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SAFETY OF LAMOTRIGINE IN PAEDIATRICS: A SYSTEMATIC REVIEW

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ABSTRACT

Objectives: To identify adverse drug reactions associated with lamotrigine in children and compare the safety profile with other antiepileptic drugs.

Setting: Databases EMBASE (1974-November 2013), Medline (1946-November 2013), PubMed and the Cochrane library for randomised controlled trials were searched for studies on safety of lamotrigine.

Participants: All studies involving paediatric patients aged ≤ 18years who have received at least a single dose of lamotrigine with safety as an outcome measure were included.

Primary and secondary outcome measures: The primary outcome measure was safety of lamotrigine. Drug interaction of lamotrigine was the secondary outcome.

Results: A total of 77 articles involving 3,782 paediatric patients were identified. There were 2,221 AEs reported. Rash was the most commonly reported AE, occurring in 7.5% of the patients. Discontinuation due to an adverse drug reaction (ADR) was recorded in 72 children (1.9% of all treated patients). Fifty eight percent of treatment discontinuation was attributed to different forms of rash and 21% due to increased seizures. Children on lamotrigine monotherapy had lower incidences of AEs. Headache (p=0.02), somnolence (<0.001), nausea (p=0.01), vomiting (p<0.001), dizziness (p<0.001) and abdominal pain (p=0.01) were significantly lower among children on monotherapy.

Conclusions: Rash was the most common ADR of lamotrigine and the most common reason for treatment discontinuation. Children receiving polytherapy have a higher risk of AEs than monotherapy users.

Registration: PROSPERO/ CRD42013006910

STRENGTHS AND LIMITATIONS OF THIS STUDY

1. This systematic review assessed the quality of all the prospective studies
2. Randomised controlled trials (RCTs), cohort studies and case reports were reviewed.
3. Only a limited number of RCTs of lamotrigine in children have been published, thus limiting the power of the meta-analysis.
4. The risks of adverse reactions between monotherapy and polytherapy users were compared in RCTs alone, because only one prospective cohort study involving children receiving lamotrigine monotherapy was identified.

BACKGROUND

Lamotrigine (LTG) was first synthesised in the early 1980s. It was approved for adult use in Ireland in 1990, the UK in 1991 and by the US Food and Drug Administration (FDA) in 1994[1]. Since its market authorisation over two decades ago, it has been used increasingly for the treatment of paediatric epilepsy. It is the most commonly prescribed new generation AED, accounting for 65% of new anti-epileptic drug (AED) prescriptions in the UK[2] and 12% of all AED prescriptions for children in the Netherlands[3].

In the UK, LTG is recommended as monotherapy for the first line treatment for newly diagnosed focal seizures and as an adjunct for refractory focal seizures in children[4]. It is a second line monotherapy drug for new onset generalised seizures and a useful adjunct for refractory generalised seizures. It is the third drug of choice, after ethosuximide and valproate for absence seizures, for which it may be administered as a monotherapy or polytherapy[4].

Dosing of LTG in children on adjunctive therapy is dependent on the effect of the co-administered drug. Higher doses may be required when co-administered with AEDs such as phenobarbital, phenytoin, carbamazepine and oxcarbazepine, which have been shown to increase the drug's clearance and reduce its plasma concentration. Conversely, valproic acid reduces LTG clearance and raises its plasma concentration by as much as two fold, hence a lower dose is recommended[5].

A safety concern with LTG in children is the occurrence of a skin rash. This can vary in intensity, from transient mild rash to Steven Johnson's syndrome, which can be fatal[6]. Children are generally more predisposed to skin rashes than adults[7]. Most of the other known adverse reactions are neurological and are largely dose dependent[7]. LTG can worsen myoclonic seizures and is usually avoided in patients with severe myoclonic epilepsy of infancy (Dravets syndrome)[8].

This systematic review was performed to identify all studies of LTG safety in children, determine the adverse reactions of LTG and compare the safety of the drug with other AEDs.

METHODS

Search strategy

Databases EMBASE (1974-November 2013), Medline (1946- November 2013), PubMed and the Cochrane database of randomised controlled trials (RCTs) were searched for original research or reports in which paediatric patients received at least a single dose of LTG with safety as an outcome measure. 'Paediatrics' was defined as any patient ≤18 years old. All studies satisfying these criteria were included irrespective of the language of publication. A search combining Lamotrigine with paediatric* or child* or neonate* or infan* or newborn adolescent* or boy* or girl* or toddler in title was done. All included articles were independently evaluated by two reviewers. Study was conducted in compliance with the PRISMA guidelines and registered on PROSPERO (Number: CRD42013006910 available from:

http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42013006910)

Data extraction

Data extracted from each study included: year of study, setting, age of patients, study design, number of patients receiving LTG and comparator, dose, type of seizure, study outcome, summary of result, type of therapy, number of withdrawals and reason for withdrawal and the number and type of adverse events (AEs) for both LTG and the comparator drug(s).

Data quality assessment

The RCTs were assessed for quality using the Cochrane collaboration's tool for assessing risk of bias in randomised trials[9]. Observational studies were assessed using the System for the Unified Management of the Review and Assessment of Information (SUMARI)[10]. This form comprises of nine appraisal criteria and any study that met more than 4 of these criteria was considered to be of a sufficiently good quality. All studies were independently assessed by two reviewers; a third blinded reviewer was involved only if both reviewers did not agree on any study.

Data collection and statistical analysis

All relevant data were extracted onto an Excel spread sheet. Chi square analysis was used to compare categorical data. The RCTs were aggregated and meta-analyses were conducted using Revman version 5. The relative risks of AEs present in at least two RCTs were calculated. A relative risk (RR) greater than 1 indicates a positive effect of LTG. After testing for homogeneity (I^2 ≤50% or Chi^2 p≥0.05), the fixed effect model was used for homogeneous data and random model for heterogeneous data.

RESULTS

Summary of studies

A total of 77 articles with reports on safety of lamotrigine were identified after the literature search (Figure 1). A total of 3,782 paediatric patients were administered LTG. The most common types of articles were case reports (Table 1). The largest number of patients was in cohort studies (3,012, 80%). There were 17 cohort studies and 9 RCTs. There were 49 case reports involving 52 children.

Quality assessment

The risk of bias was assessed from 5 parameters: random sequence generation, allocation concealment, blinding of personnel and participant, attrition bias and reporting bias. All RCTs fulfilled at least 4 of these parameters and were considered to be of sufficiently good quality and eligible for meta-analyses. All cohort studies were considered to be of good quality and were included in the final data aggregation.

Table 1: Summary of all articles

Study type	Number of studies	Number of AEs	Number of patients (%)
Prospective cohort	12	1524	2712 (71.7%)
Retrospective cohort	5	56	313 (8.3%)
RCT	9	549	593 (15.7%)
Case report	49	52	52 (1.4%)
Cross sectional	1	27	65 (1.7%)
Case control	1	13	47 (1.2%)
	77	**2221**	**3782**

Safety results

There were 2,221 documented adverse events (AEs) in 3,782 children in the reviewed articles. The majority (1,524) of the AEs were reported in 12 prospective cohort studies [11-22][Supplementary Table 1]. There were 549 AEs reported from RCTs [23-31].

Prospective studies

Common adverse events (≥1/100 and <1/10) from pooled prospective studies (RCTs and cohorts) were: rash, headache, fever, somnolence, vomiting, seizure aggravation, dizziness, cough, aggression, ataxia and insomnia. Uncommon AEs (≥1/1000 and <1/100) were: behavioural disturbance, nausea and anorexia (Table 2). About one-third of all AEs (30.7%) were neurological events, while respiratory and gastrointestinal events were 12.9% and 11.1% of all AEs respectively.

Rash was the most common AE in children receiving LTG. From all prospective studies, the risk of rash was 7.45 per 100 patients (Table 2). It accounted for 10.3% of all AEs. It was also the most common reason for withdrawal of therapy, with 58% of treatment discontinuation attributed to different forms of rash (Table 3). The relative risk of rash with LTG compared with placebo from two RCTs, involving 112 patients on LTG, was 3.66 [95% CI: 0.11-123.11], which was not statistically significant (p=0.47). Seventy two children had a deterioration in seizure control and the risk of aggravated seizures was 2.14 per 100 patients (Table 2).

There were significantly higher risks of dizziness [RR 4.57, 95% CI: 1.88-11.12, p <0.001], abdominal pain [RR: 2.53, 95% CI: 1.12-5.70, p=0.03] and nausea [RR: 5.94, 95% CI: 1.59-22.13, p=0.008] with LTG than placebo in the RCTs (Table 4). Twenty one percent of children receiving LTG had dizziness compared with 4.5% on placebo. Sixteen percent and 12.5% of LTG treated children had abdominal pain and nausea respectively, compared with 6% and 1.7% of placebo treated children. The relative risks of other common AEs from RCTs identified were not significantly different between LTG and placebo treated children (Table 4).

When compared with valproic acid, the risk of somnolence and vomiting, were significantly lower for LTG [RR: 0.35, 95% CI: 0.13-0.89, p=0.04) and [RR: 0.20, 95% CI: 0.04-0.89, p=0.03), respectively. Three percent and 1.3% of children on LTG had somnolence and vomiting, while these symptoms were recorded in 9.5% and 6.8% of those on valproic acid. The risk of other common adverse events such as, rash, dizziness, headache and seizure aggravation, were not significantly different (Table 4).

Discontinuation of LTG treatment due to adverse drug reactions (ADRs) was recorded in 72 children (1.9% of all treated patients). Rash (58%) and seizure aggravation (21%) were the most common reasons (Table 3).

Table 2: Risk of all adverse events from pooled prospective cohort studies and RCTs according to body system (number of children=3,305)

Adverse events	No of Events	Risk per 100 patients
Central nervous system		
Somnolence	140	4.15
Headache	132	3.92
Aggravated seizures	72	2.14
Dizziness	63	1.84
Irritability	37	1.08
Aggression	32	0.94
Ataxia	29	0.85
Insomnia	31	0.91
Drowsiness	22	0.65
Hyperactivity	18	0.53
Hyperkinesia	17	0.50
Tremor	15	0.44
Behaviour change	13	0.38
Attention disturbance	10	0.29
Hostility	10	0.29
Depression	9	0.26
Personality change	9	0.26
Loss of concentration	5	0.15
Lethargy	3	0.09
Loss of memory	4	0.12
	650	
Gastrointestinal tract		
Vomiting	127	3.77
Abdominal pain	39	1.14
Constipation	36	1.05
Nausea	34	1.00
Diarrhoea	32	0.94
Anorexia	11	0.32
	274	
Ear, Nose and Throat		
Nasopharyngitis	119	3.48
Ear disorders	104	3.04
Nasal congestion	12	0.35
	235	
Respiratory system		
Respiratory infection	197	5.85
Cough	59	1.73
Wheeze	6	0.18
	235	
Others		
Rash	251	7.45
Fever	146	4.27

Asthenia	15	0.44
Fatigue	14	0.41
Increased appetite	8	0.23
	402	

Table 3: Adverse reactions leading to discontinuation of treatment

Adverse reaction	Number of patients (%)
Rash	42 (58.3%)
Aggravated seizure	15 (20.8%)
Headache	3 (4.2%)
Somnolence	3 (4.2%)
Vomiting	2 (2.8%)
Fever	2 (2.8%)
Tremor	1 (1.4%)
Paraesthesia	1 (1.4%)
Apnoea	1 (1.4%)
Disorientation	1 (1.4%)
Behavioural disturbance	1 (1.4%)
Total	72

Table 4: Relative risks of AEs of lamotrigine and comparators in RCTs

Relative risks of AEs between LTG and placebo					
AE	**Risk LTG (%)**	**Risk Comparator (%)**	**Relative risk (95% CI)**	**(p value * significant)**	**Reference**
Rash	24.1	15.7	3.66 [0.11-123.11]	0.47	23, 25
Fever	13.7	11.7	1.17 [0.60-2.29]	0.64	25, 26
Somnolence	24.5	7.9	1.37 [0.80-2.37]	0.25	25
Vomiting	22.5	18.8	1.19 [0.69-2.06]	0.53	25
Headache	16.5	15.1	1.10 [0.63-1.90]	0.74	23, 25
Aggravated seizure	3.0	11.4	0.32 [0.13-0.79]	0.01*	25, 27, 28
Dizziness	21.4	4.5	4.57 [1.88-11.12]	<0.001*	23, 25
Cough	10.5	0	5.00 [0.26-97.7]	0.29	26
Abdominal pain	16.1	6.1	2.52 [1.12-5.70]	0.03*	23, 25
Nausea	12.5	1.7	5.94 [1.59-22.13]	<0.001*	23, 25
Relative risks between LTG and Valproic acid					
Rash	3.6	1.2	2.48 [0.59-10.50]	0.22	24, 29
Somnolence	3.4	9.5	0.35 [0.13-0.95]	0.04*	24
Vomiting	1.3	6.8	0.20 [0.04-0.89]	0.03*	24
Headache	8.3	7.4	1.13 [0.54-2.34]	0.75	24, 29
Aggravated seizures	0.7	2.7	0.25 [0.03-2.18]	0.21	24
Dizziness	2.7	1.4	1.97 [0.37-10.61]	0.43	24

Case Reports

There were more case reports of rash than any other AE, accounting for about half (48%) of all reports [Supplementary Table 2]. Rash varied in severity from mild morbilliform rash to Toxic Epidermal Necrolysis (TEN). Other variants were urticarial, Steven Johnson Syndrome (SJS) and Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS syndrome). The period of onset of rash after commencement of LTG treatment varied between one day and 103 weeks, with the median duration of onset of 25 days [IQR: 14-35 days]. In half (48%) of the cases of rash, LTG was co-administered with valproic acid There were 7 case reports of seizure aggravation [Supplementary Table 2]. Other adverse reactions reported were: movement disorders, disseminated intravascular coagulopathy, paraguesia and syndrome of inappropriate anti-diuretic hormone secretion.

Effect of dosing and polytherapy on ADRs

LTG doses were titrated over several weeks until the maximum maintenance dose was achieved. Patients receiving LTG monotherapy received an almost similar median initial dose (median 0.5mg/kg [1QR:0.4-1.1]) as those receiving combination treatment with valproic acid (median: 0.5mg/kg, [IQR: 0.15 -0.75]). Patients treated with combination therapy with enzyme inducing drugs received a higher median dose of initial LTG (1mg/kg [IQR: 0.6-2]). Children on mixed AED regimen, excluding valproic acid, received a higher median maintenance dose of LTG (median=15mg/kg [15-15.1]) than those on monotherapy (median 11mg/kg [IQR 10-14.4]) and valproic acid combination (5mg/kg [IQR: 5-5.1]).

LTG was given as part of a polytherapy regimen in 5 RCTs. The most frequent reports of rash (16%) were in a study with a high initial LTG starting dose of 0.5mg/kg/day in VPA co-medicated patients and 2mg/kg/day in those receiving enzyme inducing AEDs. The dose escalation to reach maintenance doses of 1-3 and 5-15mg/kg/day respectively, was achieved in 6 weeks[25]. Three other polytherapy studies [26-28] introduced LTG treatment at much lower doses (0.15-0.2mg/kg in VPA co-medicated patients and 0.6-1mg/kg/day in those receiving enzyme inducing drugs). The rates of dose escalation were much slower

(12-19 weeks). Of these 3 studies, only one reported a single case of rash (5%) [26], while the other two did not record any rash. A fifth study administered 0.2mg/kg/day initial dose to VPA co-medicated patients and 2mg/kg/day to those on enzyme inducing AEDs. This study recorded a 6% rash rate [31].

There were 4 RCTs in which LTG was administered as monotherapy [23, 24, 29, 30]. The initial dose in one study was 0.3mg/kg/day (24), dose escalation was slow (up to 16 weeks) and a 3% incidence of rash reported. The three other studies administered 0.5mg/kg/day as initial doses [23, 29, 30]. Two of these each reported a rash incidence rate of 7% [23, 30], one of these escalated the dose rapidly over 6 weeks [30]. The third study reported a 5% rate [29].

All but one of the prospective cohort studies used LTG polytherapy. Comparison of the incidence rates of ADRs between RCTs involving children who received LTG monotherapy or polytherapy showed that monotherapy users had significantly lower rates of AEs than polytherapy users (Table 5). The incidence rates of dizziness, somnolence, headache, vomiting, nausea and abdominal pain were all significantly lower in patients on LTG monotherapy than polytherapy. There was also a trend towards a decreased incidence of rash in patients on LTG monotherapy, although this was not statistically significant [p=0.09].

Table 5: Incidence rates of AEs in monotherapy and polytherapy LTG users in RCTs

Adverse event	Monotherapy n=340 (%)	Polytherapy, n=253 (%)	P value
Rash	18 (5.3)	21(8.3)	0.09
Headache	16 (4.7)	20 (7.9)	0.02*
Nasopharyngitis	13 (3.8)	14 (5.5)	0.33
Somnolence	5 (1.5)	47 (18.6)	<0.001*
Abdominal pain	5 (1.5)	13 (5.1)	0.01*
Dizziness	4 (1.2)	27 (10.7)	<0.001*
Nausea	3 (0.9)	11 (4.3)	0.01*
Increased seizure	1 (0.3)	0 (0)	1.00
Vomiting	0 (0)	22 (8.7)	<0.001*
Fever	0 (0)	16 (6.3)	<0.001*
Ear infection	0 (0)	9 (3.6)	<0.001*
Cough	0 (0)	2 (0.7)	0.18
Others	65 (19.1)	111 (43.9)	-
Total	127	313	-

% ,incidence rate; * significant; n= number of patients

DISCUSSION

Rash was the most common AE in children receiving LTG treatment. The risk of rash was 7.45 episodes per 100 children. It also accounted for 10% of all AEs. Other commonly reported AEs were neurological symptoms, mainly somnolence, headache, aggravated seizures, dizziness, as well as vomiting. A previous safety review of 13 manufacturer sponsored clinical trials involving 1,096 children had also shown a similar result [32].

Children are more likely than adults to develop a rash with lamotrigine[33]. Simple maculopapular rashes were the most common types of rash identified in this review. They were usually transient and often without long term complications. LTG associated rashes are usually highly variable and the most severe forms are SJS and TEN. TEN is the more severe of these two, with an average background mortality rate of 25-35% compared to 1-5% in patients with SJS[34]. Patients with TEN are also more likely to have long term complications, with up to 50% of them reported to have long term problems[34]. Despite rash being the most common ADR with LTG, there were no statistically significant differences between LTG and either placebo or valproic acid in relation to the occurrence of rash in the RCTs reviewed. Only two RCTs compared the risks of rash between LTG and placebo or valproic acid, but these studies were insufficiently powered to adequately compare the risk of rash.

Rapid dose escalation and high initial doses have been reported to predispose to rash[7]. According to the current recommendations in the UK and USA, an initial dose of 0.15mg/kg/day should be given to VPA co-medicated children, 0.3mg/kg/day to those receiving enzyme inducing AEDs and monotherapy[35, 36]. The protective mechanism of the introduction of small incremental doses, although not fully understood, is believed to involve the desensitisation of antigen presenting cells and T lymphocytes[37]. HLA B genotyping may be useful in determining the predisposition to LTG induced rash, but the level of HLA involvement is not fully determined [38]. Co-medication with valproic acid is also a significant predictor of rash in LTG treated patients[33]. Half of the case reports of

rash identified in this review occurred when LTG was concomitantly administered with valproic acid. Valproic acid is a glucuronide inhibitor which increases the half-life of LTG and decreases its clearance[39]. Due to this inhibitory effect, LTG starting and maintenance doses are recommended to be lower during concurrent valproic acid therapy.

Neurological effects are the most common ADRs of AEDs [40]. Somnolence, headache and dizziness were frequently reported among patients in this review. A previous study had identified somnolence as the most common ADR in patients receiving LTG as add-on treatment; while a much lower incidence was reported in monotherapy users [32]. A similar pattern has been shown in this study, with a significantly lower incidence of somnolence ($p<0.001$) reported in patients on monotherapy. Comparative safety analysis of RCTs in this review however shows that patients receiving LTG had significantly lower risk of somnolence than those treated with valproic acid. The small number of studies included in the meta-analyses necessitates a cautious interpretation of this result.

About 2% of patients had an increase in seizures. Additionally, increased seizures was the second most common reason for discontinuing LTG. Seizure aggravation is a recognised problem in patients with epilepsy receiving LTG, the cause and mechanisms of these paradoxical drug-induced seizures are unknown. New seizures may not be easily traced to antiepileptic drugs since there is usually an inherently high variability in seizure frequency in epileptic patients. [41]. It is thought to be most common in children with myoclonic epilepsy[8].

For most of the ADRs, children on polytherapy had significantly higher incidence of ADRs than those on monotherapy (Table 5). We have only compared ADRs in RCTs, because only one prospective monotherapy cohort study was identified. In addition to the potential interactions between the drugs, the addition of one or more AED also adds to the chances of more ADRs. The relationship between polytherapy and increased ADRs has been established in a previous study of AEDs [42]. Polytherapy with valproic acid has also been shown to be associated with a greater risk of hepatotoxicity, pancreatitis and other serious ADRs [43].

In conclusion, rash, which occurred in a spectrum of varying intensity, was the most common ADR associated with LTG; it was also the most common reason for the

discontinuation of treatment. High initial LTG dose and rapid dose escalation are risk factors for rash. Patients on LTG polytherapy are more likely to develop ADRs than monotherapy users.

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CONTRIBUTORS

OE, HS and IC conceived the idea as part of OE's PhD. OE did the literature search and extracted the data. HS and IC reviewed the extracted data. OE wrote the first draft and IC and HS edited the draft and subsequent drafts. OE wrote the final draft. OE, HS and IC agreed to the final draft.

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IMAGE LEGEND

Figure 1: Flow chart for screened articles

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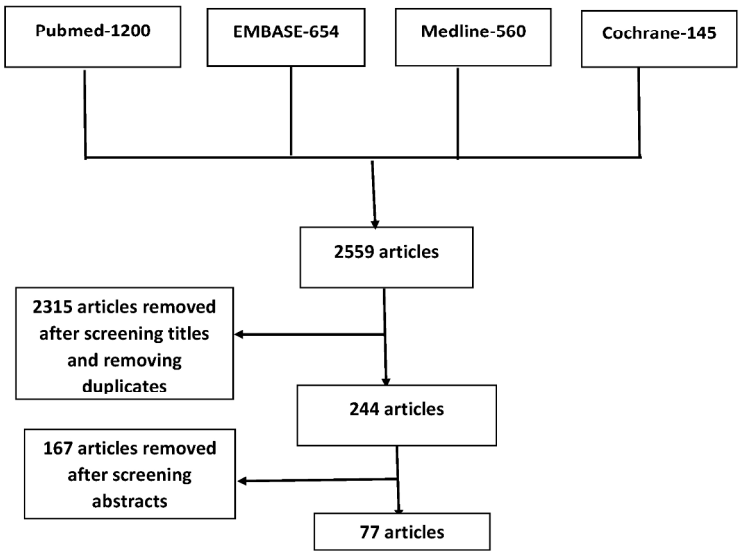

Flow chart for screened articles
210x297mm (300 x 300 DPI)

Table 1: Summary of data from cohort studies

Ref	Comparator	Design	No on LTG	No on comparator	Seizure type	Dose (mg/kg/day)	Duration of follow up (weeks)	Funding	AEs LTG	AEs comparator
1	None	Prospective	125	-	Partial	0.15-15.6	48	Industry	637	-
2	None	Prospective	285	-	Unspecified	1-15	48	None	342	-
3	None	Prospective	13	-	Infantile Spasm	2-10	12	Institutional	0	-
4	None	Prospective	57	-	Unspecified	0.4-3	24	None	0	-
5	None	Prospective	40	-	Lennox-Gastaut	4-10	12	None	9	-
6	None	Prospective	252	-	Unspecified	NA	≤192	Industry	129	-
7	None	Prospective	40	-	Unspecified	1-15	12	None	5	-
8	None	Prospective	37	-	Unspecified	0.5-15	1-104	None	6	-
9	None	Prospective	56	-	Generalised	0.3-15	≤104	None	29	-
10	None	Prospective	155	-	Unspecified	1-15	53-221	None	87	-
11	None	Prospective	54	-	Absence	0.3-10.2	80	Industry	114	-
12	None	Prospective	1598		Unspecified	NA	≥24 weeks	Institutional	166	-
1	VPA	Retrospective	82	132	Unspecified	3-13	≤160	None	2	0
14	None	Retrospective	72	-	Unspecified	1.1-13.7	3-552	None	6	-
15	ETX/VPA	Retrospective	11	35/41*	Absence	1-6	NA	None	3	12/17*
16	VGB/GBP	Retrospective	132	80/39*	Unspecified	NA	NA	None	20	10/24*
17	None	Retrospective	16	-	Lennox-Gastaut	NA	NA	None	25	-

* Values for second comparator

Table 2: Adverse reactions from 49 case reports

Reference	ADR	Number of cases	Median days of onset	ł Comments
(18-39)	Mucocutaneous reactions	22	28	One child died
40-46)	Worsening/new seizures	7	21.5	All recovered
47-49	Ballism/chorea/movement disorders	6	*5	All recovered
(50-52)	Mania	3	*14	All recovered
(53,54)	Prolonged aPTT	2	*168	Both recovered
(55, 56)	SIADH	2	*5	Both recovered
(57)	Paraguesia	1	*5	Recovered
(58)	Hepatic failure	1	-	Recovered
(59)	Hyponatremia	1	-	Recovered
(60)	Myocarditis	1	-	Recovered
(61)	DIC	1	-	Recovered
(62)	Vanishing bile duct	1	-	Recovered
(63)	Haemophagocytic syndrome	1	21	Recovered

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PRISMA 2009 Checklist

SAFETY OF LAMOTRIGINE IN PAEDIATRICS: A SYSTEMATIC REVIEW

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	5
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	6

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	6
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	-
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Fig 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	-
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	6
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	12
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	12
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	6
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	-
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	16
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	17
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	16, 17
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	18

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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SAFETY OF LAMOTRIGINE IN PAEDIATRICS: A SYSTEMATIC REVIEW

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SAFETY OF LAMOTRIGINE IN PAEDIATRICS: A SYSTEMATIC REVIEW

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Word count: 2,479

ABSTRACT

Objectives: To identify adverse drug reactions associated with lamotrigine in children and compare the safety profile with other antiepileptic drugs.

Setting: Databases EMBASE (1974-April 2015), Medline (1946-April 2015), PubMed and the Cochrane library for randomised controlled trials were searched for studies on safety of lamotrigine.

Participants: All studies involving paediatric patients aged ≤ 18years who have received at least a single dose of lamotrigine with safety as an outcome measure were included.

Primary and secondary outcome measures: The primary outcome measure was safety of lamotrigine. Drug interaction of lamotrigine was the secondary outcome.

Results: A total of 78 articles involving 3,783 paediatric patients were identified. There were 2,222 AEs reported. Rash was the most commonly reported AE, occurring in 7.3% of the patients. Stevens-Johnson syndrome was rarely reported, with a risk of 0.09 per 100 patients. Discontinuation due to an adverse drug reaction (ADR) was recorded in 72 children (1.9% of all treated patients). Fifty eight percent of treatment discontinuation was attributed to different forms of rash and 21% due to increased seizures. Children on lamotrigine monotherapy had lower incidences of AEs. Headache (p=0.02), somnolence (<0.001), nausea (p=0.01), vomiting (p<0.001), dizziness (p<0.001) and abdominal pain (p=0.01) were significantly lower among children on monotherapy.

Conclusions: Rash was the most common ADR of lamotrigine and the most common reason for treatment discontinuation. Children receiving polytherapy have a higher risk of AEs than monotherapy users.

STRENGTHS AND LIMITATIONS OF THIS STUDY

1. This systematic review assessed the quality of all the prospective studies
2. Randomised controlled trials (RCTs), cohort studies and case reports were reviewed.
3. Only a limited number of RCTs of lamotrigine in children have been published, thus limiting the power of the meta-analysis.
4. The risks of adverse reactions between monotherapy and polytherapy users were compared in RCTs alone, because only one prospective cohort study involving children receiving lamotrigine monotherapy was identified.

BACKGROUND

Lamotrigine (LTG) was first synthesised in the early 1980s. It was approved for adult use in Ireland in 1990, the UK in 1991 and by the US Food and Drug Administration (FDA) in 1994[1]. Since its market authorisation over two decades ago, it has been used increasingly for the treatment of paediatric epilepsy. It is the most commonly prescribed new generation AED, accounting for 65% of new anti-epileptic drug (AED) prescriptions in the UK[2] and 12% of all AED prescriptions for children in the Netherlands[3].

In the UK, LTG is recommended as monotherapy for the first line treatment for newly diagnosed focal seizures and as an adjunct for refractory focal seizures in children[4]. It is a second line monotherapy drug for new onset generalised seizures and a useful adjunct for refractory generalised seizures. It is the third drug of choice, after ethosuximide and valproate for absence seizures, for which it may be administered as a monotherapy or polytherapy[4].

Dosing of LTG in children on adjunctive therapy is dependent on the effect of the co-administered drug. Higher doses may be required when co-administered with AEDs such as phenobarbital, phenytoin, carbamazepine and oxcarbazepine, which have been shown to increase the drug's clearance and reduce its plasma concentration. Conversely, valproic acid reduces LTG clearance and raises its plasma concentration by as much as two fold, hence a lower dose is recommended[5].

A safety concern with LTG in children is the occurrence of a skin rash. This can vary in intensity, from transient mild rash to Stevens-Johnson's syndrome (SJS), which can be fatal[6]. Children are generally more predisposed to skin rashes than adults[7]. Most of the other known adverse reactions are neurological and are largely dose dependent[7]. LTG can worsen myoclonic seizures and is usually avoided in patients with severe myoclonic epilepsy of infancy (Dravets syndrome)[8].

This systematic review was performed to identify all studies of LTG safety in children, determine the adverse reactions of LTG and compare the safety of the drug with other AEDs.

METHODS

Search strategy

Databases EMBASE (1974-April 2015), Medline (1946-April 2015), PubMed and the Cochrane database of randomised controlled trials (RCTs) were searched for original research or reports in which paediatric patients received at least a single dose of LTG with safety as an outcome measure. 'Paediatrics' was defined as any patient ≤18 years old. All studies satisfying these criteria were included irrespective of the language of publication. A search combining Lamotrigine with pediatric* or paediatric* or child* or neonate* or neonat* or infan* or newborn or adolescent* or boy* or girl* or toddler as multipurpose search was done. All included articles were independently evaluated by two reviewers. Study was conducted in compliance with the PRISMA guidelines and registered on PROSPERO (Number: CRD42013006910 available from:

http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42013006910)

Data extraction

Data extracted from each study included: year of study, setting, age of patients, study design, number of patients receiving LTG and comparator, dose, type of seizure, study outcome, summary of result, type of therapy, number of withdrawals and reason for withdrawal and the number and type of adverse events (AEs) for both LTG and the comparator drug(s).

Data quality assessment

The RCTs were assessed for quality using the Cochrane collaboration's tool for assessing risk of bias in randomised trials[9]. Observational studies were assessed using the System for the Unified Management of the Review and Assessment of Information (SUMARI)[10]. This form comprises of nine appraisal criteria and any study that met more than 4 of these criteria was considered to be of a sufficiently good quality. All studies were independently assessed by two reviewers; a third blinded reviewer was involved only if both reviewers did not agree on any study.

Data collection and statistical analysis

All relevant data were extracted onto an Excel spread sheet. Chi square analysis was used to compare categorical data. The RCTs were aggregated and meta-analyses were conducted using Revman version 5. The relative risks of AEs present in at least two RCTs were calculated. A relative risk (RR) greater than 1 indicates a positive effect of LTG. After testing for homogeneity (I^2 ≤50% or Chi^2 p≥0.05), the fixed effect model was used for homogeneous data and random model for heterogeneous data.

RESULTS

Summary of studies

A total of 78 articles with reports on safety of lamotrigine were identified after the literature search (Figure 1). A total of 3,783 paediatric patients were administered LTG. The most common types of articles were case reports (Table 1). The largest number of patients was in cohort studies (3,012, 80%). There were 17 cohort studies and 9 RCTs. There were 50 case reports involving 53 children.

Quality assessment

The risk of bias was assessed from 5 parameters: random sequence generation, allocation concealment, blinding of personnel and participant, attrition bias and reporting bias. All RCTs fulfilled at least 4 of these parameters and were considered to be of sufficiently good quality and eligible for meta-analyses. All cohort studies were considered to be of good quality and were included in the final data aggregation.

Table 1: Summary of all articles

Study type	Number of studies	Number of AEs	Number of patients (%)
Prospective cohort	12	1524	2712 (71.7%)
Retrospective cohort	5	56	313 (8.3%)
RCT	9	549	593 (15.7%)
Case report	50	53	53 (1.4%)
Cross sectional	1	27	65 (1.7%)
Case control	1	13	47 (1.2%)
	78	**2222**	**3783**

Safety results

There were 2,222 documented adverse events (AEs) in 3,783 children in the reviewed articles. The majority (1,524) of the AEs were reported in 12 prospective cohort studies [11-22][Supplementary Table 1]. There were 549 AEs reported from RCTs [23-31].

Prospective studies

Common adverse events (≥1/100 and <1/10) from pooled prospective studies (RCTs and cohorts) were: rash, headache, fever, somnolence, vomiting, seizure aggravation, dizziness, cough, aggression, ataxia and insomnia. Uncommon AEs (≥1/1000 and <1/100) were: behavioural disturbance, nausea and anorexia (Table 2). About one-third of all AEs (35.8%) were neurological events, while gastrointestinal and respiratory events were 14.8% and 13.9% of all AEs respectively.

Rash was the most common AE in children receiving LTG. From all prospective studies, the risk of rash was 7.3 per 100 patients (Table 2). It accounted for 13% of all AEs. It was also the most common reason for withdrawal of therapy, with 58% of treatment discontinuation attributed to different forms of rash (Table 3). Stevens-Johnson syndrome was rarely reported, with a risk of 0.09 per 100 patients. All cases of SJS resulted in treatment discontinuation. The relative risk of rash with LTG compared with placebo from two RCTs, involving 112 patients on LTG, was 3.66 [95% CI: 0.11-123.11], which was not statistically significant (p=0.47). Seventy two children had a deterioration in seizure control and the risk of aggravated seizures was 2.14 per 100 patients (Table 2).

There were significantly higher risks of dizziness [RR 4.57, 95% CI: 1.88-11.12, p <0.001], abdominal pain [RR: 2.53, 95% CI: 1.12-5.70, p=0.03] and nausea [RR: 5.94, 95% CI: 1.59-22.13, p=0.008] with LTG than placebo in the RCTs (Table 4). Twenty one percent of children receiving LTG had dizziness compared with 4.5% on placebo. Sixteen percent and 12.5% of LTG treated children had abdominal pain and nausea respectively, compared with 6% and 1.7% of placebo treated children. The relative risks of other common AEs from RCTs identified were not significantly different between LTG and placebo treated children (Table 4).

When compared with valproic acid, the risk of somnolence and vomiting, were significantly lower for LTG [RR: 0.35, 95% CI: 0.13-0.89, p=0.04) and [RR: 0.20, 95% CI: 0.04-0.89, p=0.03), respectively. Three percent and 1.3% of children on LTG had somnolence and vomiting, while these symptoms were recorded in 9.5% and 6.8% of those on valproic acid. The risk of other common adverse events such as, rash, dizziness, headache and seizure aggravation, were not significantly different (Table 4).

Discontinuation of LTG treatment due to adverse drug reactions (ADRs) was recorded in 72 children (1.9% of all treated patients). Rash (58%) and seizure aggravation (21%) were the most common reasons (Table 3).

Table 2: Risk of all adverse events from pooled prospective cohort studies and RCTs according to body system (number of children=3,417)

Adverse events	No of Events	Risk per 100 patients
Central nervous system		
Somnolence	140	4.10
Headache	132	3.86
Aggravated seizures	72	2.11
Dizziness	63	1.84
Irritability	37	1.08
Aggression	32	0.94
Insomnia	31	0.91
Ataxia	29	0.85
Drowsiness	22	0.64
Hyperactivity	18	0.53
Hyperkinesia	17	0.50
Tremor	15	0.44
Behaviour change	13	0.38
Attention disturbance	10	0.29
Hostility	10	0.29
Depression	9	0.26
Personality change	9	0.26
Loss of concentration	5	0.15
Loss of memory	4	0.12
Lethargy	3	0.09
Disorientation	1	0.03
Anxiety	1	0.03
Nystagmus	1	0.03
Paraesthesia	1	0.03
Attempted suicide	1	0.03
	676	
Gastrointestinal tract		
Vomiting	127	3.72
Abdominal pain	39	1.14
Constipation	36	1.05
Nausea	34	1
Diarrhoea	32	0.94
Anorexia	11	0.32
	279	
Respiratory system		
Respiratory infection	197	5.77
Cough	59	1.73
Wheeze	6	0.18
Apnoea	1	0.03
	263	
Ear, Nose and Throat		
Nasopharyngitis	119	3.48
Ear disorders	104	3.04
Nasal congestion	12	0.35
	235	6.88
Others		
Rash	249	7.26
Fever	146	4.27
Asthenia	15	0.44
Fatigue	14	0.41
Increased appetite	8	0.23
Stevens-Johnson syndrome	3	0.09
	434	

Table 3: Adverse reactions leading to discontinuation of treatment

Adverse reaction	Number of patients (%)
Rash	42 (58.3%)
Aggravated seizure	15 (20.8%)
Headache	3 (4.2%)
Somnolence	3 (4.2%)
Vomiting	2 (2.8%)
Fever	2 (2.8%)
Tremor	1 (1.4%)
Paraesthesia	1 (1.4%)
Apnoea	1 (1.4%)
Disorientation	1 (1.4%)
Behavioural disturbance	1 (1.4%)
Total	72

Table 4: Relative risks of AEs of lamotrigine and comparators in RCTs

Relative risks of AEs between LTG and placebo					
AE	**Risk LTG (%)**	**Risk Comparator (%)**	**Relative risk (95% CI)**	**(p value * significant)**	**Reference**
Rash	24.1	15.7	3.66 [0.11-123.11]	0.47	23, 25
Fever	13.7	11.7	1.17 [0.60-2.29]	0.64	25, 26
Somnolence	24.5	7.9	1.37 [0.80-2.37]	0.25	25
Vomiting	22.5	18.8	1.19 [0.69-2.06]	0.53	25
Headache	16.5	15.1	1.10 [0.63-1.90]	0.74	23, 25
Aggravated seizure	3.0	11.4	0.32 [0.13-0.79]	0.01*	25, 27, 28
Dizziness	21.4	4.5	4.57 [1.88-11.12]	<0.001*	23, 25
Cough	10.5	0	5.00 [0.26-97.7]	0.29	26
Abdominal pain	16.1	6.1	2.52 [1.12-5.70]	0.03*	23, 25
Nausea	12.5	1.7	5.94 [1.59-22.13]	<0.001*	23, 25
Relative risks between LTG and Valproic acid					
Rash	3.6	1.2	2.48 [0.59-10.50]	0.22	24, 29
Somnolence	3.4	9.5	0.35 [0.13-0.95]	0.04*	24
Vomiting	1.3	6.8	0.20 [0.04-0.89]	0.03*	24
Headache	8.3	7.4	1.13 [0.54-2.34]	0.75	24, 29
Aggravated seizures	0.7	2.7	0.25 [0.03-2.18]	0.21	24
Dizziness	2.7	1.4	1.97 [0.37-10.61]	0.43	24

Case Reports

There were more case reports of rash than any other AE, accounting for about half (49%) of all reports [Supplementary Table 2]. Rash varied in severity from mild morbilliform rash to Toxic Epidermal Necrolysis (TEN). Other variants were urticarial, Stevens-Johnson syndrome and Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS syndrome). The period of onset of rash after commencement of LTG treatment varied between one day and 103 weeks, with the median duration of onset of 25 days [IQR: 14-35 days]. In half (48%) of the cases of rash, LTG was co-administered with valproic acid There were 7 case reports of seizure aggravation [Supplementary Table 2]. Other adverse reactions reported were: movement disorders, disseminated intravascular coagulopathy, parageusia and syndrome of inappropriate anti-diuretic hormone secretion.

Effect of dosing and polytherapy on ADRs

LTG doses were titrated over several weeks until the maximum maintenance dose was achieved. Patients receiving LTG monotherapy received an almost similar median initial dose (median 0.5mg/kg [1QR:0.4-1.1]) as those receiving combination treatment with valproic acid (median: 0.5mg/kg, [IQR: 0.15 -0.75]). Patients treated with combination therapy with enzyme inducing drugs received a higher median dose of initial LTG (1mg/kg [IQR: 0.6-2]). Children on mixed AED regimen, excluding valproic acid, received a higher median maintenance dose of LTG (median=15mg/kg [15-15.1]) than those on monotherapy (median 11mg/kg [IQR 10-14.4]) and valproic acid combination (5mg/kg [IQR: 5-5.1]).

LTG was given as part of a polytherapy regimen in 5 RCTs. The most frequent reports of rash (16%) were in a study with a high initial LTG starting dose of 0.5mg/kg/day in VPA co-medicated patients and 2mg/kg/day in those receiving enzyme inducing AEDs. The dose escalation to reach maintenance doses of 1-3 and 5-15mg/kg/day respectively, was achieved in 6 weeks[25]. Three other polytherapy studies [26-28] introduced LTG treatment at much lower doses (0.15-0.2mg/kg in VPA co-medicated patients and 0.6-1mg/kg/day in those receiving enzyme inducing drugs). The rates of dose escalation were much slower (12-19 weeks). Of these 3 studies, only one reported a single case of rash (5%) [26], while the other two did not record any rash. A fifth study administered 0.2mg/kg/day initial dose

to VPA co-medicated patients and 2mg/kg/day to those on enzyme inducing AEDs. This study recorded a 6% rash rate [31].

There were 4 RCTs in which LTG was administered as monotherapy [23, 24, 29, 30]. The initial dose in one study was 0.3mg/kg/day (24), dose escalation was slow (up to 16 weeks) and a 3% incidence of rash reported. The three other studies administered 0.5mg/kg/day as initial doses [23, 29, 30]. Two of these each reported a rash incidence rate of 7% [23, 30], one of these escalated the dose rapidly over 6 weeks [30]. The third study reported a 5% rate [29].

All but one of the prospective cohort studies used LTG polytherapy. Comparison of the incidence rates of ADRs between RCTs involving children who received LTG monotherapy or polytherapy showed that monotherapy users had significantly lower rates of AEs than polytherapy users (Table 5). The incidence rates of dizziness, somnolence, headache, vomiting, nausea and abdominal pain were all significantly lower in patients on LTG monotherapy than polytherapy. There was also a trend towards a decreased incidence of rash in patients on LTG monotherapy, although this was not statistically significant [p=0.09].

Table 5: Incidence rates of AEs in monotherapy and polytherapy LTG users in RCTs

Adverse event	Monotherapy n=340 (%)	Polytherapy, n=253 (%)	P value
Rash	18 (5.3)	21(8.3)	0.09
Headache	16 (4.7)	20 (7.9)	0.02*
Nasopharyngitis	13 (3.8)	14 (5.5)	0.33
Somnolence	5 (1.5)	47 (18.6)	<0.001*
Abdominal pain	5 (1.5)	13 (5.1)	0.01*
Dizziness	4 (1.2)	27 (10.7)	<0.001*
Nausea	3 (0.9)	11 (4.3)	0.01*
Increased seizure	1 (0.3)	0 (0)	1.00
Vomiting	0 (0)	22 (8.7)	<0.001*
Fever	0 (0)	16 (6.3)	<0.001*
Ear infection	0 (0)	9 (3.6)	<0.001*
Cough	0 (0)	2 (0.7)	0.18
Others	65 (19.1)	111 (43.9)	-
Total	127	313	-

% ,incidence rate; * significant; n= number of patients

DISCUSSION

Rash was the most common AE in children receiving LTG treatment. The risk of rash was 7.3 episodes per 100 children. It also accounted for 10% of all AEs. Other commonly reported AEs were neurological symptoms, mainly somnolence, headache, aggravated seizures, dizziness, as well as vomiting. A previous safety review of 13 manufacturer sponsored clinical trials involving 1,096 children had also shown a similar result [32].

Children are more likely than adults to develop a rash with lamotrigine[33]. Simple maculopapular rashes were the most common types of rash identified in this review. They were usually transient and often without long term complications. LTG associated rashes are usually highly variable and the most severe forms are SJS and TEN. TEN is the more severe of these two, with an average background mortality rate of 25-35% compared to 1-5% in patients with SJS[34]. Patients with TEN are also more likely to have long term complications, with up to 50% of them reported to have long term problems[34]. Despite rash being the most common ADR with LTG, there were no statistically significant differences between LTG and either placebo or valproic acid in relation to the occurrence of rash in the RCTs reviewed. Only two RCTs compared the risks of rash between LTG and placebo or valproic acid, but these studies were insufficiently powered to adequately compare the risk of rash.

Rapid dose escalation and high initial doses have been reported to predispose to rash[7]. According to the current recommendations in the UK and USA, an initial dose of 0.15mg/kg/day should be given to VPA co-medicated children, 0.3mg/kg/day to those receiving enzyme inducing AEDs and monotherapy[35, 36]. The protective mechanism of the introduction of small incremental doses, although not fully understood, is believed to involve the desensitisation of antigen presenting cells and T lymphocytes[37]. HLA B genotyping may be useful in determining the predisposition to LTG induced rash, but the level of HLA involvement is not fully determined [38]. Co-medication with valproic acid is also a significant predictor of rash in LTG treated patients[33]. Half of the case reports of rash identified in this review occurred when LTG was concomitantly administered with valproic acid. Valproic acid is a glucuronide inhibitor which increases the half-life of LTG and

decreases its clearance[39]. Due to this inhibitory effect, LTG starting and maintenance doses are recommended to be lower during concurrent valproic acid therapy.

Neurological effects are the most common ADRs of AEDs [40]. Somnolence, headache and dizziness were frequently reported among patients in this review. A previous study had identified somnolence as the most common ADR in patients receiving LTG as add-on treatment; while a much lower incidence was reported in monotherapy users [32]. A similar pattern has been shown in this study, with a significantly lower incidence of somnolence ($p<0.001$) reported in patients on monotherapy. Comparative safety analysis of RCTs in this review however shows that patients receiving LTG had significantly lower risk of somnolence than those treated with valproic acid. The small number of studies included in the meta-analyses necessitates a cautious interpretation of this result.

About 2% of patients had an increase in seizures. Additionally, increased seizures was the second most common reason for discontinuing LTG. Seizure aggravation is a recognised problem in patients with epilepsy receiving LTG, the cause and mechanisms of these paradoxical drug-induced seizures are unknown. New seizures may not be easily traced to antiepileptic drugs since there is usually an inherently high variability in seizure frequency in epileptic patients. [41]. It is thought to be most common in children with myoclonic epilepsy[8].

For most of the ADRs, children on polytherapy had significantly higher incidence of ADRs than those on monotherapy (Table 5). We have only compared ADRs in RCTs, because only one prospective monotherapy cohort study was identified. In addition to the potential interactions between the drugs, the addition of one or more AED also adds to the chances of more ADRs. The relationship between polytherapy and increased ADRs has been established in a previous study of AEDs [42]. Polytherapy with valproic acid has also been shown to be associated with a greater risk of hepatotoxicity, pancreatitis and other serious ADRs [43].

A limitation of this study is that only one reviewer searched and selected the included articles. However, the quality of all the included articles was independently assessed by two reviewers. The relationship between rash and age could not be established because most of the studies did not report the ages of children with rash.

In conclusion, rash, which occurred in a spectrum of varying intensity, was the most common ADR associated with LTG; it was also the most common reason for the discontinuation of treatment. High initial LTG dose and rapid dose escalation are risk factors for rash. Patients on LTG polytherapy are more likely to develop ADRs than monotherapy users.

IMAGE LEGEND

Figure 1: Flow chart for screened articles

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CONTRIBUTORS

OE, HS and IC conceived the idea as part of OE's PhD. OE did the literature search and extracted the data. HS and IC reviewed the extracted data. OE wrote the first draft and IC and HS edited the draft and subsequent drafts. OE wrote the final draft. OE, HS and IC agreed to the final draft.

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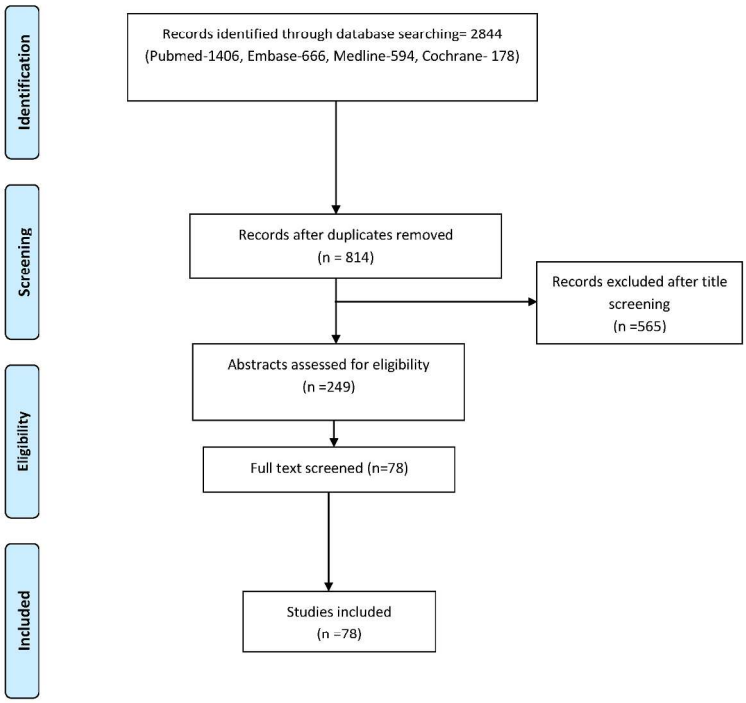

Search outcome for included articles
210x297mm (300 x 300 DPI)

Table 1: Summary of data from cohort studies

Ref	Comparator	Design	No on LTG	No on comparator	Seizure type	Dose (mg/kg/day)	Duration of follow up (weeks)	Funding	AEs LTG	AEs comparator
1	None	Prospective	125	-	Partial	0.15-15.6	48	Industry	637	-
2	None	Prospective	285	-	Unspecified	1-15	48	None	342	-
3	None	Prospective	13	-	Infantile Spasm	2-10	12	Institutional	0	-
4	None	Prospective	57	-	Unspecified	0.4-3	24	None	0	-
5	None	Prospective	40	-	Lennox-Gastaut	4-10	12	None	9	-
6	None	Prospective	252	-	Unspecified	NA	≤192	Industry	129	-
7	None	Prospective	40	-	Unspecified	1-15	12	None	5	-
8	None	Prospective	37	-	Unspecified	0.5-15	1-104	None	6	-
9	None	Prospective	56	-	Generalised	0.3-15	≤104	None	29	-
10	None	Prospective	155	-	Unspecified	1-15	53-221	None	87	-
11	None	Prospective	54	-	Absence	0.3-10.2	80	Industry	114	-
12	None	Prospective	1598		Unspecified	NA	≥24 weeks	Institutional	166	-
1	VPA	Retrospective	82	132	Unspecified	3-13	≤160	None	2	0
14	None	Retrospective	72	-	Unspecified	1.1-13.7	3-552	None	6	-
15	ETX/VPA	Retrospective	11	35/41*	Absence	1-6	NA	None	3	12/17*
16	VGB/GBP	Retrospective	132	80/39*	Unspecified	NA	NA	None	20	10/24*
17	None	Retrospective	16	-	Lennox-Gastaut	NA	NA	None	25	-

* Values for second comparator

Table 2: Adverse reactions from 50 case reports

Reference	ADR	Number of cases	Median days of onset	ł Comments
(18-40)	Mucocutaneous reactions	26	28	One child died
41-47)	Worsening/new seizures	7	21.5	All recovered
48-50	Ballism/chorea/movement disorders	6	*5	All recovered
(51-53)	Mania	3	*14	All recovered
(54,55)	Prolonged aPTT	2	*168	Both recovered
(56, 57)	SIADH	2	*5	Both recovered
(58)	Paraguesia	1	*5	Recovered
(59)	Hepatic failure	1	-	Recovered
(60)	Hyponatremia	1	-	Recovered
(61)	Myocarditis	1	-	Recovered
(62)	DIC	1	-	Recovered
(63)	Vanishing bile duct	1	-	Recovered
(64)	Haemophagocytic syndrome	1	21	Recovered

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PRISMA 2009 Checklist

SAFETY OF LAMOTRIGINE IN PAEDIATRICS: A SYSTEMATIC REVIEW

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	5
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	6

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	6
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	-
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Fig 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	-
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	6
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	12
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	12
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	6
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	-
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	16
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	17
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	18
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	20

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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SAFETY OF LAMOTRIGINE IN PAEDIATRICS: A SYSTEMATIC REVIEW

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SAFETY OF LAMOTRIGINE IN PAEDIATRICS: A SYSTEMATIC REVIEW

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Keywords –Lamotrigine, safety, adverse reaction, rash

Word count: 2,479

ABSTRACT

Objectives: To identify adverse drug reactions associated with lamotrigine in children and compare the safety profile with other antiepileptic drugs.

Setting: Databases EMBASE (1974-April 2015), Medline (1946-April 2015), PubMed and the Cochrane library for randomised controlled trials were searched for studies on safety of lamotrigine.

Participants: All studies involving paediatric patients aged ≤ 18years who have received at least a single dose of lamotrigine with safety as an outcome measure were included.

Primary and secondary outcome measures: The primary outcome measure was safety of lamotrigine. Drug interaction of lamotrigine was the secondary outcome.

Results: A total of 78 articles involving 3,783 paediatric patients were identified. There were 2,222 AEs reported. Rash was the most commonly reported AE, occurring in 7.3% of the patients. Stevens-Johnson syndrome was rarely reported, with a risk of 0.09 per 100 patients. Discontinuation due to an adverse drug reaction (ADR) was recorded in 72 children (1.9% of all treated patients). Fifty eight percent of treatment discontinuation was attributed to different forms of rash and 21% due to increased seizures. Children on lamotrigine monotherapy had lower incidences of AEs. Headache (p=0.02), somnolence (<0.001), nausea (p=0.01), vomiting (p<0.001), dizziness (p<0.001) and abdominal pain (p=0.01) were significantly lower among children on monotherapy.

Conclusions: Rash was the most common ADR of lamotrigine and the most common reason for treatment discontinuation. Children receiving polytherapy have a higher risk of AEs than monotherapy users.

STRENGTHS AND LIMITATIONS OF THIS STUDY

1. This systematic review assessed the quality of all the prospective studies
2. Randomised controlled trials (RCTs), cohort studies and case reports were reviewed.
3. Only a limited number of RCTs of lamotrigine in children have been published, thus limiting the power of the meta-analysis.
4. The risks of adverse reactions between monotherapy and polytherapy users were compared in RCTs alone, because only one prospective cohort study involving children receiving lamotrigine monotherapy was identified.

BACKGROUND

Lamotrigine (LTG) was first synthesised in the early 1980s. It was approved for adult use in Ireland in 1990, the UK in 1991 and by the US Food and Drug Administration (FDA) in 1994[1]. Since its market authorisation over two decades ago, it has been used increasingly for the treatment of paediatric epilepsy. It is the most commonly prescribed new generation AED, accounting for 65% of new anti-epileptic drug (AED) prescriptions in the UK[2] and 12% of all AED prescriptions for children in the Netherlands[3].

In the UK, LTG is recommended as monotherapy for the first line treatment for newly diagnosed focal seizures and as an adjunct for refractory focal seizures in children[4]. It is a second line monotherapy drug for new onset generalised seizures and a useful adjunct for refractory generalised seizures. It is the third drug of choice, after ethosuximide and valproate for absence seizures, for which it may be administered as a monotherapy or polytherapy[4].

Dosing of LTG in children on adjunctive therapy is dependent on the effect of the co-administered drug. Higher doses may be required when co-administered with AEDs such as phenobarbital, phenytoin, carbamazepine and oxcarbazepine, which have been shown to increase the drug's clearance and reduce its plasma concentration. Conversely, valproic acid reduces LTG clearance and raises its plasma concentration by as much as two fold, hence a lower dose is recommended[5].

A safety concern with LTG in children is the occurrence of a skin rash. This can vary in intensity, from transient mild rash to Stevens-Johnson's syndrome (SJS), which can be fatal[6]. Children are generally more predisposed to skin rashes than adults[7]. Most of the other known adverse reactions are neurological and are largely dose dependent[7]. LTG can worsen myoclonic seizures and is usually avoided in patients with severe myoclonic epilepsy of infancy (Dravets syndrome)[8].

This systematic review was performed to identify all studies of LTG safety in children, determine the adverse reactions of LTG and compare the safety of the drug with other AEDs.

METHODS

Search strategy

Databases EMBASE (1974-April 2015), Medline (1946-April 2015), PubMed and the Cochrane database of randomised controlled trials (RCTs) were searched for original research or reports in which paediatric patients received at least a single dose of LTG with safety as an outcome measure. 'Paediatrics' was defined as any patient ≤18 years old. All studies satisfying these criteria were included irrespective of the language of publication. A search combining Lamotrigine with pediatric* or paediatric* or child* or neonate* or neonat* or infan* or newborn or adolescent* or boy* or girl* or toddler as multipurpose search was done. All included articles were independently evaluated by two reviewers. Study was conducted in compliance with the PRISMA guidelines and registered on PROSPERO (Number: CRD42013006910 available from:

http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42013006910)

Data extraction

Data extracted from each study included: year of study, setting, age of patients, study design, number of patients receiving LTG and comparator, dose, type of seizure, study outcome, summary of result, type of therapy, number of withdrawals and reason for withdrawal and the number and type of adverse events (AEs) for both LTG and the comparator drug(s).

Data quality assessment

The RCTs were assessed for quality using the Cochrane collaboration's tool for assessing risk of bias in randomised trials[9]. Observational studies were assessed using the System for the Unified Management of the Review and Assessment of Information (SUMARI)[10]. This form comprises of nine appraisal criteria and any study that met more than 4 of these criteria was considered to be of a sufficiently good quality. All studies were independently assessed by two reviewers; a third blinded reviewer was involved only if both reviewers did not agree on any study.

Data collection and statistical analysis

All relevant data were extracted onto an Excel spread sheet. Chi square analysis was used to compare categorical data. The RCTs were aggregated and meta-analyses were conducted using Revman version 5. The relative risks of AEs present in at least two RCTs were calculated. A relative risk (RR) greater than 1 indicates a positive effect of LTG. After testing for homogeneity (I^2 ≤50% or Chi^2 p≥0.05), the fixed effect model was used for homogeneous data and random model for heterogeneous data.

RESULTS

Summary of studies

A total of 78 articles with reports on safety of lamotrigine were identified after the literature search (Figure 1). A total of 3,783 paediatric patients were administered LTG. The most common types of articles were case reports (Table 1). The largest number of patients was in cohort studies (3,012, 80%). There were 17 cohort studies and 9 RCTs. There were 50 case reports involving 53 children. All RCTs were of sufficiently good quality and eligible for meta-analyses (Figure 2). All cohort studies were considered to be of good quality and were included in the final data aggregation (Supplementary Table 1).

Table 1: Summary of all articles

Study type	Number of studies	Number of AEs	Number of patients (%)
Prospective cohort	12	1524	2712 (71.7%)
Retrospective cohort	5	56	313 (8.3%)
RCT	9	549	593 (15.7%)
Case report	50	53	53 (1.4%)
Cross sectional	1	27	65 (1.7%)
Case control	1	13	47 (1.2%)
	78	**2222**	**3783**

Safety results

There were 2,222 documented adverse events (AEs) in 3,783 children in the reviewed articles. The majority (1,524) of the AEs were reported in 12 prospective cohort studies [11-22][Supplementary Table 2]. There were 549 AEs reported from RCTs [23-31].

Prospective studies

Common adverse events (≥1/100 and <1/10) from pooled prospective studies (RCTs and cohorts) were: rash, headache, fever, somnolence, vomiting, seizure aggravation, dizziness, cough, aggression, ataxia and insomnia. Uncommon AEs (≥1/1000 and <1/100) were: behavioural disturbance, nausea and anorexia (Table 2). About one-third of all AEs (35.8%) were neurological events, while gastrointestinal and respiratory events were 14.8% and 13.9% of all AEs respectively.

Rash was the most common AE in children receiving LTG. From all prospective studies, the risk of rash was 7.3 per 100 patients (Table 2). It accounted for 13% of all AEs. It was also the most common reason for withdrawal of therapy, with 58% of treatment discontinuation attributed to different forms of rash (Table 3). Stevens-Johnson syndrome was rarely reported, with a risk of 0.09 per 100 patients. All cases of SJS resulted in treatment discontinuation. The relative risk of rash with LTG compared with placebo from two RCTs, involving 112 patients on LTG, was 3.66 [95% CI: 0.11-123.11], which was not statistically significant (p=0.47). Seventy two children had deterioration in seizure control and the risk of aggravated seizures was 2.14 per 100 patients (Table 2).

There were significantly higher risks of dizziness [RR 4.57, 95% CI: 1.88-11.12, p <0.001], abdominal pain [RR: 2.53, 95% CI: 1.12-5.70, p=0.03] and nausea [RR: 5.94, 95% CI: 1.59-22.13, p=0.008] with LTG than placebo in the RCTs. Twenty one percent of children receiving LTG had dizziness compared with 4.5% on placebo. Sixteen percent and 12.5% of LTG treated children had abdominal pain and nausea respectively, compared with 6% and 1.7% of placebo treated children. The relative risks of other common AEs from RCTs identified were not significantly different between LTG and placebo treated children (Figures 3 &4).

When compared with valproic acid, the risk of somnolence and vomiting, were significantly lower for LTG [RR: 0.35, 95% CI: 0.13-0.89, p=0.04) and [RR: 0.20, 95% CI: 0.04-0.89, p=0.03),

respectively. Three percent and 1.3% of children on LTG had somnolence and vomiting, while these symptoms were recorded in 9.5% and 6.8% of those on valproic acid. The risk of other common adverse events such as, rash, dizziness, headache and seizure aggravation, were not significantly different (Figure 5).

Discontinuation of LTG treatment due to adverse drug reactions (ADRs) was recorded in 72 children (1.9% of all treated patients). Rash (58%) and seizure aggravation (21%) were the most common reasons (Table 3).

Table 2: Risk of all adverse events from pooled prospective cohort studies and RCTs according to body system (number of children=3,417)

Adverse events	No of Events	Risk per 100 patients
Central nervous system		
Somnolence	140	4.10
Headache	132	3.86
Aggravated seizures	72	2.11
Dizziness	63	1.84
Irritability	37	1.08
Aggression	32	0.94
Insomnia	31	0.91
Ataxia	29	0.85
Drowsiness	22	0.64
Hyperactivity	18	0.53
Hyperkinesia	17	0.50
Tremor	15	0.44
Behaviour change	13	0.38
Attention disturbance	10	0.29
Hostility	10	0.29
Depression	9	0.26
Personality change	9	0.26
Loss of concentration	5	0.15
Loss of memory	4	0.12
Lethargy	3	0.09
Disorientation	1	0.03
Anxiety	1	0.03
Nystagmus	1	0.03
Paraesthesia	1	0.03
Attempted suicide	1	0.03
	676	
Gastrointestinal tract		
Vomiting	127	3.72
Abdominal pain	39	1.14
Constipation	36	1.05
Nausea	34	1
Diarrhoea	32	0.94
Anorexia	11	0.32
	279	
Respiratory system		
Respiratory infection	197	5.77
Cough	59	1.73
Wheeze	6	0.18
Apnoea	1	0.03
	263	
Ear, Nose and Throat		
Nasopharyngitis	119	3.48
Ear disorders	104	3.04
Nasal congestion	12	0.35
	235	6.88
Others		
Rash	249	7.26
Fever	146	4.27
Asthenia	15	0.44
Fatigue	14	0.41
Increased appetite	8	0.23
Stevens-Johnson syndrome	3	0.09
	434	

Table 3: Adverse reactions leading to discontinuation of treatment

Adverse reaction	Number of patients (%)
Rash	42 (58.3%)
Aggravated seizure	15 (20.8%)
Headache	3 (4.2%)
Somnolence	3 (4.2%)
Vomiting	2 (2.8%)
Fever	2 (2.8%)
Tremor	1 (1.4%)
Paraesthesia	1 (1.4%)
Apnoea	1 (1.4%)
Disorientation	1 (1.4%)
Behavioural disturbance	1 (1.4%)
Total	72

Case Reports

There were more case reports of rash than any other AE, accounting for about half (49%) of all reports [Supplementary Table 3]. Rash varied in severity from mild morbilliform rash to Toxic Epidermal Necrolysis (TEN). Other variants were urticarial, Stevens-Johnson syndrome and Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS syndrome). The period of onset of rash after commencement of LTG treatment varied between one day and 103 weeks, with the median duration of onset of 25 days [IQR: 14-35 days]. In half (48%) of the cases of rash, LTG was co-administered with valproic acid There were 7 case reports of seizure aggravation [Supplementary Table 3]. Other adverse reactions reported were: movement disorders, disseminated intravascular coagulopathy, parageusia and syndrome of inappropriate anti-diuretic hormone secretion.

Effect of dosing and polytherapy on ADRs

LTG doses were titrated over several weeks until the maximum maintenance dose was achieved. Patients receiving LTG monotherapy received an almost similar median initial dose (median 0.5mg/kg [1QR:0.4-1.1]) as those receiving combination treatment with valproic acid (median: 0.5mg/kg, [IQR: 0.15 -0.75]). Patients treated with combination therapy with enzyme inducing drugs received a higher median dose of initial LTG (1mg/kg [IQR: 0.6-2]). Children on mixed AED regimen, excluding valproic acid, received a higher median maintenance dose of LTG (median=15mg/kg [15-15.1]) than those on monotherapy (median 11mg/kg [IQR 10-14.4]) and valproic acid combination (5mg/kg [IQR: 5-5.1]).

LTG was given as part of a polytherapy regimen in 5 RCTs. The most frequent reports of rash (16%) were in a study with a high initial LTG starting dose of 0.5mg/kg/day in VPA co-medicated patients and 2mg/kg/day in those receiving enzyme inducing AEDs. The dose escalation to reach maintenance doses of 1-3 and 5-15mg/kg/day respectively, was achieved in 6 weeks[25]. Three other polytherapy studies [26-28] introduced LTG treatment at much lower doses (0.15-0.2mg/kg in VPA co-medicated patients and 0.6-1mg/kg/day in those receiving enzyme inducing drugs). The rates of dose escalation were much slower (12-19 weeks). Of these 3 studies, only one reported a single case of rash (5%) [26], while the other two did not record any rash. A fifth study administered 0.2mg/kg/day initial dose

to VPA co-medicated patients and 2mg/kg/day to those on enzyme inducing AEDs. This study recorded a 6% rash rate [31].

There were 4 RCTs in which LTG was administered as monotherapy [23, 24, 29, 30]. The initial dose in one study was 0.3mg/kg/day (24), dose escalation was slow (up to 16 weeks) and a 3% incidence of rash reported. The three other studies administered 0.5mg/kg/day as initial doses [23, 29, 30]. Two of these each reported a rash incidence rate of 7% [23, 30], one of these escalated the dose rapidly over 6 weeks [30]. The third study reported a 5% rate [29].

All but one of the prospective cohort studies used LTG polytherapy. Comparison of the incidence rates of ADRs between RCTs involving children who received LTG monotherapy or polytherapy showed that monotherapy users had significantly lower rates of AEs than polytherapy users (Table 4). The incidence rates of dizziness, somnolence, headache, vomiting, nausea and abdominal pain were all significantly lower in patients on LTG monotherapy than polytherapy. There was also a trend towards a decreased incidence of rash in patients on LTG monotherapy, although this was not statistically significant [p=0.09].

Table 4: Incidence rates of AEs in monotherapy and polytherapy LTG users in RCTs

Adverse event	Monotherapy n=340 (%)	Polytherapy, n=253 (%)	P value
Rash	18 (5.3)	21(8.3)	0.09
Headache	16 (4.7)	20 (7.9)	0.02*
Nasopharyngitis	13 (3.8)	14 (5.5)	0.33
Somnolence	5 (1.5)	47 (18.6)	<0.001*
Abdominal pain	5 (1.5)	13 (5.1)	0.01*
Dizziness	4 (1.2)	27 (10.7)	<0.001*
Nausea	3 (0.9)	11 (4.3)	0.01*
Increased seizure	1 (0.3)	0 (0)	1.00
Vomiting	0 (0)	22 (8.7)	<0.001*
Fever	0 (0)	16 (6.3)	<0.001*
Ear infection	0 (0)	9 (3.6)	<0.001*
Cough	0 (0)	2 (0.7)	0.18
Others	65 (19.1)	111 (43.9)	-
Total	127	313	-

% ,incidence rate; * significant; n= number of patients

DISCUSSION

Rash was the most common AE in children receiving LTG treatment. The risk of rash was 7.3 episodes per 100 children. It also accounted for 10% of all AEs. Other commonly reported AEs were neurological symptoms, mainly somnolence, headache, aggravated seizures, dizziness, as well as vomiting. A previous safety review of 13 manufacturer sponsored clinical trials involving 1,096 children had also shown a similar result [32].

Children are more likely than adults to develop a rash with lamotrigine[33]. Simple maculopapular rashes were the most common types of rash identified in this review. They were usually transient and often without long term complications. LTG associated rashes are usually highly variable and the most severe forms are SJS and TEN. TEN is the more severe of these two, with an average background mortality rate of 25-35% compared to 1-5% in patients with SJS[34]. Patients with TEN are also more likely to have long term complications, with up to 50% of them reported to have long term problems[34]. Despite rash being the most common ADR with LTG, there were no statistically significant differences between LTG and either placebo or valproic acid in relation to the occurrence of rash in the RCTs reviewed. Only two RCTs compared the risks of rash between LTG and placebo or valproic acid, but these studies were insufficiently powered to adequately compare the risk of rash.

Rapid dose escalation and high initial doses have been reported to predispose to rash[7]. According to the current recommendations in the UK and USA, an initial dose of 0.15mg/kg/day should be given to VPA co-medicated children, 0.3mg/kg/day to those receiving enzyme inducing AEDs and monotherapy[35, 36]. The protective mechanism of the introduction of small incremental doses, although not fully understood, is believed to involve the desensitisation of antigen presenting cells and T lymphocytes[37]. HLA B genotyping may be useful in determining the predisposition to LTG induced rash, but the level of HLA involvement is not fully determined [38]. Co-medication with valproic acid is also a significant predictor of rash in LTG treated patients[33]. Half of the case reports of rash identified in this review occurred when LTG was concomitantly administered with valproic acid. Valproic acid is a glucuronide inhibitor which increases the half-life of LTG and

decreases its clearance[39]. Due to this inhibitory effect, LTG starting and maintenance doses are recommended to be lower during concurrent valproic acid therapy.

Neurological effects are the most common ADRs of AEDs [40]. Somnolence, headache and dizziness were frequently reported among patients in this review. A previous study had identified somnolence as the most common ADR in patients receiving LTG as add-on treatment; while a much lower incidence was reported in monotherapy users [32]. A similar pattern has been shown in this study, with a significantly lower incidence of somnolence ($p<0.001$) reported in patients on monotherapy. Comparative safety analysis of RCTs in this review however shows that patients receiving LTG had significantly lower risk of somnolence than those treated with valproic acid. The small number of studies included in the meta-analyses necessitates a cautious interpretation of this result.

About 2% of patients had an increase in seizures. Additionally, increased seizures was the second most common reason for discontinuing LTG. Seizure aggravation is a recognised problem in patients with epilepsy receiving LTG, the cause and mechanisms of these paradoxical drug-induced seizures are unknown. New seizures may not be easily traced to antiepileptic drugs since there is usually an inherently high variability in seizure frequency in epileptic patients. [41]. It is thought to be most common in children with myoclonic epilepsy[8].

For most of the ADRs, children on polytherapy had significantly higher incidence of ADRs than those on monotherapy (Table 4). We have only compared ADRs in RCTs, because only one prospective monotherapy cohort study was identified. In addition to the potential interactions between the drugs, the addition of one or more AED also adds to the chances of more ADRs. The relationship between polytherapy and increased ADRs has been established in a previous study of AEDs [42]. Polytherapy with valproic acid has also been shown to be associated with a greater risk of hepatotoxicity, pancreatitis and other serious ADRs [43].

A limitation of this study is that only one reviewer searched and selected the included articles. However, the quality of all the included articles was independently assessed by two reviewers. The relationship between rash and age could not be established because most of the studies did not report the ages of children with rash.

In conclusion, rash, which occurred in a spectrum of varying intensity, was the most common ADR associated with LTG; it was also the most common reason for the discontinuation of treatment. High initial LTG dose and rapid dose escalation are risk factors for rash. Patients on LTG polytherapy are more likely to develop ADRs than monotherapy users.

IMAGE LEGEND

Figure 1: Flow chart for screened articles

Figure 2: Risk of Bias summary for RCTs

Figure 3: Relative risks of AEs between LTG and placebo

Figure 4: Relative risks of AEs between LTG and placebo

Figure 5: Relative risks of AEs between LTG and Valproic acid

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CONTRIBUTORS

OE, HS and IC conceived the idea as part of OE's PhD. OE did the literature search and extracted the data. HS and IC reviewed the extracted data. OE wrote the first draft and IC and HS edited the draft and subsequent drafts. OE wrote the final draft. OE, HS and IC agreed to the final draft.

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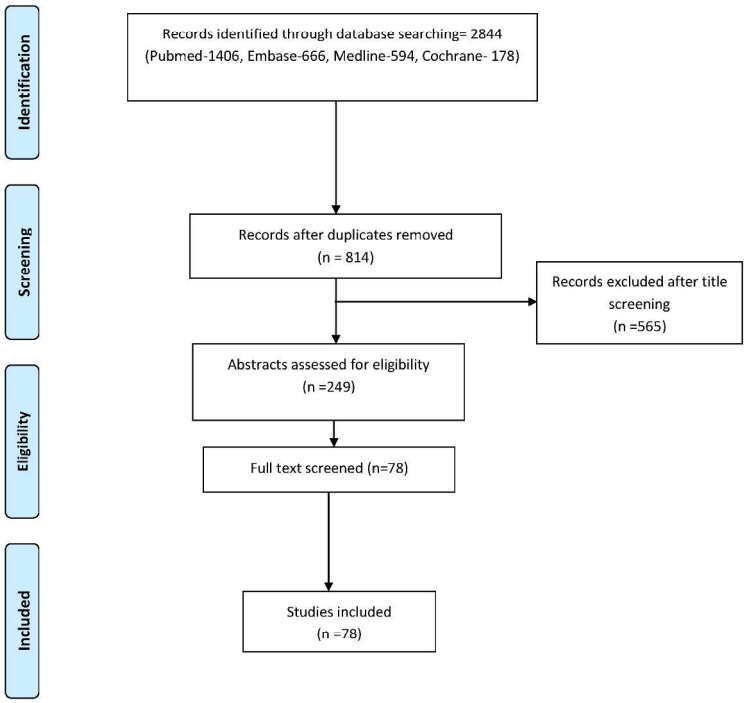

Search outcome for included articles
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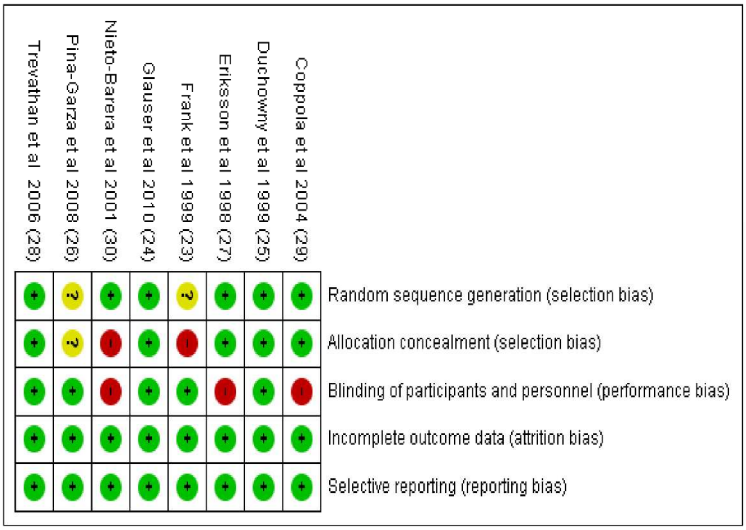

Green: low risk, Red: High risk, Yellow: unclear
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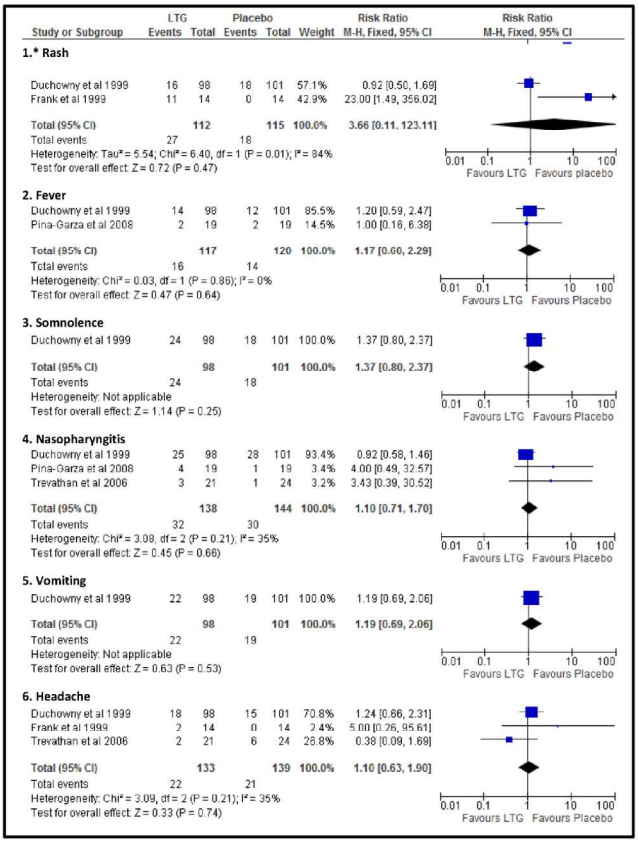

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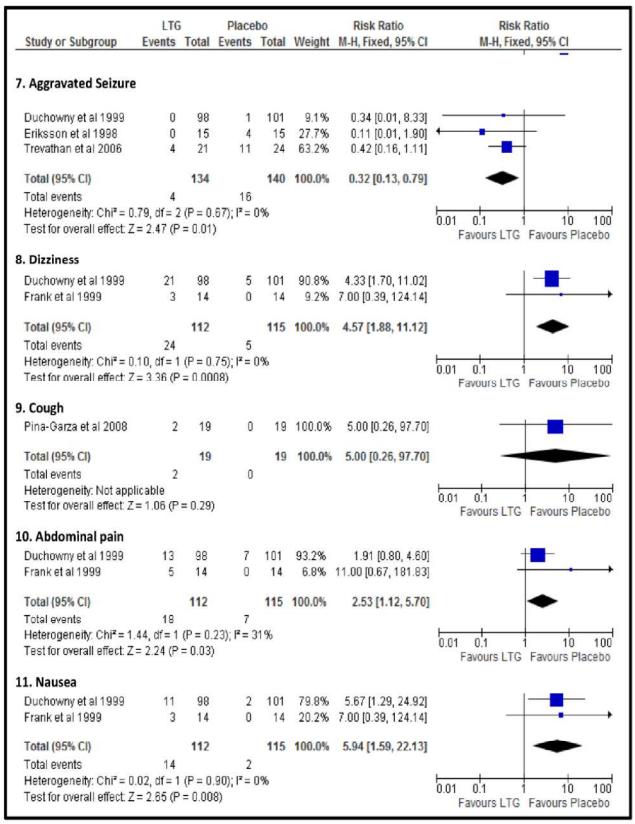

Relative risks of AEs: LTG vs placebo
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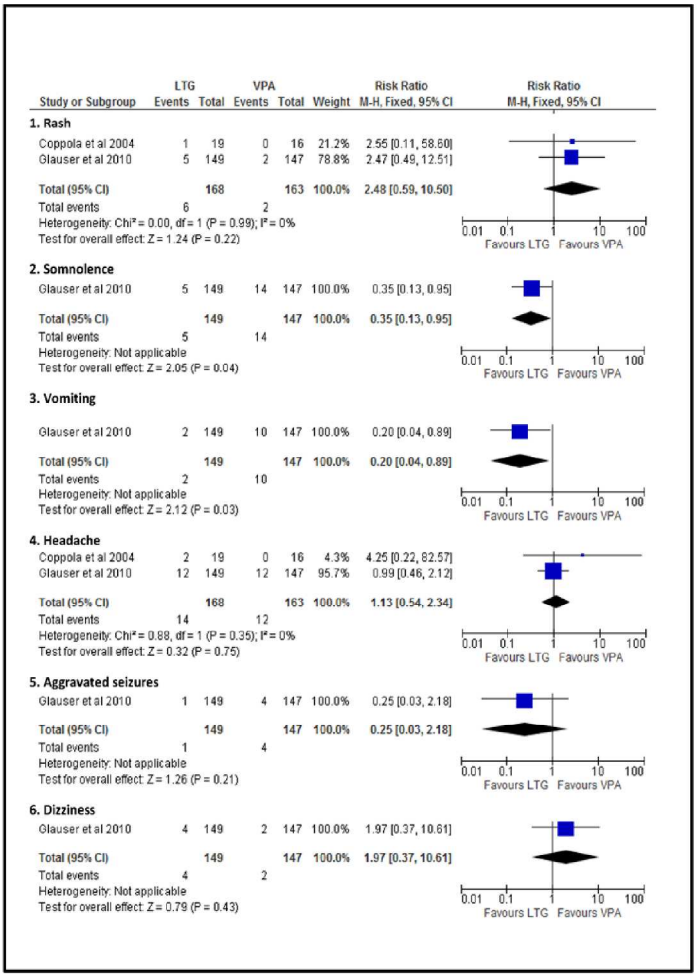

Relative risks of AEs: LTG vs valproic acid
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Table 1: Quality assessment of observational studies using the System for the Unified Management of the Review and Assessment of Information

References	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Sample size representative of population	Unclear	Yes	No	No	No	Yes	Unclear	No	No	Unclear	Yes	Yes	Yes	Yes	Yes	No	Yes
Patients at similar points in course of illness	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Unclear	Yes	Yes
Has selection bias been minimised	Unclear	Yes	Unclear	Unclear	Unclear	No	Unclear	Unclear	No	Yes	Yes	Yes	Yes	Yes	Yes	No	Unclear
Confounding factors identified	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Outcomes assessed objectively	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes
Sufficient follow up	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	No	Yes	Yes	Unclear	Yes	Yes	Unclear
Withrawal outcome stated/analysed	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Outcomes measured reliably	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes
Approriate statistics	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Table 2: Summary of data from cohort studies

Ref	Comparator	Design	No on LTG	No on comparator	Seizure type	Dose (mg/kg/day)	Duration of follow up (weeks)	Funding	AEs LTG	AEs comparator
1	None	Prospective	125	-	Partial	0.15-15.6	48	Industry	637	-
2	None	Prospective	285	-	Unspecified	1-15	48	None	342	-
3	None	Prospective	13	-	Infantile Spasm	2-10	12	Institutional	0	-
4	None	Prospective	57	-	Unspecified	0.4-3	24	None	0	-
5	None	Prospective	40	-	Lennox-Gastaut	4-10	12	None	9	-
6	None	Prospective	252	-	Unspecified	NA	≤192	Industry	129	-
7	None	Prospective	40	-	Unspecified	1-15	12	None	5	-
8	None	Prospective	37	-	Unspecified	0.5-15	1-104	None	6	-
9	None	Prospective	56	-	Generalised	0.3-15	≤104	None	29	-
10	None	Prospective	155	-	Unspecified	1-15	53-221	None	87	-
11	None	Prospective	54	-	Absence	0.3-10.2	80	Industry	114	-
12	None	Prospective	1598		Unspecified	NA	≥24 weeks	Institutional	166	-
13	VPA	Retrospective	82	132	Unspecified	3-13	≤160	None	2	0
14	None	Retrospective	72	-	Unspecified	1.1-13.7	3-552	None	6	-
15	ETX/VPA	Retrospective	11	35/41*	Absence	1-6	NA	None	3	12/17*
16	VGB/GBP	Retrospective	132	80/39*	Unspecified	NA	NA	None	20	10/24*
17	None	Retrospective	16	-	Lennox-Gastaut	NA	NA	None	25	-

* Values for second comparator

Table 3: Adverse reactions from 50 case reports

Reference	ADR	Number of cases	Median days of onset	Comments
(18-40)	Mucocutaneous reactions	26	28	One child died
41-47)	Worsening/new seizures	7	21.5	All recovered
48-50	Ballism/chorea/movement disorders	6	*5	All recovered
(51-53)	Mania	3	*14	All recovered
(54,55)	Prolonged aPTT	2	*168	Both recovered
(56, 57)	SIADH	2	*5	Both recovered
(58)	Paraguesia	1	*5	Recovered
(59)	Hepatic failure	1	-	Recovered
(60)	Hyponatremia	1	-	Recovered
(61)	Myocarditis	1	-	Recovered
(62)	DIC	1	-	Recovered
(63)	Vanishing bile duct	1	-	Recovered
(64)	Haemophagocytic syndrome	1	21	Recovered

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PRISMA 2009 Checklist

SAFETY OF LAMOTRIGINE IN PAEDIATRICS: A SYSTEMATIC REVIEW

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	5
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	6

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	6
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	-
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Fig 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	-
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	6
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	12
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	12
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	6
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	-
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	16
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	17
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	18
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	20

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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