Supplementary material: Neuropsychiatric Events Associated with Leukotriene-modifying Agents: A Systematic Review

Sharon W. Y. Law[1], Angel Y. S. Wong[1], Shweta Anand[1], Ian C. K. Wong[1,2], Esther W. Y. Chan[1]

Affiliations

[1]Centre for Safe Medication Practice and Research, Department of Pharmacology and Pharmacy, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Office 02-08, 2/F Laboratory Block, 21 Sassoon Road, Hong Kong SAR, China

[2]Research Department of Practice and Policy, School of Pharmacy, University College London, 29-39 Brunswick Square, London WC1N 1AX, United Kingdom

Corresponding Author

Esther W. Y. Chan

Centre for Safe Medication Practice and Research, Department of Pharmacology and Pharmacy,

Li Ka Shing Faculty of Medicine, The University of Hong Kong,

Office 02-08, 2/F Laboratory Block, 21 Sassoon Road,

Hong Kong SAR, China.

Email: ewchan@hku.hk

Telephone: +852 2831 5110

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Supplementary material 1. Search strategy

1. Search in Pudmed

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2. Search in EMBASE Classic+EMBASE 1980- via Ovid

1	neuropsychiatric.mp.
2	psychiatric.mp.
3	hallucination/
4	psychosis/
5	psychotic disorder.mp.
6	mental disease/
7	mania/
8	bipolar.mp.
9	personality disorder/
10	delirium/
11	delusion/
12	agitation/
13	aggression/
14	aggressiveness/
15	hostility/
16	irritability/
17	impulse control disorder/
18	nervousness/
19	stress/
20	anxiety/
21	depression/
22	mood disorder/
23	suicide/
24	suicidal.mp.
25	self-harm.mp.
26	hyperactivity/
27	ADHD.mp.
28	attention deficit hyperactivity disorder.mp.
29	sleep disorder/
30	insomnia/
31	somnolence/
32	dream/
33	nightmare/
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35	behavior/
36	restlessness/
37	confusion/
38	disorientation/
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40	memory loss.mp.
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42	memory disorder/
43	seizure/
44	tremor/
45	violence/
46	attention deficit disorder/
47	irritable mood.mp.
48	montelukast/
49	accolate.mp.
50	zafirlukast/
51	zyflo.mp.
52	zileuton/
53	leukotriene inhibitor.mp.
54	leukotriene antagonist.mp.
55	leukotriene-modifying agent.mp.
56	LTMA.mp.
57	leukotriene receptor antagonist.mp.
58	leukotriene receptor blocker.mp.
59	leukotriene receptor blocking agent/
60	singulair.mp.
61	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 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
62	48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60
63	61 and 62

3. Search in Ovid MEDLINE 1946

1	neuropsychiatric.mp.
2	psychiatric.mp.
3	hallucination/
4	psychosis/
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25	self-harm.mp.
26	hyperactivity.mp.
27	ADHD.mp.
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29	sleep disorder/
30	insomnia/
31	somnolence.mp.
32	dream/
33	nightmare/
34	behavioural disorder.mp.
35	behavior/
36	restlessness/
37	confusion/
38	disorientation/
39	cognitive impairment.mp.
40	memory loss.mp.
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42	memory disorder/
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44	tremor/
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47	irritable mood.mp.
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54	leukotriene antagonist.mp.
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56	LTMA.mp.
57	leukotriene receptor antagonist.mp.
58	leukotriene receptor blocker.mp.
59	leukotriene receptor blocking agent.mp.
60	singulair.mp.
61	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 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
62	48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60
63	61 and 62

4. Search in Cochrane Library

(leukotriene-modifying agent OR LTMA OR leukotriene inhibitor OR leukotriene antagonist OR leukotriene receptor antagonist OR leukotriene receptor blocker OR zafirlukast OR accolate OR zileuton OR zyflo OR montelukast OR singulair) AND (neuropsychiatric OR psychiatric OR mental disorder OR hallucination OR psychosis OR psychotic disorder OR mania OR bipolar disorder OR personality disorder OR delusion OR agitation OR aggression OR aggressiveness OR hostility OR irritability OR irritable mood OR impulse control disorder OR violence OR nervousness OR stress OR anxiety OR depression OR mood disorder OR suicide OR suicidal OR self-harm OR hyperactivity OR ADHD OR attention deficit hyperactivity disorder OR attention deficit disorder with hyperactivity OR sleep disorder OR insomnia OR somnolence OR dreams OR nightmares OR behavioural disorder OR behaviour OR restlessness OR confusion OR delirium OR disorientation OR cognitive impairment OR memory loss OR memory disorder OR amnesia OR seizure OR tremor)

Supplementary material 2. Study characteristics of case series and review of case reports

Study	Region	Data source	Study period	Inclusion criteria	Exposure	Results and outcomes of interest
Cheng et al. [14]	China	Chinese National Knowledge Infrastructure and VIP database	2002–Aug 2013	Any ADRs	Montelukast	1) 5 psychiatric ADRs in 18 total ADRs (27.8%) 2) NEs reported: psychosis, sleep disorder, irritability, suicide attempt, attention deficit
Erdem et al. [19]	Turkey	Dr Behcet Uz Children's Hospital, Allergy Department	2008–2013	Patients with asthma or symptoms of wheezing who were on LTMAs only; ADRs not detected before treatment; positive dechallenge and rechallenge; and not on other medications	LTMAs	1) 24 psychiatric ADRs (58.53%) 2) NEs reported: hyperactivity, excessive sleepiness, nyctophobia and nervousness, agitation, hallucination, sleep disorder, depression

ADRs adverse drug reactions, *LTMAs* leukotriene-modifying agents, *NEs* neuropsychiatric events

Supplementary material 3. Study characteristics of case reports

Study	Gender	Age (years)	Neuropsychiatric events	History of neuropsychiatric events	Exposure	Concomitant treatment	Duration of exposure	Time to onset	Positive dechallenge[a]
Anandan et al. [1]	Female	29	Increased hallucinations with no signs of delirium	Yes (Schizophrenia and auditory hallucinations)	Montelukast 10 mg	---	---	48 hours	Yes (new symptoms subsided)
Skillman et al. [4]	Male	4	Anxiety and sleep disturbances	---	Montelukast 4 mg	---	5 months	---	Yes (2 weeks after discontinuation)
Byrne et al. [9]	Male	9	Anxiety and sleeping disorder	No	Montelukast 5 mg	Beclomethasone inhaler 50mcg	2.5 years	2.5 years	Yes
	Female	6	Anxiety	---	Montelukast dose increased from 4 mg to 5 mg	---	3 weeks	---	Yes (4 weeks after dose reduction)
Callero-Viera et al. [10]	Male	9	Behavioral disturbances, aggressiveness and nightmares	No	Montelukast 5 mg	Budesonide, salbutamol	3 weeks	---	Yes (2 days after discontinuation)
	Male	14	Aggressiveness	No	Montelukast 5 mg	Salbutamol	3 months	---	Yes (5 days after discontinuation)
	Male	14	Behavioral disturbances, aggressiveness and suicidal ideation	Yes (Mania induced by corticosteroids)	Montelukast 10 mg	Salbutamol	3 weeks	---	Yes (10 days after discontinuation)
	Male	8	Behavioral disturbances, aggressiveness and nightmares	No	Montelukast 5 mg	Salbutamol, immunotherapy	6 weeks	---	---
Kocyigit et al. [12]	Male	13	Visual hallucinations	Yes (Hyperactivity but no treatment for 5 years)	Montelukast	---	---	24 hours	Yes
Ibarra-Barrueta et al. [15]	Female	41	Sleep disturbance, vivid dreams, irritability, confusion, and concentration difficulties	Yes (Vivid dreams and confusion when antiretroviral therapy was first introduced, but symptoms disappeared a few days later)	Montelukast 10 mg	Efavirenz, emtricitabine/ tenofovir disoproxil fumarate, LABA/ICS, formoterol, antihistamines	2 months	2 months	Yes (1 month after discontinuation)

[a]All included case reports did not describe or present a positive rechallenge. *LABA/ICS* long-acting beta-agonist/inhaled corticosteroid

Supplementary material 4. Study characteristics of conference abstracts (observational and intervention studies)

Study	Study design	Region	Data source	Study period	Inclusion criteria	Exclusion criteria	Exposure	Sample size	Follow up	Covariates	Results and outcomes of interest
Rhee et al. [5]	Cohort study	Korea	Health insurance Review and Assessment Service claims database	1 Apr 2005–30 Jun 2006	Patients aged > 65 years with asthma	---	LTMAs Comparator: Inhaled corticosteroid	8545	---	---	119 new onset depression Hazard ratio = 1.50 (95% CI 1.02–2.21)
Iessa et al. [13]	Self-controlled case series study	United Kingdom	The Health Improvement Network database Electronic healthcare records	1998–2011	Records of suicide attempt (including suicide and self - harm, poisoning-self-inflicted, injury-self-inflicted, cause of overdose-deliberate)	---	LTMAs	370	30 days	---	Suicide attempt Incidence rate ratio = 1.69 (95% CI 0.80–3.58)
Narang et al. [16]	Pre and post intervention study	United States	---	---	Patients with asthma and allergic rhinitis with or without history of depression	Patients with symptoms of depression in the previous 6 months	Montelukast 10 mg	24	1 month	---	Depression by HAM-D score assessment Mean initial HAM-D score = 4.29 ± 3.76 Mean HAM-D score upon completion = 3.75 ± 3.82

LTMAs leukotriene-modifying agents, *CI* confidence interval, *HAM-D* Hamilton Depression Rating Scale

Supplementary material 5. Study characteristics of conference abstracts (pharmacovigilance studies)

Study	Region	Data source	Study period	Inclusion criteria	Exposure	Results and outcomes of interest
Gadde et al. [3]	United States	Metropolitan private practice self-reported ADRs	Jul 2006–Aug 2009	Reports of NEs	Montelukast	1) 20 patients experienced NEs (out of 814 patients) 2) NEs reported: aggression, anger, agitation, hyperactivity, emotional lability, misbehaving; insomnia, hallucinations, vivid dreams, night terrors, screaming at night, anxiety, depression, sense of doom
Aldea-Perona et al. [6]	Spain	Spanish Pharmacovigilance Database	Up to Jun 2011	Reports of psychiatric disorders in children and adolescents	Montelukast and zafirlukast	1) 82 reports (81 with montelukast) identified involving 119 NEs 2) 49% of reports were severe 3) The most frequent notifications were in 2–3 years old and the predominant sex was male 4) NEs reported: sleep disorders and disturbances (dream abnormalities, sleep terror, nightmares, somnambulism and insomnia), anxiety disorders (agitation, anxiousness, nervousness), personality disorders (aggression, personality change), disturbances in thinking and perception (hallucination), suicidal thinking
Iessa et al. [7]	Worldwide	World Health Organization Vigibase	Jan 1986–Mar 2010	Suicide related adverse events in patients aged 2–17 years	Montelukast	1) 321 reports identified 2) 96% originating from the United States 3) The number of reports increased from 9 to 263 in mid-2008 4) Causality assessment of 47 original cases: 21% possible (n = 10), 32% unlikely (n = 15) and 47% assessable (n = 22)
Trotta et al. [8]	Italy	National Pharmacovigilance Network	Jan 2001–Jun 2011	Reports of psychiatric disorders and nervous system disorders of all asthma medications	LTMAs	1) 88 psychiatric ADRs 2) 57 (65%) ADRs were related to children 3) NEs reported: insomnia, nightmares, headache, hyperactivity

ADRs adverse drug reactions, *NEs* neuropsychiatric events, *LTMAs* leukotriene-modifying agents

Supplementary material 6. Study characteristics of conference abstracts (case reports)

Study	Gender	Age (Years)	Neuropsychiatric events	History of neuropsychiatric events	Suspected treatment	Concomitant treatment	Duration of exposure	Time to onset	Positive dechallenge	Positive rechallenge
Burgos Pimentel et al. [17]	Female	9	Nervousness and visual hallucinations	No	Montelukast	---	6 months		Yes (30 days after discontinuation)	---
	Male	3	Nervousness, aggression, insomnia, nightmares and hallucinations	No	Montelukast 4 mg	---	15 days	3 days	Yes (7 days after discontinuation)	---
	Male	49	Trouble sleeping and frequent nightmares	No	Montelukast	---	7 days	---	Yes (5 days after discontinuation)	---
Erdem et al. [20]	Female	15	Convulsions	Yes (History of seizures)	LTMAs	Valproic acid, ICS	---	3 days	Yes	Yes
	Female	6	Seizures	Yes (History of seizures)	LTMAs	Antiepileptics	---	---	Yes	Yes
	Male	2.5	Afebrile convulsions	No	LTMAs	Ketotifen	---	3 days	Yes	Yes

LTMAs leukotriene-modifying agents, *ICS* inhaled corticosteroid

Supplementary material 7. Newcastle-Ottawa quality assessment scale for cohort studies

Study	Selection				Comparability		Outcome			Total Quality Score
	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Adjust for psychiatric disorders	Adjust for severity of asthma	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow-up of cohorts	
Jick et al. [2]	1	0	1	0	0	0	1	0	0	3
Chen et al. [18]	1	1	1	0	1	0	1	1	0	6

A study can be awarded a maximum of one star for each numbered item within the selection and outcome 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 population in the community; 0: Selected group of users 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 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: Adjust for psychiatric disorders; 1: Adjust for severity of asthma

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: Duration of follow-up less than 3 years; 0: Duration of follow-up 365 days or above
C. Adequacy of follow up of cohorts
   1: Complete follow-up or loss of follow-up rate less than 20%; 0: Loss of follow up rate 80% or above and no description of those lost or no statement

Supplementary material 8. Newcastle-Ottawa quality assessment scale for case-control studies

Study	Selection				Comparability		Exposure			Total Quality Score
	Adequacy of case definition	Representativeness of the cases	Selection of controls	Definition of controls	Adjust for psychiatric disorders	Adjust for severity of asthma	Ascertainment of exposure	Same method of ascertainment for cases and controls	Non-response rate	
Schumock et al. [11]	1	1	1	1	1	1	1	1	1	9
Ali et al. [21]	1	1	1	1	1	1	1	1	1	9

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. Adequacy of case definition
   1: Yes with independent validation; 0: Yes without validation 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 disease (endpoint); 0: No description of source

Comparability:

A. Comparability of cohorts on the basis of the design or analysis
   1: Adjust for psychiatric disorders; 1: Adjust for severity of asthma

Exposure:

A. Ascertainment of exposure
   1: Secure record or structured interview where blind to case/control status; 0: Interview not blinded to case/control status or 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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