disorder [All Fields]) OR amnesia [MeSH Terms] OR amnesia [All Fields] OR seizures [MeSH Terms] OR seizures [All Fields] OR tremor [MeSH Terms] OR tremor [All Fields])

Searching Terms in EMBASE

1	**montelukast**
2	singulair
3	leukotriene modifying
4	leukotriene antagonist
5	leukotriene receptor antagonist
6	leukotriene receptor blocker
7	LTMA
8	LTRA
9	psychiatric
10	neuropsychiatric
11	mental
12	schizophrenia
13	bipolar
14	mania
15	mood disorder
16	depression
17	psychotic disorder
18	psychosis
19	confusion
20	anxiety
21	stress
22	personality disorder
23	sleep disorder
24	insomnia
25	somnolence
26	parasomnia
27	nightmare
28	dream
29	aggression
30	aggressiveness

31	hostility
32	psychomotor agitation
33	restlessness
34	disorientation
35	hyperkinesis
36	hyperactivity
37	behavioural disorder
38	behavior
39	irritability
40	suicide
41	suicidal
42	self-harm
43	self-injury
44	hallucination
45	delusion
46	vertigo
47	speech disorder
48	impulse control disorder
49	violence
50	attention deficit disorder
51	cognitive impairment
52	memory loss
53	memory disorder
54	amnesia
55	seizure
56	tremor
57	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
58	9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56
59	57 and 58

60	limit 59 to human

Search Terms for Cochrane Library

(montelukast OR singulair OR leukotriene-modifying agents OR leukotriene receptor antagonist OR leukotriene antagonist OR leukotriene receptor blocker OR leukotriene inhibitor) AND (neuropsychiatric OR psychiatry OR psychiatric OR mental disorder OR psychiatric disease OR psychiatric illness OR psychiatric diagnosis OR schizophrenia OR schizophrenic disorder OR bipolar OR bipolar disorder OR mania OR depression OR depressive disorder OR mood disorder OR psychotic disorder OR psychosis OR confusion OR anxiety OR anxiety disorders OR stress OR nervousness OR personality disorder OR sleep OR sleep-wake transition disorders OR sleep arousal disorders OR sleep stages OR sleep wake disorders OR insomnia OR somnolence OR parasomnia OR night terrors OR nightmare OR dreams OR aggression OR aggressiveness OR hostility OR psychomotor agitation OR agitation OR restlessness OR disorientation OR hyperkinesis OR hyperactivity OR problem behavior OR behavioural disorders OR behavior OR irritable mood OR irritability OR suicide OR suicidal ideation OR suicidal behaviour OR self-harm OR self-injury OR hallucination OR delusion OR vertigo OR speech disorders OR ADHD OR disruptive impulse control conduct disorders OR impulse control disorders OR violence OR attention deficit disorder hyperactivity OR attention deficit disorder OR hyperactivity OR ADHD OR cognitive dysfunction OR cognitive impairment OR memory disorders OR memory loss OR memory disorder OR amnesia OR seizure OR tremor)

Terminologies defined as NEs in this review

Neuropsychiatric Events	Terminologies included in this review
Events listed in montelukast FDA product label	
Neuropsychiatric Events	neuropsychiatric events, neuropsychiatric adverse drug reactions, neuropsychiatric disturbances, psychiatric events, psychiatric adverse drug reactions, psychiatric disturbances, psychiatric disorders, psychiatric diseases, psychiatric illness, mental disorders
Agitation	agitation, psychomotor agitation
Aggressive Behaviour / Hostility	aggression, aggressiveness, aggressive behaviour, hostility, hostile, violence
Anxiousness	anxiety, anxiety disorders, nervousness, excitation
Depression	depression, depressive disorders, mood disorders
Disorientation	disorientation
Dream Abnormalities	night terrors, nightmares, dreams, abnormal dreams
Hallucinations	hallucinations
Insomnia	sleep-wake transition disorders, sleep arousal disorders, sleep stages, sleep wake disorders, sleep initiation and maintenance disorders, insomnia, sleep disorders, sleep disturbances
Irritability	irritable mood, irritability
Restlessness	restlessness, hyperkinesis
Somnambulism	parasomnia
Suicidal thinking and behavior (including suicide)	suicide, completed suicide, suicidal events, suicidal ideation, suicidal behaviour, suicidal attempts, self-harm, self-injury
Tremor	tremor
Drowsiness	somnolence, excessive sleepiness
Seizures	seizures, epilepsy
Events not listed in montelukast FDA product label	
Attention-deficit/hyperactivity disorders	hyperactivity, attention deficit disorder with hyperactivity, ADHD, attention deficit disorder
Bipolar disorders	bipolar disorder, mania
Psychosis	psychotic disorders, psychosis
Confusion	confusion, delusions, vertigo

Abnormal behaviour	personality disorders, problem behaviour, behavioural disorders
Speech disorders	speech disorders
Impulse control disorders	disruptive, impulse control and conduct disorders, impulse control disorders
Neurodegenerative diseases	cognitive dysfunction, cognitive impairment, memory disorders, memory loss, amnesia
Schizophrenia	schizophrenia, schizophrenic disorders

Grouping of Neuropsychiatric Events into broad definition of outcomes in this review

Outcome definitions in this review	Mapped neuropsychiatric events
Primary Outcomes	
Suicide-related outcomes	suicidal thinking and behavior (including suicide)
Depression-related outcomes	depression, antidepressants prescription
Anxiety-related outcomes	Aggressive behaviour, anxiousness, anxiety, generalized anxiety, other anxiety
Sleeping disorders	dream abnormalities, insomnia, somnambulism, nightmare, hypersomnia, circadian rhythm disorder, prescription of sleeping medications
Neurodegenerative disease-related outcomes	cognitive dysfunction, cognitive impairment, memory disorders, memory loss, amnesia, dementia
Secondary Outcomes	
Other neuropsychiatric outcomes	neuropsychiatric events listed above, but not classified in in primary outcomes

SUPPLEMENTARY MATERIAL 2. Data extraction strategy under the PICO tool

PICO Tool Element	Description
Population	Patients who have a diagnosis for asthma upon receiving the first prescription of montelukast, with or without allergic rhinitis. In prescription databases which diagnoses cannot be ascertained, prescriptions for drugs used in asthma will be used a proxy for asthma diagnosis.
Intervention	Use of montelukast
Comparison	Non-users of montelukast, including placebo, inhaled corticosteroids, or inhaled corticosteroids plus long-acting beta-agonists combinations
Outcome	<u>Primary Outcomes</u> Suicide-related outcomes, depression-related outcomes, anxiety-related outcomes, sleeping disorders, neurodegenerative disease-related outcomes. <u>Secondary Outcomes</u> Other neuropsychiatric outcomes

SUPPLEMENTARY MATERIAL 3. Study characteristics of pharmacovigilance studies

Study	Publish Year	Study Period	Data Source	Inclusion Criteria	Exposure	Results and Outcomes
Shin et al. [1]	2022	Jan 2014-Dec 2018	Korean Adverse Event Reporting System	1. ADRs of montelukast and pranlukast	MTK or pranlukast	ADR reports related to MTK by gender (male / female) for: 1. psychiatric ADRs: 131; 0.067% / 278; 0.139% 2. somnolence: 62 / 135 3. insomnia: 45 / 113
Fox et al. [2]	2022	2014	United States Veterans Affairs Corporate Data Warehouse	1. Ratio of patients with incident NE detected within the year post- to pre- MTK initiation (expressed as SR)	MTK	SR between MTK initiation and: 1. incident NE: 0.84 (0.80-0.89) 2. incident antidepressant prescription: 0.75 (0.68-0.83)
Watson et al. [3]	2022	Up to 3 May 2020	VigiBase from the WHO	1. Reports of nightmares with MTK	MTK	Disproportionality analysis of nightmare reports based on: 1. reports (reported / expected): 1118 / 44 2. IC value: 4.6
Umetsu et al. [4]	2021	Jan 2004-Dec 2018	FDA Adverse Event Reporting System	1. ADR reports related to MTK 2. MTK-associated genes retrieved from DGIdb	MTK	Reported ORs for: 1. abnormal behaviour: 33.9 (31.8-36.2) 2. aggression: 31.7 (29.8-33.8) 3. suicidal ideation: 21.5 (20.3-22.9) 4. suicidal attempts: 9.5 (8.5-10.5) 5. depression: 8.2 (7.8-8.7)
Neha et al. [5]	2021	2009-2013	FDA Adverse Event Reporting System	1. ADR reports for 4 quarters before and after safety alert change by FDA	31 drugs with label changes within study period, including MTK	Figures (before; after FDA label changes) 1. Number of ADRs (322; 274) 2. Reported OR (8.77; 3.35) 3. PRR (9.6; 3.41)
Bian et al. [6]	2021	2004-2020	FDA Adverse Event Reporting System	1. ADR events of neuropsychiatric symptoms 2. Disproportionality to LTRA reported as reported OR, PRR and IC values	LTRA, H1-antihistamines and ICS	Disproportionality of montelukast to neuropsychiatric symptoms measured by: 1. reported OR: 10.35 (10.00-10.70) 2. PRR: 7.21 3. IC Value: 2.84 Mean time to onset (interquartile range) of neuropsychiatric symptoms for 1. LTRA: 31 (1-306) days

Ekhart et al. [7]	2020	2003-2016	Netherlands Pharmacovigilance Center Lareb	1. All reports of children aged 1-18 years 2. Excluded reports of children < 1 years	MTK	1. Reports of psychiatric ADRs associated with MTK use: 40/918 (4%) 2. NEs reported: abnormal behavior, aggression, agitation, anxiety, irritability, restlessness
Arnold et al. [8]	2020	2000-2016	National Poison Data System of the American Association of Poison Control Centers	1. 5-17 years old 2. Single, weight-based, high-dose montelukast ingestions (≥ 50 mg)	MTK	1. 20 ADRs among 312 individuals with body weight available 2. Adjusted OR for increased ADR with increasing mg/kg doses ≥50 mg: 1.16 (0.97-1.38, p-value = 0.10)
Winkel et al. [9]	2018	2000-2016	Register of Medicinal Products Statistics; Danish National Patient Register; Danish Civil Registration System	1. All adults (≥18 years) who were Denmark residents during study period 2. Redeemed first prescription of MTK and antidepressants within 1-year interval	MTK / Antidepressants as proxy for depression	1. Crude SR between MTK initiation and antidepressant prescription afterwards: 1.99 (1.11-1.28) 2. Crude SR subgroup analysis for ICS patients: 1.27 (1.03-1.58) / LABA + ICS: 1.19 (1.04-1.37) / short-acting inhalation and nasal topical antiallergic treatment: 3.17 (1.46-9.69)
Haarman et al. [10]	2017	Up to July 2016	Netherlands Pharmacovigilance Center Lareb and VigiBase from the WHO	1. All ADRs of MTK reported in all ages 2. Grouped by 0-18 yo / > 19 yo	MTK	Reported OR for VigiBase / Lareb: 1. Depression: 6.93 (6.5-7.4) / 1.91 (0.8-4.6) 2. Aggression: 24.99 (23.5-26.6) / 9.27 (5.1-17.0) 3. Suicidal ideation: 20.4 (19.0-22.0) / - 4. Insomnia 5.08 (4.77-5.41) / 3.45 (2.05-5.81) 5. Anxiety 5.11 (4.79-5.46) / 2.79 (1.24-6.26) 6. Abnormal behavior: 34.05 (31.8-36.5) / 12.02 (5.6-25.6) 7. Nightmares: 22.46 (20.9-24.2) / 19.29 (12.8-29.2)
Arnold et al. [11]	2018	2000-2016	American Association of Poison Control Centers (AAPCC) National Poison Data System database	1. MTK users aged 5-17 years 2. Subgrouped by dose of exposure (≥ 50 mg / all ingested doses)	MTK	1. Most common ADR: abdominal pain (40/17069) 2. Neuropsychiatric ADR: 22/17069 (composite of confusion, dizziness or vertigo, hallucinations or delusions, slurred speech)
Aldea Perona et al. [12]	2016	Up to 1 January 2015	VigiBase from the WHO	1. Subjects < 18 years with MTK exposure 2. Subgrouped into infants (< 2 yo), children (2-11 yo) and adolescents (12-17 yo)	MTK	1. 2630 ICSRs were psychiatric disorders in 14670 of ICSR reported for MTK IC Values for suicidal behavior in 2. Aged 2-11: 5.01 3. Aged 12-18: 3.85 4. Aged above 18: 2.80

Lafay-Chebassier et al.[a] [13]	2015	2007-2011	French Pharmacovigilance Database (FPVD)	1. Reports of depression in the FPVD between study period	MTK	1. Reporting OR for MTK = 8.9 (3.3-24.3) [14]
Aagaard & Hansen [15]	2014	2007-2011	EudraVigilance database from the European Union	1. ADRs in children below 18 years and taking asthma medications	MTK	1. 31 reports of psychiatric disorders out of 76 cases reported for MTK 2. NEs reported: nightmare and aggression
Marchand et al. [16]	2013	1998-2012	French National Pharmacovigilance Database (BNPV)	1. ADRs of psychiatric disorders 2. Suspected to be related to MTK prescription	MTK	1. 56 ADRs (19%) are psychiatric disorders out of 295 ADRs reported in MTK 2. NEs reported: insomnia, nightmares, behavioral disorders, hallucination, depression (suicidal ideation, attraction to emptiness, total lack of desire)
Cereza et al. [17]	2012	Up to December 2011	Spanish System of Pharmacovigilance	1. Reports for psychiatric ADRs especially nightmares 2. Montelukast users	MTK	1. 24 reports of nightmare, age ranging from 2-66 years, age ranging from 2-66 years 2. Concomitant NEs other than nightmare: insomnia, nervousness, hallucinations, aggressiveness, irritability, anxiety
Bygdell et al. [18]	2012	2001-2010	Swedish Drug Information System (SWEDIS)	1. ICSRs registered during 2001-2010 2. Children < 18 years old 3. Psychiatric Disorder Class according to the term in Medical Product Agency adverse reaction terminology 4. Possible causal relationship between suspected drugs and reported ADR	MTK	1. 60 ICSRs of psychiatric disorders reported were linked with MTK 2. Most frequent NEs reported (by order): nightmares, aggressiveness, sleep disorders, anxiety, personality disorders, hyperactivity, depressed mood, irritability, hallucination
Schumock et al. [19]	2011	1999-2009	FDA Adverse Events Reporting System & Xponent database, IMS Health Incorporated	1. Initial reports of completed suicides 2. Reports in which montelukast/zafirlukast/zileuton was listed as the primary suspected, secondary suspected or concomitant drug 3. Reports involving SSRIs also examined	LTRA (MTK, zafirlukast, zileuton)	1. 101 (96%) cases of completed suicides related to MTK among 105 reports related to LTRAs 2. 96/105 (91%) of reports occurred in 2008 or 2009, when FDA warning was strengthened 3. Suicide rate for MTK (per million prescriptions): 0.06 (0.03-0.12) in 1999-2007, 1.83 (1.47-2.24) in 2008-2009 4. EB rate multiplier for MTK compared with SABA: 1.80 (1.48-2.18) in 1999-2009, 0.69 (0.44-1.08) in 1999-2007, 5.61 (4.56-6.89) in 2008-2009

Wallerstedt et al. [20]	2009	1998-2007	Swedish Drug Information System (SWEDIS)	1. ADRs of psychiatric disorders with MTK 2. Aged < 18 years	MTK	1. 44/103 (43%) of reports on MTK were psychiatric disorders 2. IC value for composite psychiatric disorders outcome: 2.51 ($95\%_{low}$: 2.14) 3. NEs reported with disproportionality (IC $95\%_{low}$ > 0): hyperreactivity, anxiety, nightmares, insomnia, aggressiveness
Brunlöf et al.[21]	2008	January to December 2005	Swedish Drug Information System (SWEDIS)	1. ICSRs reported to SWEDIS 2. Children aged < 15 years	MTK	1. 16 ICSRs reported were linked to montelukast 2. 12 out of 16 ICSRs were reported in children aged < 5 years old 3. NEs reported: nightmare, sleep disorders, anxiety, aggressiveness
Biswas et al. [22]	2001	February to December 1998	Drug Safety Research Unit	1. Reports of all event data collected from patient after prescriptions of MTK	MTK	1. 191 (1.2%) of patients reported ADRs 2. NEs reported: insomnia, depression, abnormal dreams

Abbreviations

ADR = adverse drug reactions; EB = Empirical Bayes; IC = information component (measure of disproportionality between expected and reported rates of ADR); ICS = inhaled corticosteroids; IC025 = lower 95% confidence interval for IC values; ICSRs = individual case safety reports; LABA = long-acting beta-agonists; LTRA = leukotriene receptor antagonists; MTK = montelukast; NE: neuropsychiatric events; OR = odds ratio; PRR = proportional reporting ratio; SABA = short-acting beta-agonists; SR = sequence ratio; SSRI = selective serotonin reuptake inhibitors; WHO = World Health Organization.

[a] Only abstract of the article can be accessed. Results of the study are extracted from another study.

SUPPLEMENTARY MATERIAL 4. Study characteristics of case reports

Study	Publish Year	Age (in years), Gender	Indication	Onset of NEs after therapy started (or withdrawal)	Concomitant Medications	NEs Reported; Prognosis
Els & Webb [23]	2022	5, M	Asthma	5 days (after withdrawal of MTK)	ICS	1. NEs reported: severe agitation and anxiety, nightmare, panic attack and auditory hallucinations
McCarter & Blanchard [24]	2017	56, M	Asthma	2-3 weeks	Fluticasone 100 mcg/salmeterol 50 mcg, albuterol HFA	1. NEs reported: worsening generalized anxiety, wake up suddenly after several hours of sleep, sympathetic activation, elevated heart rate, flushing, panic symptoms 2. Completely resolved in several months 3. The patient takes eicosapentaenoic acid as fish oil supplement
Erdem et al. [25]	2016	15, F	Asthma	3 days	Valproic acid, budesonide 400 mcg/day	1. NEs reported: seizures 2. Resolved when LTRA stopped 3. The patient uses valproic acid for epilepsy
Erdem et al. [25]	2016	6, F	Asthma	Unknown	Valproic acid	1. NEs reported: seizures 2. Resolved when LTRA discontinued
Celmeli et al. [26]	2014	13, M	Asthma	1 month	Fluticasone propionate 125 mcg BD	1. NEs reported: anxiety, suicidal attempt, sleepiness, depression 2. Resolved within 1 week after withdrawal
Ibarra-Barrueta et al. [27]	2014	41, F	Asthma (started MTK in 2011)	Days (after concomitant use of antiretrovirals with MTK)	Efavirenz, emitricitabine and TDF (HIV since 2007), ICS, formoterol, antihistamines	1. NEs reported: disturbed sleep, vivid dreams, irritability, confusion, difficulties with concentration 2. Resolved within 1 months after MTK discontinued
Alkhuja et al. [28]	2013	16, F	Relief for allergy-related symptoms	1 day	Fluticasone propionate 250 mcg/salmeterol 50 mcg, albuterol sulfate inhalers	1. NEs reported: daily parasomnias (sleeptalking and sleepwalking) 2. Resolved after MTK discontinued, re-challenge on MTK failed
Kocyigit et al. [29]	2013	13, M	Asthma	24-36 hours	Formoterol and budesonide inhaler, prednisolone (Asthma), thioridazine (hyperreactivity at 7 yo)	1. NEs reported: visual hallucinations, severe anxiety, insomnia 2. Hallucination resolved quickly after MTK discontinued

Byrne et al. [30]	2012	9, M	Asthma	2.5 years	Beclomethasone inhaler 50 mcg BD	1. NEs reported; difficulty sleeping, anxiety, sleepwalking 2. MTK was not withdrawn, resolved 7 months after onset
Skillman et al. [31]	2011	4, M	Asthma	5 months	Albuterol 2.5 mg nebulized mist every 4 to 6 hours as needed, cetirizine 5 mg daily	1. NEs reported: sleepwalking, night terrors, sleep disturbances, anxiety, irritability 2. Resolved in 2 weeks after discontinuation
Skillman et al. [31]	2011	6, F	Asthma	1-2 weeks[a]	Albuterol as needed	1. NEs reported: anxiety, sleeping disturbances 2. Resolved in 1 month after reduction in MTK dose
Anandan & Ibitoye [32]	2008	29, F	Asthma	Within 48 hours	Quetiapine 750 mg daily	1. NEs reported: hallucinations 2. Resolved after 2 days

Abbreviations

BD = twice daily; F = female; HIV = human immunodeficiency viruses; ICS = inhaled corticosteroids M = male; MTK = montelukast; NE = neuropsychiatric events; TDF = tenofovir disoproxil fumarate; yo = years old

[a] Dose of montelukast has been escalated from 4 mg to 5 mg 11 weeks before the patient seeks medical attention. The patient reported anxiety symptoms to start 2 months before the clinical visit.

SUPPLEMENTARY MATERIAL 5. Study characteristics of case series

Study	Publish Year	Number of Case Reports	Indication(s)	Inclusion Criteria	Key Findings
Lafuente et al. [33]	2021	20	Asthma / recurrent wheezing	1. Recurrent wheezing and/or asthma 2. Aged 0-15 yo	1. 20 (5.7%) of patients presented with ADRs 2. NEs reported: insomnia (n=7), hyperactivity (n=4), nightmares (n=3), hallucinations (n=1)
Erdem et al. [34]	2015	1024	Asthma / Early wheezing	1. Early wheezing or asthma (including episodic or mild persistent) 2. Only LTRA use as anti-inflammatory drug 3. No other concomitant medications 4. No ADRs before LTRA initiation and disappearance after discontinuation	1. 24 (59%) of ADRs are psychiatric Most commonly reported NEs: 1. Hyperactivity: 7 (17%) 2. Excessive sleepiness: 4 (9.7%) 3. Nyctophobia: 4 (9.7%) 4. Agitation: 4 (9.7%) 5. Hallucination: 4 (9.7%)
Xie et al. [35]	2013	19	Asthma	1. ADRs associated with MTK use in China 2. Inclusion period: 1999-2013	1. 5 (26%) of reported ADRs were psychiatric disorders 2. NEs reported: excitation (3 cases), sleeping disorders, inattention
Callero-Viera et al. [36]	2012	4	Asthma	Reports of children experiencing NE side effects	1. All reports contain aggressive behavior 2. Other NEs reported: behavioral disturbances, night terrors

Abbreviations

ADR = adverse drug reactions; LTRA = leukotriene receptor antagonists; MTK = montelukast; NE = neuropsychiatric events.

SUPPLEMENTARY MATERIAL 6. Newcastle-Ottawa Scale scores for cohort studies

Study	Publication Year	Selection				Comparability		Exposure			Total Quality Score
		Representativeness of exposed cohort	Representativeness of non-exposed cohort	Ascertainment of exposure	Demonstration that the outcome of interest was not present at start of study	Adjusted for asthma severity	Adjusted for demographics	Assessment of outcome	Was follow-up long enough for outcomes to occur?	Adequacy of follow up of cohorts	
Paljarvi et al. [37]	2022	0	0	1	0	1	1	1	1	0	**5**
Özata et al. [38]	2022	0	0	0	1	0	0	1	0	0	**2**
Shim et al. [39]	2021	1	1	1	1	0	1	1	1	1	**8**
Ishikura et al. [40]	2021	0	0	1	1	0	1	1	1	1	**6**
Xiong et al. [41]	2021	0	0	1	0	0	1	1	1	0	**5**
Grinde et al. [42]	2017	0	0	1	1	0	1	1	1	0	**5**
Sansing-Foster et al. [43]	2020	1	1	1	0	1	1	1	0	0	**6**
Bayer et al. [44]	2020	0	0	1	1	0	0	1	0	1	**4**
Huang et al.[45]	2020	0	0	1	1	1	1	1	1	1	**7**
Benard et al. [46]	2017	0	0	1	0	1	0	1	1	0	**4**
Chen et al. [47]	2014	1	1	1	0	0	1	1	1	1	**7**
Jick et al. [48]	2009	1	0	1	0	0	0	1	0	0	**3**

Key

A study can be awarded a maximum of one star for each numbered item within the Selection and Exposure categories. A maximum of two stars can be given for Comparability.

Selection

A) Representativeness of the exposed cohort

1) Truly or somewhat representative of the average population with asthma in the community

0) Selected group of users (e.g.: nurses, volunteers, patients in specific age groups) or no description of the derivation of the cohort

B) Selection of the non-exposed cohort

1) Drawn from the same community as the exposed cohort

0) Drawn from a different source or no description of the derivation of the non-exposed cohort

C) Ascertainment of exposure

1) Secure record (e.g.: surgical records) or structured interview

0) Written self-report or no description

D) Demonstration that outcome of interest was not present at start of study

1) Yes

0) No

Comparability

A) Comparability of cohorts on the basis of the design or analysis

1) Adjusted for severity of asthma

1) Adjusted for demographics

Outcome

A) Assessment of outcome

1) Independent blind assessment or record linkage

0) Self-report or no description

B) Was follow-up long enough for outcomes to occur

1) Followed-up for 1 year or above

0) Followed-up for less than 1 year

C) Adequacy of follow up of cohort

1) Complete follow up or subjects lost to follow up < 20%

0) Follow up rate < 80 % (select an adequate %) and no description of those lost or no statement

SUPPLEMENTARY MATERIAL 7. Newcastle-Ottawa scale scores for case-control studies

Study	Publication Year	Selection				Comparability		Exposure			Total Quality Score
		Adequacy of case definition	Representativeness of cases	Selection of controls	Definition of controls	Adjusted for asthma severity	Adjusted for demographics	Ascertainment of exposure	Same method of ascertainment for cases and controls	Non-response rate	
Kang et al. [49]	2021	0	1	1	1	0	1	1	1	1	**7**
Glockler-Lauf et al. [50]	2019	0	1	1	1	1	0	1	1	1	**7**
Ali et al. [51]	2015	0	1	1	1	1	1	1	1	1	**8**
Schumock et al. [52]	2012	0	1	1	1	1	1	1	1	1	**8**

Key

A study can be awarded a maximum of one star for each numbered item within the Selection and Exposure categories. A maximum of two stars can be given for Comparability.

Selection

A) Is the case definition adequate?

1) Yes with independent validation

0) Yes (e.g.: record linkage or based on self-reports) or no description

B) Representativeness of the cases

1) Consecutive or obviously representative series of cases

0) Potential for selection biases or not stated

C) Selection of Controls

1) Community controls

0) Hospital controls or no description

D) Definition of Controls

1) No history of neuropsychiatric events

0) No description of source

Comparability

A) Comparability of cases and controls on the basis of the design or analysis

1) Adjusted for asthma severity

1) Adjusted for demographics

Exposure

A) Ascertainment of exposure

1) Secure record (e.g.: surgical records) or structured interview were blind to case/control status

0) Interview not blinded to case/control status, written self-report or medical record only or no description

B) Same method of ascertainment for cases and controls

1) Yes

0) No

C) Non-Response rate

1) Same rate for both groups

0) Non respondents described or rate different and no designation

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