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Risk of a lamotrigine-related skin rash: Current meta-analysis and postmarketing cohort analysis

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ABSTRACT

Purpose: We systematically reviewed studies to provide current evidence on the incidence and risk of skin rash in patients with LTG therapy.
Methods: PubMed and Scopus databases, up to 15 March 2014 were searched to identify relevant studies. Eligible studies included prospective studies, retrospective studies and postmarketing reports, which included data of skin rash in patients with LTG therapy.
Results: Forty-one articles met the entry criteria. A total of 4447 patients with LTG therapy from 26 prospective studies, 2977 patients from 8 retrospective studies, and 26,126 patients from 5/7 postmarketing reports were included. The overall incidence of skin rash with LTG therapy was 9.98% (444/4447) from prospective studies, 7.19% (214/2977) from retrospective studies, and 2.09% (547/26,126) from postmarketing reports. A meta-analysis of the risk of skin rash in 21 prospective studies, did not show a significant difference between patients with LTG and other drugs, including placebo, other ADEs or lithium (OR 0.99–2.41). In 6 respective studies, there was a significantly higher OR in patients with LTG compared with those with non-aromatic AEDs. However, there was no significant difference in rash risk between patients with LTG and aromatic AEDs.
Conclusions: Our study showed that LTG significantly increased the risk of developing a skin rash compared to non-aromatic AEDs. Our results support the need for large prospective population-based studies and clinical trials to determine whether LTG increases the risk of developing a skin rash than compared to other drugs.

1. Introduction

Lamotrigine (LTG) is the most commonly administered second-line antiepileptic-drugs (ADEs) and is also effective in the treatment of a variety of other abnormalities of neuronal excitability, including bipolar disorder [1,2], and neuropathic pain [3]. However, 10% of subjects in controlled trials are allergic to LTG and are susceptible to a wide spectrum of adverse cutaneous clinical manifestations including extremely painful and life-threatening conditions [4].

Skin reactions are a common side effect of antiepileptic drugs (AEDs) and a major cause of treatment discontinuation. The clinical spectrum of these reactions is wide. Most skin reactions are common and mild maculopapular rashes that disappear within a few days after discontinuing drug use. Benign rashes are relatively common with aromatic AEDs, such as carbamazepine (CBZ), phenytoin (PHT), and phenobarbital (PB), with a frequency ranging from 5 to 15% of treated individuals. Some of the newer drugs also frequently cause skin rashes, particularly lamotrigine (LTG), and oxcarbazepine (OXC).

The incidence of rash is now well recognized to be dose- and titration-dependent, and is related with concomitant therapy with valproic acid (VPA). Since the introduction of a gradual titration schedule in 1994, the rate of severe rashes with LTG has declined from 1 to 0.1–0.01 percent [5]. However, there was not a substantial reduction observed in the rate of benign rashes, which has still remained between 8 and 11 percent [6].

Although LTG has been used in everyday clinical practice for nearly 25 years and the possibility of rash is now routinely

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managed, it is still not clearly known whether LTG increases the risk of developing a skin rash compared to other drugs. Here, we systematically reviewed published studies to provide current evidence on the incidence of LTG related skin rashes and compared this risk with other drugs.

2. Methods

2.1. Search strategy

We searched the PubMed (data from 1990 to March 2014), and Scopus (up to March 2014) databases for relevant studies. The search terms used were: "lamotrigine", "lamictal", "rash", and "skin reaction". Studies were limited to human studies and were published in English.

A cutaneous adverse reaction was defined as any types of rash (erythematous, maculo-papular, papular, pustular or unspecified) that could only be caused by an antiepileptic drug effect and that resulted in contacting a physician.

2.2. Selection criteria

To determine the practical significance of the study, we evaluated the incidence and the risk of developing a skin rash in patients who received LTG therapy. Thus, we included multiple dose levels of LTG treatment. We included all prospective, retrospective and postmarketing studies reporting a skin rash with LTG therapy. Clinical trials that met the following criteria were included in the meta-analysis: (1) prospective randomized controlled trials or open-label trials of patients receiving LTG treatment and its presence with a control group; (2) retrospective study, which included the data of LTG related rashes and could be compared with other drugs.

We excluded reviews, editorials, single cases and case series, studies published only as abstracts, letters, or commentaries and studies they were a part of duplicate populations. For the meta-analysis, on the basis of the inclusion and exclusion criteria, we identified a total of 21 prospective case-controlled studies (1 study involving Asian subjects and 20 involving European–Caucasian subjects) (Table 1), and 6 retrospective studies (2 studies involving Asian subjects and 4 studies involving European–Caucasian subjects) (Table 2).

2.3. Data extraction and quality assessment

We designed and piloted a standardized data abstraction form to capture all of the relevant study-level information required for analysis. Two independent investigators performed the data extraction (W.X.Q. and X.J.), and any discrepancy between the reviewers was resolved by consensus. For each study, the following information was obtained: the author's name, year of publication, trial phase, number of enrolled subjects, treatment arms, number of patients in the treatment and control groups when available, median age, median treatment duration, and adverse outcomes of interest (skin rash).

2.4. Statistical analysis

All of the analyses were performed using STATA 12.0 (StataCorp, College Station, Texas, USA). A p-value of less than 0.05 was considered statistically significant, and all of the tests were two-sided. The crude odds ratios (ORs) and 95% confidence intervals (CIs) were used to express the risk of skin rash with LTG therapy compared with other drugs. Forest plots were used to depict the visual representation of the meta-analysis results. Meta-analysis was performed using fixed-effects [7] or random-effects [8] models. Heterogeneity was tested using w^2-based Cochran's Q statistic [9] and I^2 metric statistics [10]. Random-effects models were used only when there was considerable heterogeneity ($P < 0.05$ or $I^2 > 50\%$ among the studies).

Studies were classified according to the study type (prospective study, retrospective study and postmarketing reports). In the first two group, all of the crude OR calculated by the original data were pooled. We performed the analyses on only the observed crude rate estimates, primarily because there was no study that reported adjusted estimates. We also performed the following specified subgroup analyses: different control groups (placebo, other antiepileptic drugs, or other antidepressive drugs), different groups of patients (epilepsy, bipolar or patients with neuropathic pain), prospective study, and retrospective study.

3. Results

3.1. Study selection and characteristics

Our search yielded 748 records describing the use of LTG and a skin rash from the Pubmed and Scopus databases. The selection process is summarized in Fig.1. After the exclusion of duplicate studies and a review of the abstracts, a total of 94 human clinical studies were identified with information on LTG therapy and benign rashes. Full-text articles were retrieved for these records and carefully studied. Finally, in the prospective studies, a total of 26 studies involving LTG-induced rash were used to evaluate rash incidence [11–36] and 21 articles with controls fulfilling the inclusion and exclusion criteria were identified for meta-analysis [11–31] (Fig.1 and Table 1). In this group, 4447 patients receiving LTG treatment were investigated, including a variety of diseases: epilepsy (13 trials) [15,16,23–30,33,34,36], dipolar disorder (9 trials) [17–22,31,32,35], and neuropathic pain (1 magraine [11], 1 multiple sclerosis [12], 1 HIV-related [13], and 1 diabetic [14]). The sample sizes were within the range of 20–958 patients with LTG. The median age of study participants was 9.6–77 years.

In the retrospective studies, 8 articles were used to evaluate rash incidence [37–44] and 6 studies fulfilling the inclusion criteria were identified for meta-analysis [37–42], which were all derived from epileptic studies (Fig.1 and Table 2). The sample sizes were within the range of 8–1037 patients treated with LTG. Two articles were pediatric studies, of which one study included all age groups and 5 studies included patients older than 12 years.

There were 5/7 postmarketing studies that provided data on the skin rash incidence of LTG [45–47,49,50] (Table 3). Four studies were performed in the U.K., which were performed by Prescription-Event Monitoring (PEM) to establish the safety of LTG and other drugs, in which the entire population of prescriptions issued was accessible [45–47,50]. One study was performed in Germany [49], where the data were obtained from a database of 208,401 psychiatric inpatients who were monitored by the Safety surveillance project Drug Safety in Psychiatry from 1993 to 2005, which surveys clinically relevant adverse reactions to all marketed psychotropic drugs. One report was performed in Sweden [51], which aimed to determine the extent of the spontaneous reporting of ADRs in children. One study was on the safety profile of antiepileptic drugs in Italy [48], from January 1988 to June 2005. Only 2/7 of these studies followed cohorts of more than 10,000 subjects [45,49].

3.2. Incidence of skin rash

The overall incidence of skin rash with LTG treatment was 9.98% (444/4447) from 26 prospective clinical trials, 7.19% (214/2977) from 8 retrospective studies, and 2.09% (547/26,126) from 5 postmarketing reports.

Table 1
Characteristics of published prospective studies reporting skin rash with LTG therapy.

Study	Country	Study field	Study type	Age group	No. enrolled	Treatment arm	Median age (y)	M/F (N/N)	Median treatment	LTG dosage	No. analysis	No. rash	No. withdrawal
Steiner et al. (1997) [11]	U.K.	Pain migraine	RCTs	Adults	110	LTG	35.8	6/31	3M	200 mg/d	37	11	8
						LTG fixed dose				200 mg/d	18	7	7
						LTG escalated dose				200 mg/d	19	4	1
						Placebo	38.4	8/32	3M		40	1	1
Kapoor et al. (2010) [12]	Ireland	Pain MS	RCTs	Adults	120	LTG	51.9	16/45	48M	400 mg/d	61	12	3
				Adults	Placebo	50.1	27/42	48M			59	3	2
Simpson et al. (2003) [13]	USA	Pain HIV	RCTs	Adults	220	LTG	46	137/13	11w	402 mg/d	150	21	2
						Placebo	44	60/17	11w		77	9	1
Vinik et al. (2007) [14]	USA	Pain DM	RCTs	Adults	360	LTG 200	60.3	50/38	19w	200 mg/d	88	9	
						LTG 300	60.0	50/40	19w	300 mg/d	90	10	
						LTG 400	59.6	51/38	19w	400 mg/d	89	14	
			1			Placebo	59.8	66/22	19w		88	8	
Messenheimer et al. (1994) [15]	USA	Epi	RCTs cross over		98	LTG	35	41/47	14w	400 mg/d	94	14	3
						Placebo	35	41/47	14w		96	6	1
Motte et al. (1997) [16]	USA	Epi	RCTs	3-25y	169	LTG	9.6	54/25	16w	50–400 mg/d	79	7	
						Placebo	10.9	45/45	16w		90	6	
van der loos et al. (2010) [17]	Nertherland	Bipolar	RCTs	Adults	124	LTG	45.2	27/37	16w		64	9	
						Placebo	47.6	30/30	16w		60	4	
Calabrese et al. (1999) [18]	Lamictal study 602 Group	Bipolar	RCTs	Adults	194	LTG 50 mg/d	41	22/44	7w	50 mg/d	66	9	
						LTG 200 mg/d	42	28/35	7w	200 mg/d	63	7	
						Placebo	42	27/38	7w		65	7	
Calabrese et al. (2003) [19]	Lamictal 605 study group	Bipolar	Open-label	Adults	966	LTG	42.4	370/586	16w	200 mg/d	958	104	
			RCTs			LTG	44.1	70/89	18M	50–200 mg/d	169	12	
						Lithium	43.6	48/73	18M		121	5	
						Placebo	42.1	61/60	18M		121	3	
Normannet al. (2002) [20]	Germany	Bipolar	RCTs	Adults	40	LTG	39.6	6/14	9w	200 mg/d	20	3	
						Placebo	37.9	7/13	9w		20	1	
Bowden et al. (2003) [21]	Lamictal 606 study group	Bipolar	Open-label	Adults	349	LTG	40.7	172/175	8–16w		347	38	17
			RCTs	Adults	174	LTG	40.6	26/33	18M		59	2	0
						Lithium	41.9	22/24	18M		46	4	2
						Placebo	40.9	34/35	18M		69	6	2
Sajatovic et al. (2005) [22]	USA	Bipolar	RCTs	Elderly	98	LTG	60.5	16/17	18M	223 mg/d	33	1	
						Lithium	60.1	13/21	18M	740.7 mg/d	34	2	
						Placebo	62.2	17/14	18M		31	1	
Reunanen et al. (1996) [23]	U.K.	Epi	RCTs	12–72	343	LTG 100	33	54/61	24w	100 mg/d	115	6	2
						LTG 200	30	58/53	24w	200 mg/d	111	9	3
						CBZ600	32	50/67	24w	600 mg/d	117	10	6
Brodie et al. (1995) [24]	U.K.	Epi	RCTs	13–81	260	LTG	28	54/77	12w	150 mg/d	131	25	12
						CBZ	27	58/71	12w	600 mg/d	129	25	17
Brodie et al. (1999) [25]	U.K.	Epi	RCTs	Elderly	150	LTG	77	55/47	24w	57–500 mg/d	102	9	3
						CBZ	76	28/20	24w	200–2000 mg/d	48	25	9
ZengK et al. (2010) [26]	China	Epi	open trial	Adults	512	LTG	31	34/52	24M		86	4	4
						CBZ	27	87/81	24M		168	2	2
						PHT	30	36/23	24M		59	1	1
						VPA	28	104/88	24M		192	0	0
Gilliam et al. (1998) [27]	U.K.	Epi	RCTs	Adults	156	LTG add on	37	33/43	8w	500mgd	76	8	
						VPA add on	36	32/48	8w	1000 mg/d	80	6	
						LTG alone	37	33/43	12w	500 mgd	76	1	
						VPA alone	36	32/48	12w	1000 mg/d	80	1	
Steiner et al. (1999) [28]	U.K.	Epi	RCTs	13–70	181	LTG	28	47/39	6–48w	150 mg/d	86	12	
						PHT	27	54/41	6–48w	300 mg.d	95	9	

Labiner et al. (2009) [29]	USA	Epi	RCTs	Adults	268	LTG	38.3	63/69	12w	400 mg/d	132	8	
						LEV	39.1	56/80	12w	2000 mg/d	136	9	
Kluger et al. (2001) [30]	Germany	Epi	Open-label	Children	95	LTG	13.6	21/18	5y		39	5	2
						VGB	11.1	30/26F			56	1	
Licht et al. (2010) [31]	Sweden	Bipolar	RCTs	Adults	155	LTG	38.2	37/40	5y	400 mg/d	77	6	
						Lithium	37.3	42/36			78	5	
Brawn et al. (2006) [32]	USA	Bipolar	RCTs		410	LTG	37.2	77/128	7w		205	14	
						OFX	36.8	87/118			205	6	
Brodie et al. (1997) [33]	U.K.	Epi	RCTs	14–77	347	With VPA	28	48/69	16w	96 mg/d	117	20	
						With CBZ	31	61/68	16w	347 mg/d	129	9	
						With PHT	33	45/50	16w	359 mg/d	95	0	
Farrell et al. (1996) [34]	Canada	Epi	Open-label	Children	56	With VPA			24 M		21	4	
						Without VPA			24 M		35	1	
Calabrease et al. (1999) [35]	USA	Bipolar	Open-label	Adults	75	With VPA			48 W		15	1	
						LTG alone			48 W		60	6	
Beghi et al. (2003) [36]	U.K.	Epi	Open-label	All age	360	LTG alone			12M		158	7	
						LTG add on					111	5	

Epi: epilepsy; MS: multiple sclerosis; HIV: HIV related neuropathic pain; DM: diabetic neuropathic pain; RCTs: randomized controlled trials; LTG: lamotrigine; VPA: valproic acid; PHT:phenytoin; CBZ: carbamazepine; PB: phenobarbital; LEV: leveritacetam; VGB: vigabatrin; OFX: olanzapine/fluoxetine combination.

Table 2
Characteristics of published retrospective studies reporting skin rash with LTG therapy.

Study	Country	Study field	Age group	Median treatment (weeks)	Patients enrolled	Treatment arm	No of analysis	No of skin rash
Wang et al. (2012) [37]	China	Epi	Adults (≥18 y)	February 1999–April 2010	3793	LTG CBZ 58/1919; VPA 8/1754; OXC 15/214; TPM 7/667; GBP 1/52; LEV 2/121	261	23
Chung et al. (2007) [38]	USA	Epi	Adults (17–89 y)	104 weeks	828	LTG OXC 6/97; TPM 6/156; LEV 1/196; ZNS 4/128	251	18
Arif et al. (2007) [39]	USA	Epi	>16 y	January 2000–January 2005	5025	LTG CBZ 24/655; PHT 32/558; OXC 6/248; ZNS 10/219; GBP 1/378; VPA 3/411; LEV 4/627	1037	50
Hirsch et al. (2008) [40]	USA	Epi	≥12 y	January 2000–January 2005	1875	LTG CBZ 62/745; OXC 10/201; PHT 85/716; PB 17/276; ZNS 12/174	864	77
Alvestad et al. (2007) [41]	Norway	Epi	Adults	No data	2567 exposures	LTG CBZ 54/489; PHT 19/229; OXC 9/114; PB 4/211; VPA 1/391; LEV 1/155; TPM 0/141; VGB 0/144; GBP 0/73	359	29
Mogami et al. (2012) [42]	Japan	Epi	All age	February 1996–May 2009	76	LTG CBZ 6/55; VPA 2/57; PB 5/35; PHT 4/32; GBP 0/13	8	2
Shechter et al. [43]	Israel	Epi	Children	6–14 w	110	LTG TPM 0/45	65	4
McDonald et al. (2004) [44]	Ireland	Epi	Children	February 1996–September 2000	251	LTG VGB 0/129; GBP 0/39	132	11

Epi: epilepsy; LTG: lamotrigine; VPA: valproic acid; PHT: phenytoin; CBZ: carbamazepine; PB: phenobarbital; OXC: oxcarbazepine; GBP: gabapentin; TPM: topiramate; LEV: leveritacetam; VGB: vigabatrin; ZNS: zonisamide.

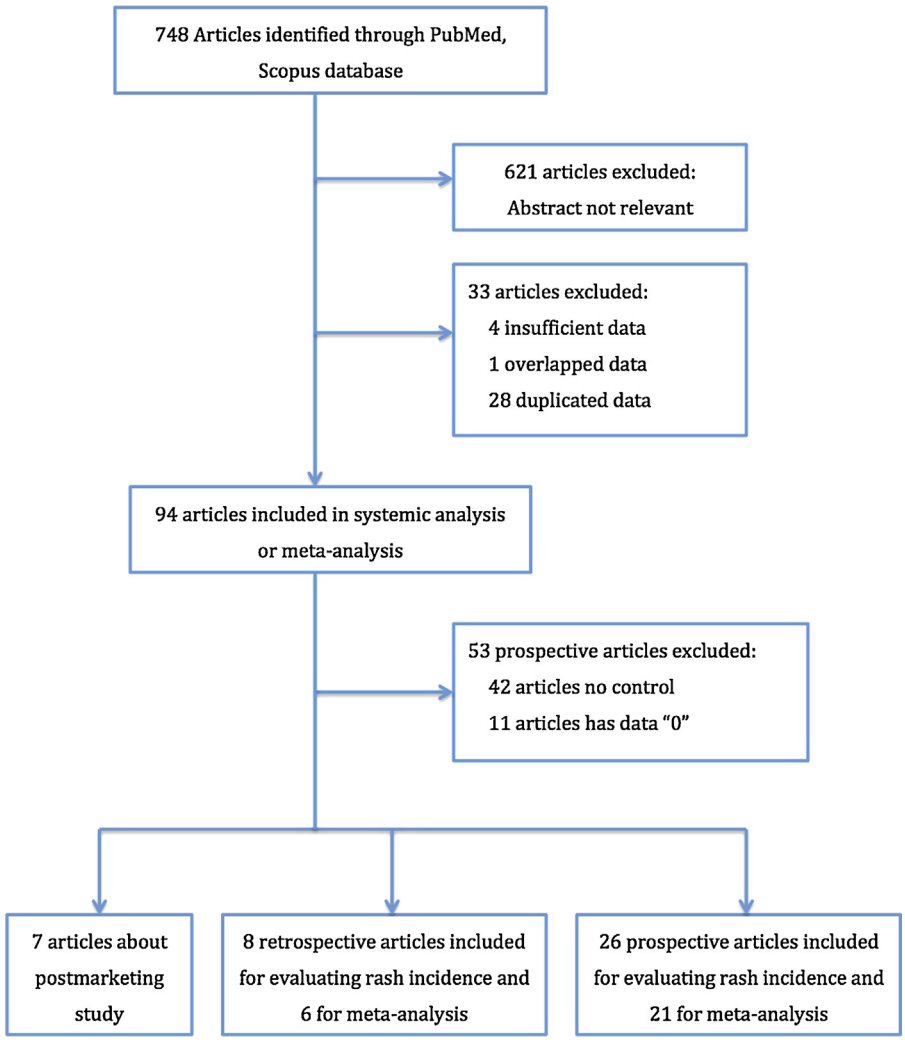

Fig. 1. Flow chart of selection of articles about skin rash in patients with LTG therapy.

3.3. Odds ratio of skin rash

3.3.1. Meta-analysis from prospective studies

To investigate the specific contribution of LTG in the development of a skin rash, we independently evaluated the OR of LTG-associated skin rashes compared with placebo control, lithium, and other AEDs. Our results showed that the use of LTG did not significantly increase the risk of developing a skin rash over placebo [in neuropathic pain group (4 studies): OR 2.41, 95% CI: 0.99–5.91; in epilepsy group (2 studies): OR 1.99, 95% CI: 0.95–4.81; and in bipolar group (6 studies): OR 1.49, 95% CI: 0.87–2.56], lithium (5 articles: OR 1.12, 95% CI: 0.62–2.03), other aromatic AEDs (5 articles: OR 0.99, 95% CI: 0.53–1.84), or non-aromatic AEDs (3 articles: OR 1.44, 95% CI: 0.75–2.76) (Fig.2). We did not perform a sensitivity analysis, and we studied the published bias to examine the stability and reliability of pooled OR of LTG-related skin rashes by the sequential omission of individual studies due to the small number of studies in each group.

3.3.2. Meta-analysis from retrospective studies

All 6 retrospective studies were epileptic studies. There was a significantly higher OR in patients with LTG treatment compared with non-aromatic AEDs [VPA (4 studies): OR 13.21, 95% CI 6.71–26.01; TPM (3 studies): OR 4.16, 95% CI 1.82–9.47; GBP (2 studies): OR 11.71, 95% CI 2.88–47.58; LEV (4 studies): OR: 8.87, 95% CI 4.32–18.23], except ZNS [(3 studies): OR 1.35, 95% CI 0.88–2.08](Fig.3). There was no significant difference in the rash risk between patients with LTG and aromatic AEDs [CBZ (6 studies): OR 1.41, 95% CI 0.93–2.15; OXC (5 studies): OR 1.38, 95% CI 0.99–1.92; and PHT (4 studies): OR 0.80, 95% CI 0.63–1.02], except PB [(3 studies): OR 1.99, 95% CI 1.25–3.17] (Fig.4). Due to the small number of studies in each group, we did not perform a sensitivity analysis, and we studies the published bias to examine the stability and reliability of pooled OR of LTG-related skin rash.

Furthermore, in prospective studies, we observed a low heterogeneity when studying LTG with placebo in epileptic patients, with placebo or lithium in bipolar patients, and with non-aromatic AEDs (I^2 = 0%, 7.4%, 0%, 8.3%, respectively). However, a considerable heterogeneity of more than 50% was observed in cases of placebo in patients with neuropathic pain and aromatic AEDs (I^2 = 59.9%, 54.7%, respectively).

In retrospective studies, we observed a low heterogeneity when studying the LTG with OXC, PHT, VPA, GBP, LEV, and ZNS (I^2 = 0%, 0%, 0%, 5%, 0%, 0%, respectively). However, a considerable heterogeneity of more than 50% was observed in cases of CBZ, TPM (I^2 = 69.8%, 65.2%, respectively).

4. Discussion

Our estimates showed that the overall incidence of skin rash with LTG therapy was 9.98% from prospective studies, 7.19% from retrospective studies, and 2.09% from postmarketing reports. The

Table 3
Characteristics of published postmarketing studies reporting skin rash with LTG therapy.

Study	Country	Age group	A group rash (*n*)	A group no rash (*n*)	B group rash (*n*)	B group no rash (*n*)	A/B	Remark
Mackay et al. (1997) [45]	U.K.	C	47	1551	212	10,529	LTG 2–12 y/ LTG total cohort	ID per 1000 patient-months in the first month of treatment
Wong et al. (2001) [46]	U.K.	All age (7–77 y)	100	950	8	353	LTG/GBP	Event frequency during first six months after starting the drug
			100	950	12	701	LTG/VGB	
Acharya et al. (2005) [47]	U.K.	D	204	10,690	12	2971	LTG/GBP	Adverse events causing treatment failure
Iorio et al. (2007) [48]	Italy	All age	LTG 34/51 (67%); CBZ 124/208 (60%); PB 68/98 (69%); GBP 20/80 (25%); PHT 30/56 (54%); VPA 14/55 (25%); OXC 11/43 (26%); VGB 0/35 (0%)				Rash	Skin reactions/number of reports total
			SJS: PB 10; CBZ 13; PHT 7; LTG 4 TEN: PB 7; CBZ 1; PHT 1; LTG 1				SJS TEN	Serious skin reactions
Lange-Asschenfeldt et al. (2009) [49]	Germany	All age	17	2731	60	18,706	LTG/CBZ	Cutaneous adverse reactions to psychotropic drugs
			17	2731	3	1409	LTG/OXC	
			17	2731	9	14,617	LTG/VPA	
Aurich-Barrera et al. (2010) [50]	U.K.	Children	48	2409	131	7248	LTG rash: children/ adults	Reasons for stopping
			5	2452	4	7373	LTG SJS: children/ adults	
Wallerstedt et al. (2011) [51]	Sweden	Children	3	1654				Serious individual case safety reports (ICSRs)

C: mean age: male 29 y, female 30 y; D: mean age: 30.5 y; LTG: lamotrigine; VPA: valproic acid; CBZ: carbamazepine; OXC: oxcarbazepine; GBP: gabapentin; VGB: vigabatrin; ID: incidence density; SJS: Stevens-Johnson syndrome; TEN: toxic epidermal necrolysis.

prospective study results were consistent with the previous pooled prospective data for 3348 patients from placebo-controlled and open trials of LTG in adults, which showed that 10% of patients exposed to LTG developed a rash [52,53].

This incidence is lower in retrospective studies compared to prospective studies, which indicates a limitation in this type of study. A retrospective study usually underestimates the true incidence due to recall bias or a physician bias when determining whether a specific rash is related to a given medication.

The postmarketing studies use relatively different methods from prospective trials or retrospective studies, which were performed by a spontaneous report or Prescription-Event Monitoring (PEM) to establish the safety of LTG and other drugs. There were four studies performed in the U.K., one study performed in Germany, one study performed in Italy, and one study performed in Sweden. The Drug Safety Research Unit (DSRU) performed PEM [54,55] of newly marketed drugs with widespread use in general practice in England, particularly with drugs that are intended for long-term use. However, systematic postmarketing surveillance of AEDs is still generally lacking, and large-scale postmarketing surveillance was performed to assess the safety of LTG in U.K. [45–47,50].

The main weakness of comparative PEM analysis is the potential for bias to confound differences between drugs [54,55]. Underreporting is a main disadvantage because the absolute number of ADR reports is not truly known. Data obtained from spontaneous reports or PEM when taken alone do not accurately quantify the risk associated with a drug. The reporting rate may vary over time and be influenced by factors, such as media attention. Although such studies cannot eliminate bias as effectively as RCTs, their strength lies where the RCT is often weakest, in providing a large number of patients from whom relative discontinuation rates can be precisely estimated.

In this meta-analysis of 21 prospective studies, we did not find a significant difference between patients with LTG and other drugs, including placebo, other ADEs and lithium (OR 0.99–2.41). In 6 respective studies, there was a significantly higher OR in patients with LTG compared with non-aromatic AEDs, which indicated that LTG treatment might significantly increase the risk of developing skin rash compared to non-aromatic AEDs. There was no significant different in rash risk between patients with LTG and aromatic AEDs, except PB. Due to few prospective control studies, we did not determine whether this merely reflected a publication bias or whether the risk of skin rash with LTG therapy is truly not higher compared to other aromatic AEDs or placebo.

Epilepsy is a serious chronic brain disorder that is characterized by recurrent unprovoked seizures that can be successfully treated and controlled using mono- or polytherapy in most patients. Skin reactions are a common side effect of AEDs and a major cause of treatment discontinuation [56]. Benign rash is relatively common with aromatic AEDs, such as CBZ, PHT and PB, with a frequency ranging from 5% to 15% of treated individuals. In addition, several newer drugs also frequently cause skin rashes, particularly LTG and OXC. Wang et al. [57] reported that skin reactions were three times more frequent with aromatic AEDs compared to non-aromatic AEDs.

5. Reliability of the study

There are several limitations to this study. First, the number of studies that addressed skin rashes with LTG therapy is small, in which only 4447 patients with LTG treatment from 26 prospective studies and 2977 patients from 8 retrospective studies were included in this study. A few studies have reported serious life-threatening rashes; however, we could not obtain the incidence of a serious rash. Second, different study designs, treatment strategies, durations and concomitant administration of drugs contribute to an increase in the clinical heterogeneity of the meta-analysis, which make the interpretation of the meta-analysis more problematic. Third, the data did not allow us to perform multivariable regression to determine which variables were

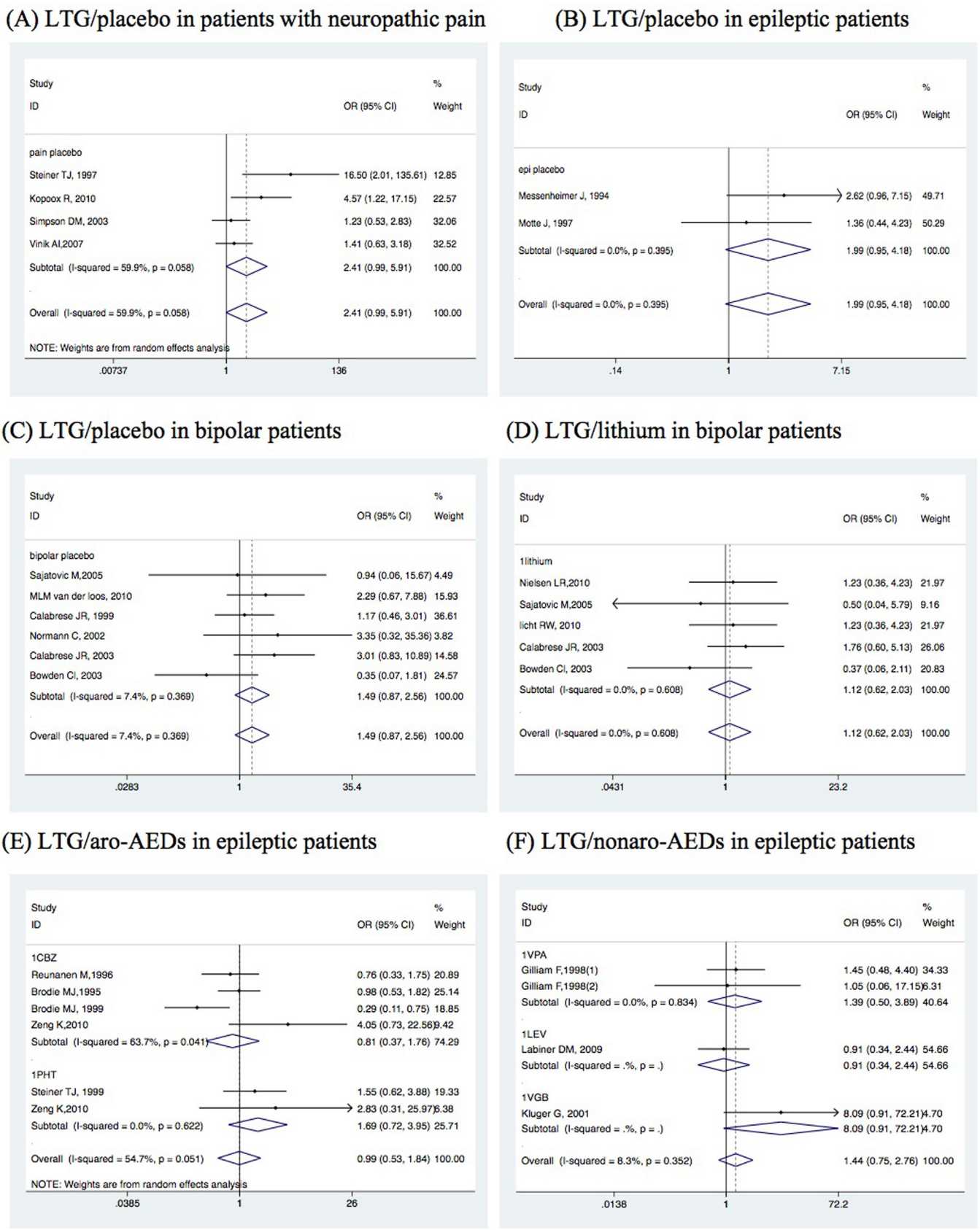

Fig. 2. The prospective studies about OR of LTG-skin rash compared with other drugs.

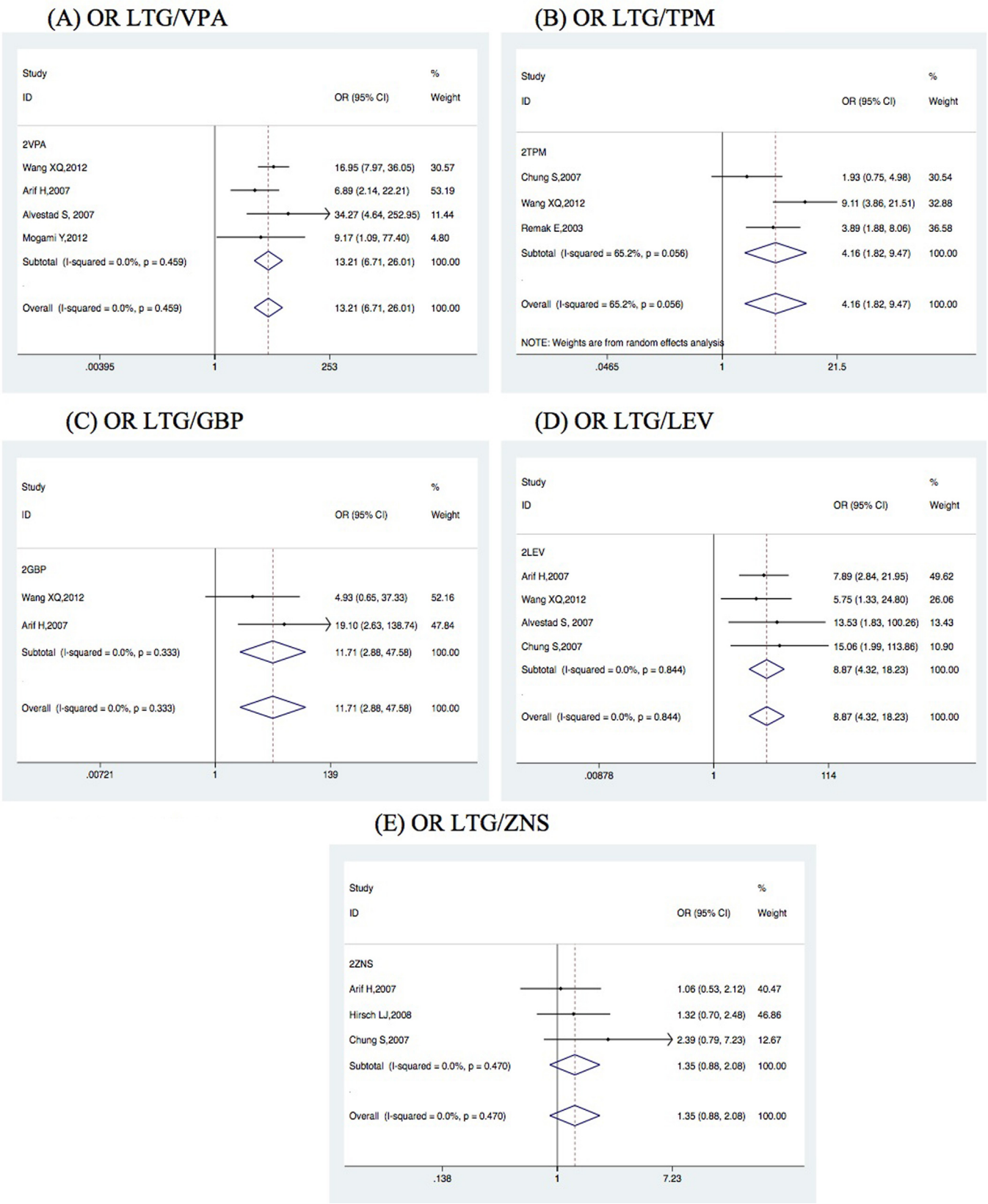

Fig. 3. The retrospective studies about OR of LTG-skin rash compared with non-aromatic AEDs.

independently related with LTG-induced skin rash, including the LTG titration speed and cotreatment with VPA. Forth, it was not possible to use narrower age categories because the studies provided either overall estimates or age-specific estimates with different age categories. Finally, we could not perform a publication bias test in our review because the meta-analyses in each group were less than 10 studies, which are considered the baseline number for testing publication bias.

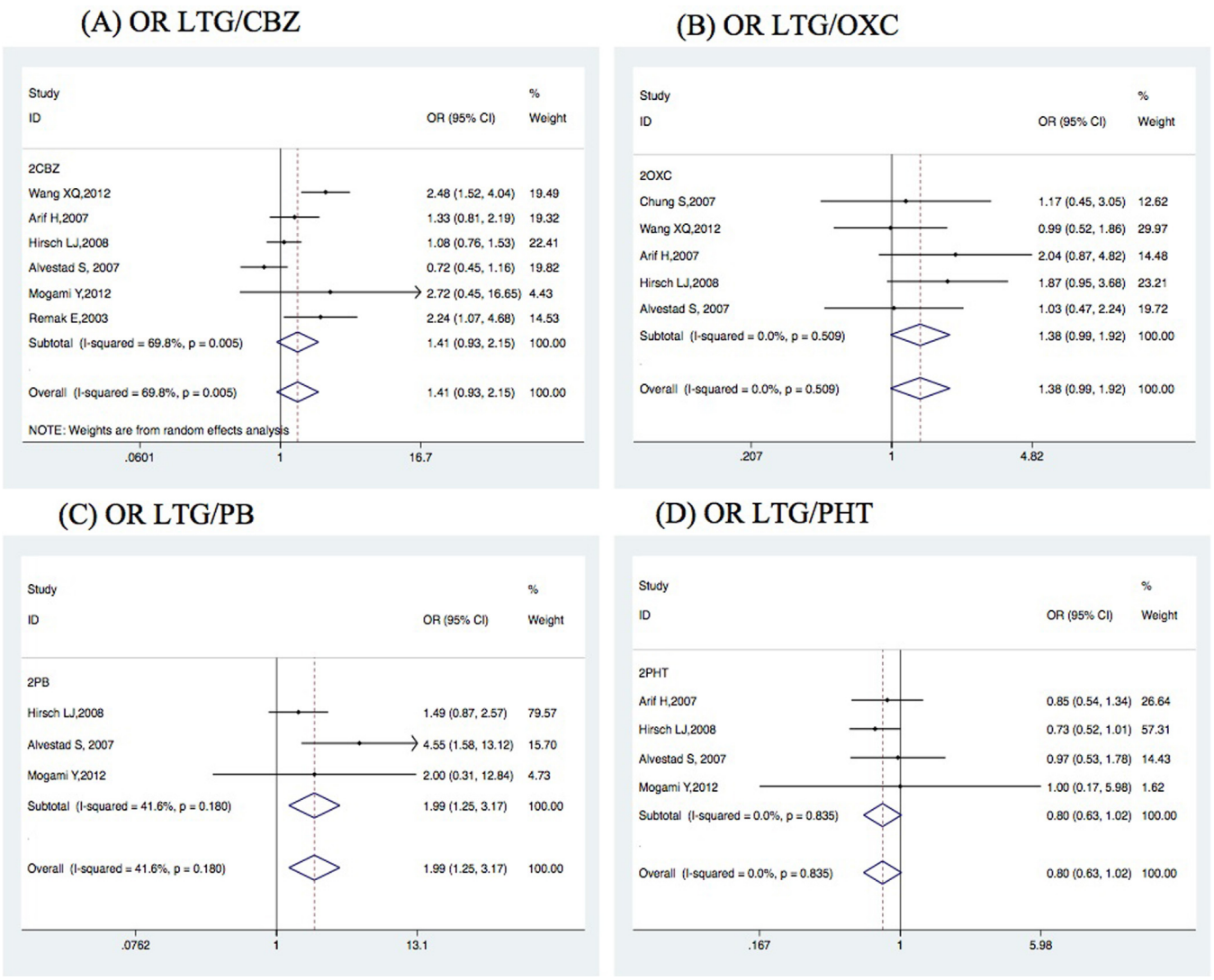

Fig. 4. The retrospective studies about OR of LTG-skin compared with aromatic AEDs.

Nevertheless, despite these limitations, our study provides a platform for vast heterogeneous data in studies exploring the risk of LTG-induced skin rash under a common roof and provides some important insights.

6. Conclusion

On the basis of the findings of the present study and the existing literature, the overall incidence of skin rash with LTG therapy was 9.98% from prospective studies, 7.19% from retrospective studies, and 2.09% from postmarketing reports. These data could potentially be used to assess the burden and analyze the risk of developing a skin rash in patients with LTG therapy. Our results showed that LTG significantly increased the risk of developing a skin rash compared to non-aromatic AEDs. Taken together, these results support the need for large prospective population-based studies and clinical trials to confirm whether LTG increases the risk of developing a skin rash compared to other drugs.

Conflicts of interest statement

None declared.

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