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Review

Lamotrigine versus valproic acid monotherapy for generalised epilepsy: A meta-analysis of comparative studies

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ABSTRACT

Purpose: The standard for generalized epilepsies (GE) monotherapy in treatment is valproic acid (VPA) and lamotrigine (LTG) has been proposed as an alternative to VPA. This study aimed to evaluate the safety and efficacy of LTG on GE seizure in comparison with VPA.
Method: A search was conducted based on the databases from Pubmed, Embase and the Cochran database up to February 2017. The relative risk odds ratios (ORs) and the relevant 95% confidence intervals (CI) were determined.
Results: Five randomized controlled trials and four observational cohort studies involving 1732 cases were included. The results indicated that VPA was significantly superior to LTG for the outcome rate to treatment withdrawal for any reason and seizure freedom. The ORs and 95% CI of VPA versus LTG for withdrawal after 12- and 24-month treatment were 0.39(0.27, 0.56) and 0.50(0.14, 1.75), respectively, and were 3.51(2.68, 4.59) and 8.58(5.40, 13.63)for 12- and 24- month seizure free intervals, respectively. Moreover, the risk of adverse effects (OR (95%CI); 1.11(0.61–2.01)) was not significantly different between the two groups. However, the treatment withdrawal due to lack of seizure control were in the LTG group (OR (95%CI); 0.15(0.10–0.23)), while the treatment withdrawal due to intolerable side effects were in the VPA group (OR (95%CI); (1.75(1.10–2.80)).
Conclusions: The meta-analysis suggests that VPA appears to be a better choice in controlling seizure following GE. However, therapy should be switched to alternative monotherapy if an adequate trial of VPA monotherapy is not effective and intolerable, especially in young women.

1. Introduction

Epilepsy influences 65 million people worldwide and entails a major burden in seizure-related disability, stigma, mortality, and costs [1,2]. Around 30–40% of patients have seizures that are generalized at onset. In general, generalized epilepsies (GE) are determined and affect otherwise normal people of both sexes and races [3]. Besides, GE was characterized by widespread involvement of bilateral cortical regions at the onset. They are usually accompanied by impairment of consciousness, which can further be divided into clonic, tonic, absence, atonic, tonic-clonic and myoclonic seizure types [4].

The goal in the first line pharmacologic management of epilepsy is monotherapy due to it is effective, well tolerated and associated with low costs, higher quality of life as well as better patient compliance. A long-term (up to 6 years) un-blinded study was designed by The Standard and New Antiepileptic Drugs (SANAD) trial, which declared that valproic acid (VPA)was identified as a first-line treatment for patients diagnosed with generalised-onset seizures [5]. VPA is a very effective anticonvulsant drug for GE, yet it carries some risks connected with its side effects profile [6,7]. Particularly for women of childbearing age, VPA was concerned about higher rates of teratogenicity and delayed cognitive development in children in utero. Taking it into consideration, lamotrigine(LTG) has been suggested as an alternative to VPA [8]. LTG has been proposed as first line new AED in

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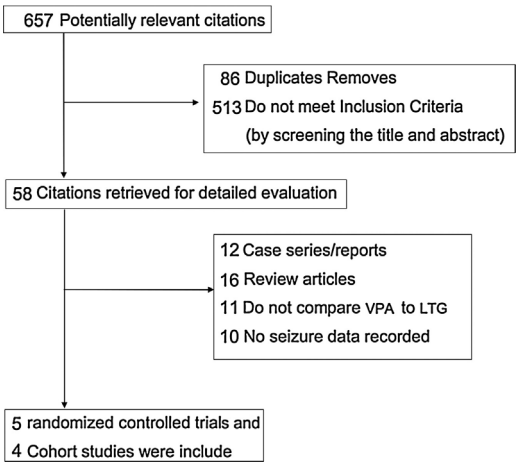

Fig. 1. The flow diagram shows the selection of studies for the meta-analysis.

treating childhood absence, juvenile absence, juvenile myoclonic and generalized tonic–clonic epilepsy according to National Institute for Health and Care Excellence (NICE) guidelines [9]. LTG is a phenyltriazine derivative which acts through inhibition of voltage-activated sodium channels and possibly calcium channels, preventing the release of glutamate [10]. Besides, LTG is also effective in controlling absence seizures and generalized tonic–clonic seizures [11,12]. Nevertheless, there are some reports of myoclonic seizure exacerbation [13].

Although conventional anti-epileptic drug VPA and the modern LTG are identified as optimal first line or second-line monotherapy for GE, effectiveness and course of treatment vary between the patients and still remain a matter of discussion [7,9,14]. In 2007, Tudur Smith et al. [15] performed a meta-analysis to compare AEDs for different types of epilepsy. However, they included only one study to compare VPA with LTG. Their result might be not robust. Therefore, we conducted a meta-analysis of published trials through comparing VPA with LTG to evaluate the effect on total withdrawal rate, the seizure-freedom rate, and adverse events in patients with GE.

2. Methods

2.1. Search strategy

The following electronic databases were searched till February 2017 such as Pubmed, Embase and the Cochrane database. The electronic search strategy included the terms, respectively, epilepsy; seizure; myoclonic epilepsy; absence epilepsy; tonic-clonic epilepsy; clonic epilepsy; tonic epilepsy; atonic epilepsy; generalised epilepsies; lamotrigine; valproate and valproic acid. Studies only in English were retrieved. Two authors reviewed the titles and abstracts of articles obtained from electronic databases respectively. If the abstract was relevant to this study, we read the full text and decided which articles were eligible for full-text review and disagreement was settled by mutual discussion.

2.2. Inclusion and exclusion criteria

Inclusion criteria were: (i) comparative study(randomized controlled trial (RCT), cohorts, case-controls and observational studies), (ii) investigated GE patients, (iii) the study compared VPA to LTG(iv) reported the number of outcome events in different interventions. The aim was to include only RCTs in the analysis. However, due to their paucity, other intervention studies and observational studies were included among which RCTs and observational studies were analyzed separately in subgroup for the reason that direct comparison between the estimates of observational studies and RCTs might be misleading. Exclusion criteria were shown as follows(i) review articles, meta-analysis, and guidelines, (ii) unavailability of a medical treatment comparison group, (iii) studies with no LTG arm, (iv) seizure data was not reported.

2.3. Data extraction

Two reviewers independently extracted the data. In case of disagreement between the two reviewers, a third reviewer extracted the data. The following information was extracted from the trails including the name of first author; country of origin; patients' characteristics (mean age, gender) as well as operational definitions and outcomes. For dichotomous outcomes, the number

Table 1
Characteristics of studies included in the meta-analyses.

First Author, Year	Country	Study type	Population Type	Analyzed		Mean Age (year)		% Males		Dosage/day		Seizures assessed at
				VPA	LTG	VPA	LTG	VPA	LTG	VPA	LTG	
Nicolson, 2004 [10]	UK	Cohort	IGE	549	156	12.2	14.1	46	26.2	1286 mg (mean)	324 mg (mean)	12 months, 24 months & 60 months
Coppola, 2004 [20]	Italy	Randomized Controlled Trial	Typical Absence Seizures	19	19	7.5	7.5	52.6	36.8	20–30 mg/kg	2–12 mg/kg	1 month, 3 months & 12 months
Steinhoff, 2005 [24]	Germany	Randomized Controlled Trial	GE	30	33	23.3	22.3	46.7	39.4	9.0–24.4 mg/kg	1.5–7.4 mg/kg	17 weeks and 24 weeks
Mazurkiewicz, 2010 [27]	Poland	Cohort	IGE	132	82	9.5	8.2	46.9	32.9	20–32 mg/kg	5–13 mg/kg	12 months & 24 months
Hwang, 2012 [26]	Korea	Cohort	Childhood Absence Epilepsy	59	21	6.4	6.6	33.9	23.8	15–45 mg/kg	3–6 mg/kg	3 months, 6 months, 12 months or 24 months
Machado, 2013 [23]	Cuba	Randomized Controlled Trial	Juvenile Myoclonic Epilepsy	31	41	15.3	16.3	32.3	36.6	900–2700 mg	150–400 mg/	3, 6 or 24 months
Glauser, 2013 [22]	America	Randomized Controlled Trial	Childhood Absence Epilepsy	146	146	7.5	7.5	48	38	10–60 mg/kg	0.3–12 mg/kg	16, 20 weeks & 12 months
Chowdhury, 2016 [25]	UK	Cohort	Juvenile Myoclonic Epilepsy	142	66	16	16	44	21	NP	NP	over 12 months
Giri, 2016 [21]	India	Randomized Controlled Trial	Idiopathic Generalized Tonic Clonic Seizures	30	30	18–70	18–70	66.7	56.7	10–30 mg/kg	1–12 mg/kg	3 months, 6 months & 12 months

UK, united kingdom; IGE, idiopathic generalised epilepsies; GE, generalised epilepsies; VPA, valproic acid; LTG, lamotrigine; mg, milligram; kg, kilogram; NP, not provided.