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Risk of valproic acid-related alopecia: A systematic review and meta-analysis

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ABSTRACT

Purpose: We systematically reviewed studies to provide current evidence about the incidence and risk of alopecia in patients undergoing valproic acid (VPA) therapy.

Methods: We retrieved relevant publications and gathered data on alopecia in patients taking VPA and other drugs from prospective studies.

Results: Twenty-five articles met the inclusion criteria, and the overall incidence of alopecia in patients receiving VPA therapy was 11% (95% confidence interval (CI): 0.08–0.13). The pooled risk of alopecia showed a significant difference between patients treated with VPA and all other drugs (odds ratio (OR) 5.02, 95% CI: 3.58–7.03), other epileptic drugs (AEDs) (OR 4.82, 95% CI: 3.32–7.00) and other non-AEDs (OR 5.84, 95% CI: 2.67–12.81). Compared to other drugs, VPA increased the risk of alopecia both in patients with migraine headaches (OR 6.05, 95% CI: 2.89–12.63) and patients with epilepsy (OR 5.29, 95% CI: 3.53–7.92), and the increase risk was reported more frequently in patients with migraine. Both lower doses (OR 4.38, 95% CI: 2.32–8.25) and shorter treatments (OR 4.98, 95% CI: 2.41–10.25) with VPA posed a high risk of alopecia compared to other drugs, as did higher doses and longer treatment times.

Conclusions: Based on our findings, VPA was significantly associated with a risk of alopecia compared to other drugs, and the risk did not depend on the dose and treatment time.

1. Introduction

Valproic acid (VPA) is the most commonly administered first-generation antiepileptic drug (AED) and is also useful for a variety of other diseases, including bipolar disorder (BD) [1,2], migraine headache (MA) [3–5] and neuropathic pain [6,7]. The side effects of antiepileptic drugs are often the main factors restricting treatment and drug retention for patients with epilepsy [8,9]. The clinical utility of VPA may be hindered by its adverse drug reactions (ADRs), such as tremors, weight gain, hair loss, gastrointestinal disturbances, heartburn, liver dysfunction, and thrombocytopenia [10].

Alopecia is a well-known psychopharmacological phenomenon caused by VPA and must be investigated and diagnosed with the utmost caution. In some cases, hair loss was partially relieved after discontinuing therapy. Hair loss is also a relatively common occurrence in patients treated with other AEDs, such as carbamazepine (CBZ) and phenytoin (PHT), and the frequency of hair loss ranges from 0.3% to 6% in treated individuals [11–13]. Tiagabine (TGB) and topiramate (TPM) may also cause alopecia in 1% of users [14], as may gabapentin [15], lamotrigine (LTG) [16] and vigabatrin [17].

Currently, although VPA-induced hair loss is well known, researchers have not clearly determined whether the dose affects how VPA increases the risk of developing alopecia compared to other drugs. The currently available information concerning VPA-associated hair loss in the existing medical literature is rather weak and often limited to case reports. In this study, we aim to systematically review related documents to provide more evidence about the incidence of VPA-related hair loss and compare this risk to other drugs.

2. Methods

Ethical approval was not necessary for the present study due to the

Abbreviations: EP, epilepsy; BD, bipolar disorder; MA, migraine headache; VPA, valproic acid; LTG, lamotrigine; CBZ, carbamazepine; OXC, oxcarbazepine; TPM, topiramate; PHT, phenytoin; AED, antiepileptic drug; ADR, adverse drug reactions; DDD, daily drug dose; RCT, randomized controlled trial; M, month; Y, year; W, week; CI, confidence interval; OR, odds ratio

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

Study	Design	Country	Study field	N (erolled)	Treatment arm	Gender (% male)	Age (year) (range/mean)	VPA dose (mean mg/d)	No. analysis	No. rash	Follow up time
Afshari, D. (2012) [45]	RCT	Iran	MA	56	TPM VPA	50%	18-65 year	400	28	9(32.1%)	12 w
Biton, V. (2001) [27]	RCT	USA	EP	133	LTG VPA	43.6%	12-76 year 30.1 ± 14	1822 ± 633	68	7(10%)	24 w
Blumenfeld, A.M. (2008) [39]	RCT	USA	MA	59	BoNTA VPA	15.3%	Adults 42.4 ± 10.3	500	29	5(17.2%)	10 m
Bostani, A. (2013) [40]	RCT	Iran	MA	104	Cinnarizine VPA	16.5%	Adults 31.85 ± 7.76	400	54	14(25.9%)	12 w
Calabrese,J.R. (2005) [46]	RCT	USA	BD	60	Lithium VPA	51.7%	≥16 year 37 ± 8.2	500	28	0(0%)	20 m
Christe, W. (1997) [24]	RCT	multicenter	EP	249	OXC VPA	51%	15-65 year	1146.2	121	21(17.4%)	45 m
Craig, I. (1994) [34]	RCT Single blind	UK	EP	38	PHT VPA	Not state	62-88year	688	17	2(12%)	1 y
Donati, F. (2007) [41]	RCT Open label	Switzerland	EP	112	CBZ OXC VPA	45.5%	6-16 year	Not state	29	3(10.3%)	6 m
Fakhoury, T.A. (2004) [35]	RCT Open label	USA	EP	302	LTG VPA	59%	≥16 year	Not state	53	6(11%)	28 w
Hebrani, P. (2009) [36]	RCT	Iran	BD	120	TPM VPA	40%	12-18 year	1200	61	2(3.3%)	8 w
Hesami,O. (2018) [37]	RCT	Iran	MA	82	Atorvastatin VPA	3.7%	Adults 30.25 ± 9.91	500	36	5(13.9%)	3 m
Kakkar,A.K. (2009) [38]	RCT	India	BD	60	OXC VPA	50%	18-50 year	1280	30	1(3.3%)	12 w
Levisohn.R.M (2007) [29]	RCT Open label	USA	EP	28	TPM VPA	61%	9-42 year	750	9	3(33%)	26 w
Mathew, N.T. (1995) [33]	RCT	USA	MA	107	placebo VPA	20%	18-70 year	1087	70	9(13%)	16 w
Mattson, R.H. (1992) [13]	RCT	USA	EP	480	CBZ VPA	93%	18-70 year	2099 ± 824	240	29(12%)	40 m
Nejad,S.E.M. (2009) [44]	RCT Open label	Iran	EP	46	LTG VPA	Not state	8-30 year	800	23	3(13%)	28 w
Park. K.M. (2013) [26]	RCT Open label	Korea	EP	33	TPM VPA	50%	13-42 year	1200	16	3(18.7%)	24 w
Richens, A. (1994) [25]	RCT Open-label	multicenter in USA	EP	300	CBZ VPA	Not state	≥16 year	924	174	5(2.9%)	3 y
Sarchielli, P. (2014) [42]	RCT	Italy	MA	88	placebo VPA	23.5%	18-65 year	800	44	5(11.4%)	6 m
Shaygannejad, V. (2006) [43]	RCT	Iran	MA	64	TPM VPA	43.7%	14-57 year	400	32	1(3.1%)	24 w
Steinhoff,B.J (2005) [30] Mattson,R.H. 1992	RCT Open label	Germany	EP	239	LTG VPA	Not state	≥12 year	1050	30	3(10%)	24 w
Wheless, J.W. (2014) [28]	RCT	USA	EP	613	CBZ TPM VPA	49.7%	≥6 year	1250	78	14(18%)	≥6 m
Verity,C.M. (1995) [12]	RCT	UK	EP	260	CBZ VPA	43.5%	5-16 year	700	118	5(4.2%)	3 y
Viteri, C. (2010) [31]	Open trial prospective	Spanish	EP	107	LTG VPA	38.3%	Adults 30.4 ± 9.1	Not state	54	13(24.5%)	6 m
Xu, L. (2015) [32]	RCT	China	BD	114	Olanzapine VPA	8.2%	Adults 30.7 ± 7.8	1530 ± 220	38	3(7.5%)	4 w

EP = epilepsy, BD = bipolar disorder, MA = migraine headache, VPA = Valproic acid, LTG = Lamotrigine, CBZ = Carbamazepine, OXC = oxcarbazepine, TPM = topiramate, PHT = phenytoin.
RCT = randomized controlled trial, m = month, y = year, w = week.

lack of patient involvement. This study was conducted according to the PRISMA (preferred reporting items for systematic reviews and meta-analyses) [18] and MOOSE (meta-analysis of observational studies in epidemiology protocol) guidelines [19]. The protocol used in this study was based on the Cochrane Review Methods (www.cochrane-handbook.org).

2.1. Search strategy

We searched the PubMed (1976 to September 20, 2018), Embase (1982 to September 20, 2018) and Cochrane Library databases (1987 to September 20, 2018) for relevant studies with no language restrictions. The search process was conducted through a combination of medical subject headings and text words, including “valproic acid”, “propylisopropylacetic acid”, “divalproex”, “depakene”, “divalproex sodium”, “valproate”, “valproate sodium”, “VPA”, “alopecia”, “hair loss”, and “baldness” (Table S1). Furthermore, we confined our literature search to human studies. Additionally, the references from all included studies or relevant reviews were screened to avoid accidental omissions.

2.2. Selection criteria

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 VPA treatment compared with a control group and (2) studies providing the original data for VPA-associated hair loss and comparisons to other drugs related to hair loss. Furthermore, we eliminated reviews, editorials, and single cases and case series, as well as studies that were exclusively published as abstracts, letters, and commentaries and studies that likely contained repeated data from duplicate populations.

According to the inclusion and exclusion criteria, we finally identified a total of 25 prospective studies (one study had a prospective cohort design and the others were randomized controlled trials) (Table 1).

2.3. Data extraction and quality assessment

We used a standardized data abstraction form to acquire the relevant information required for analysis. Two independent investigators performed the data extraction (W.X.P. and W.H.J.), and any

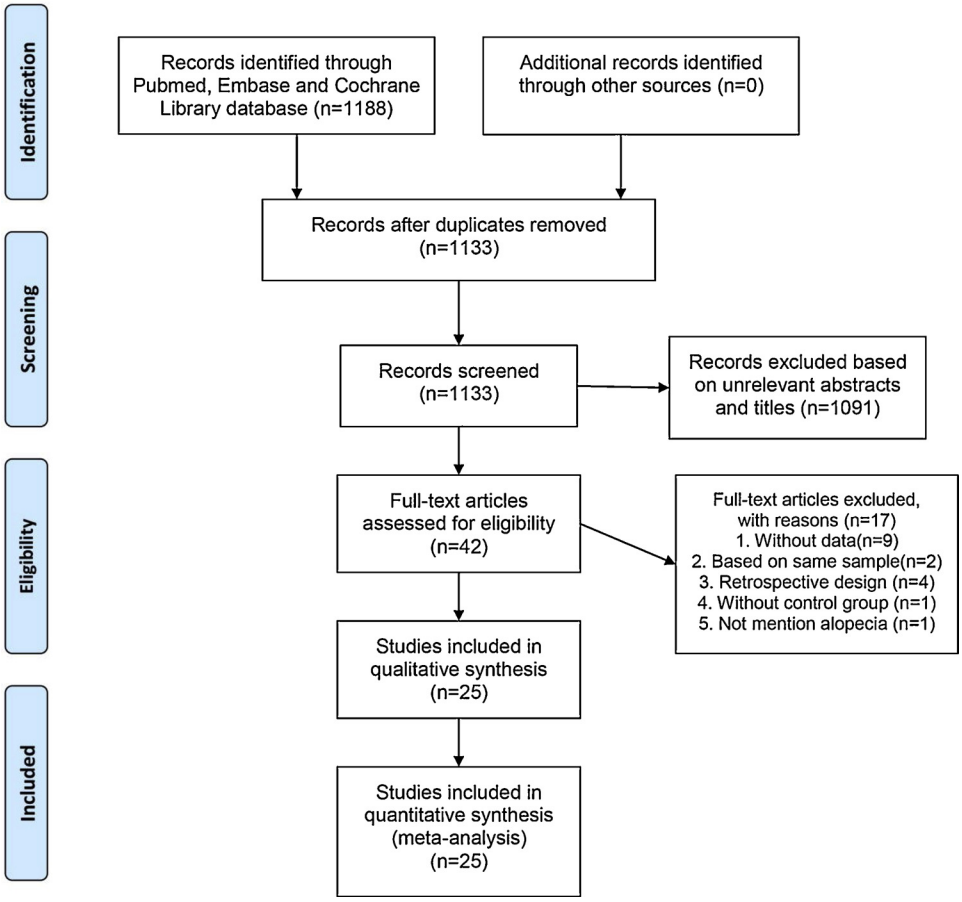

Fig. 1. Flow chart of selection of articles about alopecia in patients with VPA therapy, VPA = valproic acid.

disagreement between the two investigators was resolved by discussion with the help of a third investigator (L.L.). For each study, the following information was obtained: the first author's name, year of publication, study methods, 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 (alopecia).

The quality of the included randomized controlled trials was assessed using the Cochrane collaboration tool for estimating the risk of bias (Fig. S1).

2.4. Statistical analysis

All the analyses were performed using STATA 12.0 software (StataCorp, College Station, Texas, USA). A p-value of less than 0.05 was considered statistically significant, and all the tests were two-sided. The crude odds ratios (ORs) and 95% confidence intervals (CIs) were used to express the risk of alopecia with VPA therapy compared to other drugs. Forest plots were used to depict the visual representation of the meta-analysis results. The meta-analysis was performed using fixed-effects [20] or random-effects [21] models. Heterogeneity was assessed using Cochran's Q statistic [22] and I^2 metric statistics [23]. For the Cochran Q test, heterogeneity was considered statistically significant when $P_{hetero} < 0.05$. For I^2, no evidence of heterogeneity was defined when I^2 was 0, a low level of heterogeneity when I^2 was < 25%, a moderate level of heterogeneity when I^2 was 25–50%, and a high level of heterogeneity when I^2 was > 50%. A fixed-effects model was applied when $P_{hetero} > 0.05$ or $I^2 < 50\%$, and a random-effects model was also conducted to evaluate the stability of the results.

Potential publication biases were estimated by performing a visual inspection of funnel plots and further identified using Egger's linear regression test. A P-value < 0.05 was considered statistically significant. We performed the following analyses: different control groups (other antiepileptic drugs and other non-antiepileptic drugs) and different groups of patients (patients with epilepsy, bipolar disorder and migraine headache). We also analysed the pooled ORs of specified subgroups based on different VPA doses, sample sizes and follow-up times.

3. Results

3.1. Study selection and characteristics

Our search yielded 1188 records describing the use of VPA and alopecia from the PubMed, Embase and Cochrane library databases. The selection process is summarized in Fig. 1. After the exclusion of duplicate studies and a review of the abstracts, 42 human clinical studies that presented information on VPA therapy and alopecia were identified. Full-text articles were retrieved for these records and carefully studied. Finally, based on the inclusion criteria, 25 prospective studies examining VPA-induced alopecia were used to evaluate the hair loss incidence [12,13,24–46], as well as 2 articles with the same population, and we selected the publications with the largest sample sizes [47,48] (Table 1). In two studies, two different antiepileptic drugs were compared to VPA, and we considered them as four trials, bringing the total number of comparisons to 27 [28,41]. In this group, 1587 patients receiving VPA treatment were investigated, with a focus on a variety of diseases, including epilepsy (14 trials) [12,13,24–31,34,35,38,41,44], bipolar disorder (4 trials) [32,36,38,46], and migraine headache (7 trials) [33,37,39,40,42,43,45]. The sample sizes ranged from 28 to 480

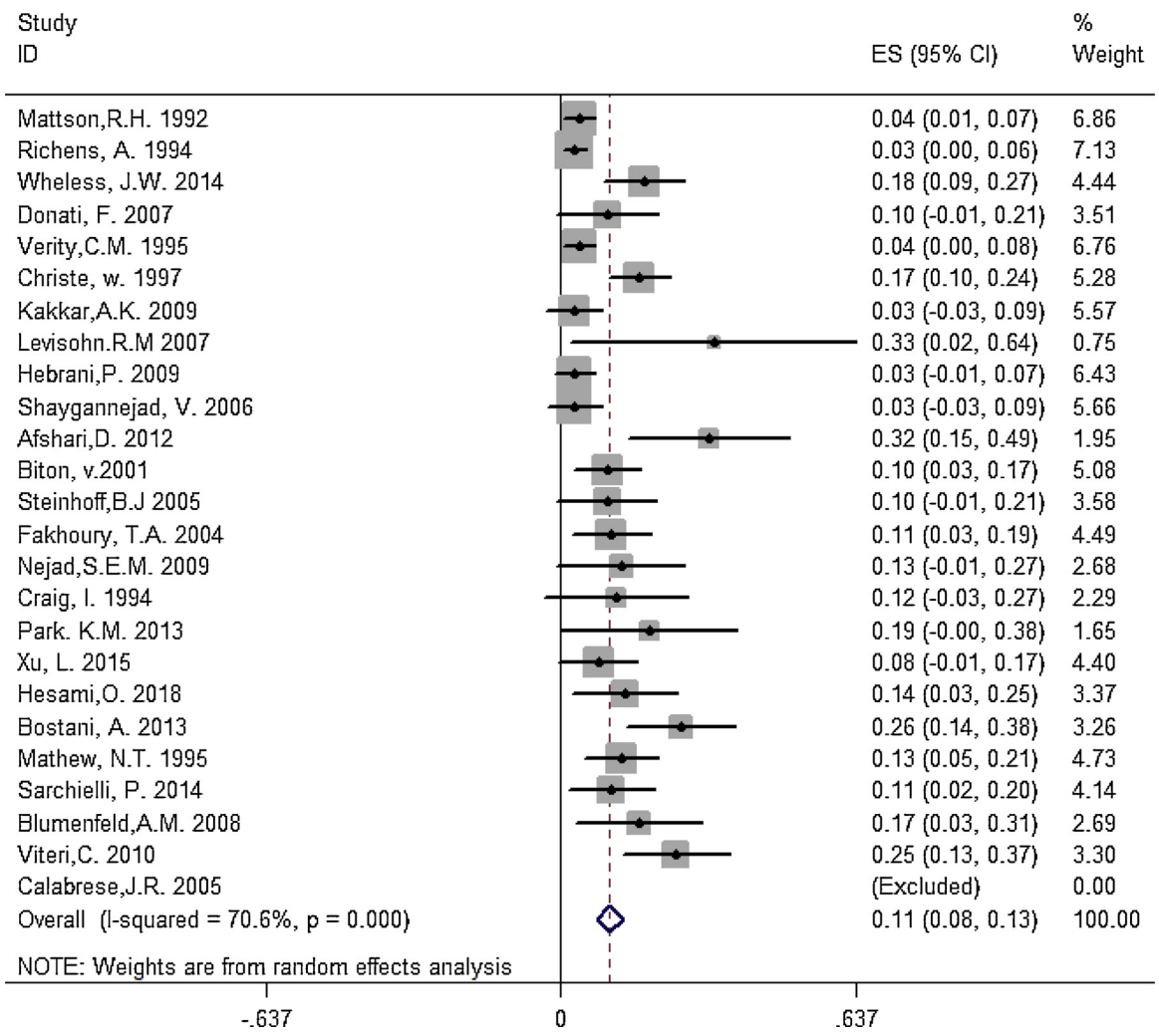

Fig. 2. Pooled analysis of the overall prevalence of VPA induced alopecia. VPA = Valproic Acid.

patients treated with VPA. The age range of the study participants was 5–88 years. The follow-up period ranged from 8 weeks to 3 years. The mean dose of VPA ranged from 400 mg/d to 2099 mg/d.

3.2. Incidence of alopecia

The overall incidence of alopecia with VPA treatment was 11% (95% CI: 0.08–0.13, P < 0.05) in 24 prospective clinical trials, because one prospective study did not identify a patient who was treated with VPA and developed alopecia [46] (Fig. 2). With $P_{hetero} = 0.00$ and $I^2 = 70.6\%$, a random-effects model was conducted.

3.3. Pooled estimates for outcomes

3.3.1. Meta-analysis of various drugs

We independently evaluated the ORs of VPA-associated alopecia compared to all other drugs, other AEDs and other non-AEDs to investigate the specific contribution of VPA to alopecia. Based on our results, the use of VPA was significantly associated with an increased risk of alopecia compared to all other drugs (OR 5.02, 95% CI: 3.58–7.03, P < 0.05) (Fig. 3A), other AEDs (20 articles, OR 4.82, 95% CI: 3.32–7.00, P < 0.05) (Fig. 3B), and other non-AEDs (7 articles, OR 5.84, 95% CI: 2.67–12.81, P < 0.05) (Fig. 3C). When we compared VPA to other AEDs separately, a significant difference in the alopecia risk was observed between patients treated with VPA and other AEDs [CBZ (4 studies): OR 5.84, 95% CI: 2.57–13.27; OXC (3 studies): OR 2.67, 95% CI: 1.30–5.48; LTG (5 studies): OR 6.29, 95% CI: 2.67–14.80; and TPM (6 studies): OR 5.59, 95% CI: 2.85–10.96] (Fig. 4). All of these comparisons exhibited little heterogeneity; therefore, we used a fixed-effects model and observed a significant difference in the risk of experiencing alopecia between VPA and all other drugs, other AEDs and other non-AEDs.

3.3.2. Meta-analysis of different groups of patients

We compared VPA to other drugs among patients with epilepsy, BD and MA to clarify the distinct risk of VPA-induced alopecia among different groups of patients. VPA was significantly associated with an increased risk of alopecia in patients with epilepsy (14 articles, OR 5.29, 95% CI: 3.53–7.92, P < 0.05) and MA (7 articles, OR 6.05, 95% CI: 2.89–12.63, P < 0.05). However, among patients with BD, the risk of VPA-induced alopecia was similar to other drugs (4 articles, OR 1.75, 95% CI: 0.53–5.66, P = 0.360) (Fig. 5). These three comparisons exhibited little heterogeneity; therefore, we used a fixed-effects model, as shown in Fig. 5.

3.4. Subgroup analysis

Although the former comparisons exhibited little heterogeneity, the sample size, drug dose and follow-up time substantially influenced the outcome, and therefore various subgroup analyses were conducted as described below. In the subgroup analysis of the sample size that included studies with more than 100 patients, the risk of VPA-related

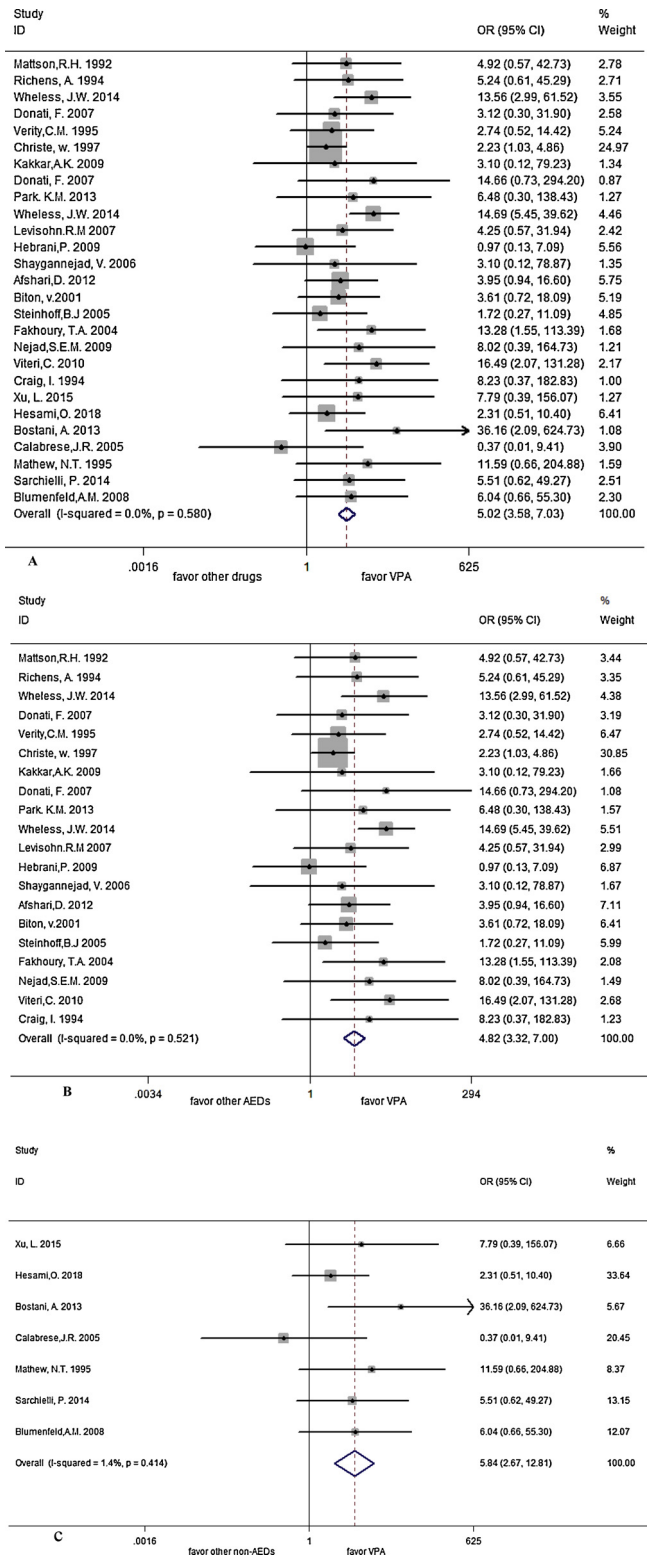

Fig. 3. A. The pooled OR of VPA-alopecia compared with all other drugs. VPA = Valproic Acid. B. The pooled OR of VPA-alopecia compared with all other AEDs. AED = antiepileptic drugs, VPA = Valproic Acid. C. The pooled OR of VPA-alopecia compared with all other non-AEDs. VPA = Valproic Acid, AEDs = antiepileptic drugs.

alopecia differed significantly from other drugs (OR 4.98, 95% CI: 3.29–7.55, P < 0.05), which also persisted in an analysis of studies with less than 100 patients (OR 3.78, 95% CI: 1.98–7.24; P = 0.001) (Fig. 6A). A subgroup analysis based on the follow-up time showed that taking VPA for longer than 6 months (OR 4.66, 95% CI: 3.13–6.93, P < 0.05) did not increase the risk of alopecia compared to taking VPA for less than 6 months (OR 4.98, 95% CI: 2.41–10.25, P < 0.05) (Fig. 6B). When combining the results from groups receiving different doses, the pooled estimate for alopecia caused by VPA was statistically significantly different from other drugs at doses that were both less than (OR 4.38, 95% CI: 2.32–8.25, P < 0.05) and greater than 750 mg/d (OR 4.14, 95% CI: 2.65–6.47, P < 0.05) (Fig. 6C), and the lower dose of VPA did not reduce the risk of alopecia.

Among the studies with larger sample sizes, the risk of alopecia induced by VPA was greater than the studies with a small sample size, which reflected the stability of our meta-analysis.

3.5. Sensitivity analysis

The variations and ranges of the pooled ORs after switching model types are listed in Table S2.

The stability of the pooled estimate was assessed by removing some studies from the meta-analysis according to various exclusion criteria, and this stability analysis is summarized in Table S3. The pooled estimate for VPA-induced alopecia did not significantly depend on some of the exclusion criteria that were used.

3.6. Publication bias

The inverted funnel plots of the outcome data in these studies were generally asymmetrical (Fig. S2). Egger's linear regression test indicated a lack of publication bias for VPA-related alopecia compared to all other drugs and other AEDs (P = 0.477 and 0.583, respectively).

4. Discussion

To date, the evidence for valproic acid-induced hair loss has been well documented. A literature review mentioned 643 cases of valproate-induced alopecia in 1995 [49]; specifically, it reported a 0.5–12% frequency [50,51], while the incidence of severe hair loss was 0.03% [52]. In addition, the incidence of alopecia is now considered to depend on the dose and time, and dose reduction leads to the re-growth of hair [53]. However, this opinion has not been verified, and a suitable and tolerable dose is difficult to identify.

A valuable and relatively complete description of the incidence and risk of VPA-associated alopecia compared to other drugs was provided in this meta-analysis. This meta-analysis includes 25 prospective studies, and the overall incidence of hair loss in patients receiving VPA therapy was estimated to be 11%. Our finding for the incidence was consistent with other studies, which showed that hair loss or changes in hair colour (greying) and structure caused by sodium valproate reached approximately 6–12% [11,54]. Furthermore, we observed a significant difference among patients treated with VPA and all other drugs, other AEDs and non-AEDs. Patients taking VPA had an approximately 5-fold higher risk of developing alopecia than patients taking other drugs, and this risk was even approximately 6-fold higher than other non-AEDs. When compared to a single AED, the risk of VPA-induced alopecia was greater than CBZ, OXC, TPM and LTG (5.84, 2.67, 5.59 and 6.29 times, respectively). When only four different AEDs were compared, the incidence of hair loss associated with other AEDs was also reported, but only a few of the included studies reported these data and we were unable to calculate a pooled estimate. This result provided insights into methods to choose other AEDs to replace VPA.

Notably, the results for VPA-induced alopecia among different patient groups differed from the overall conclusions in the literature. Only patients with epilepsy and patients with MA taking VPA experienced an approximate 5.3- and 6.05-fold higher risk of hair loss, respectively, than patients taking other drugs, but this outcome was not experienced by patients with BD. We predicted that patients with BD also take other psychotropic drugs, such as lithium, which caused hair loss in 10–19%

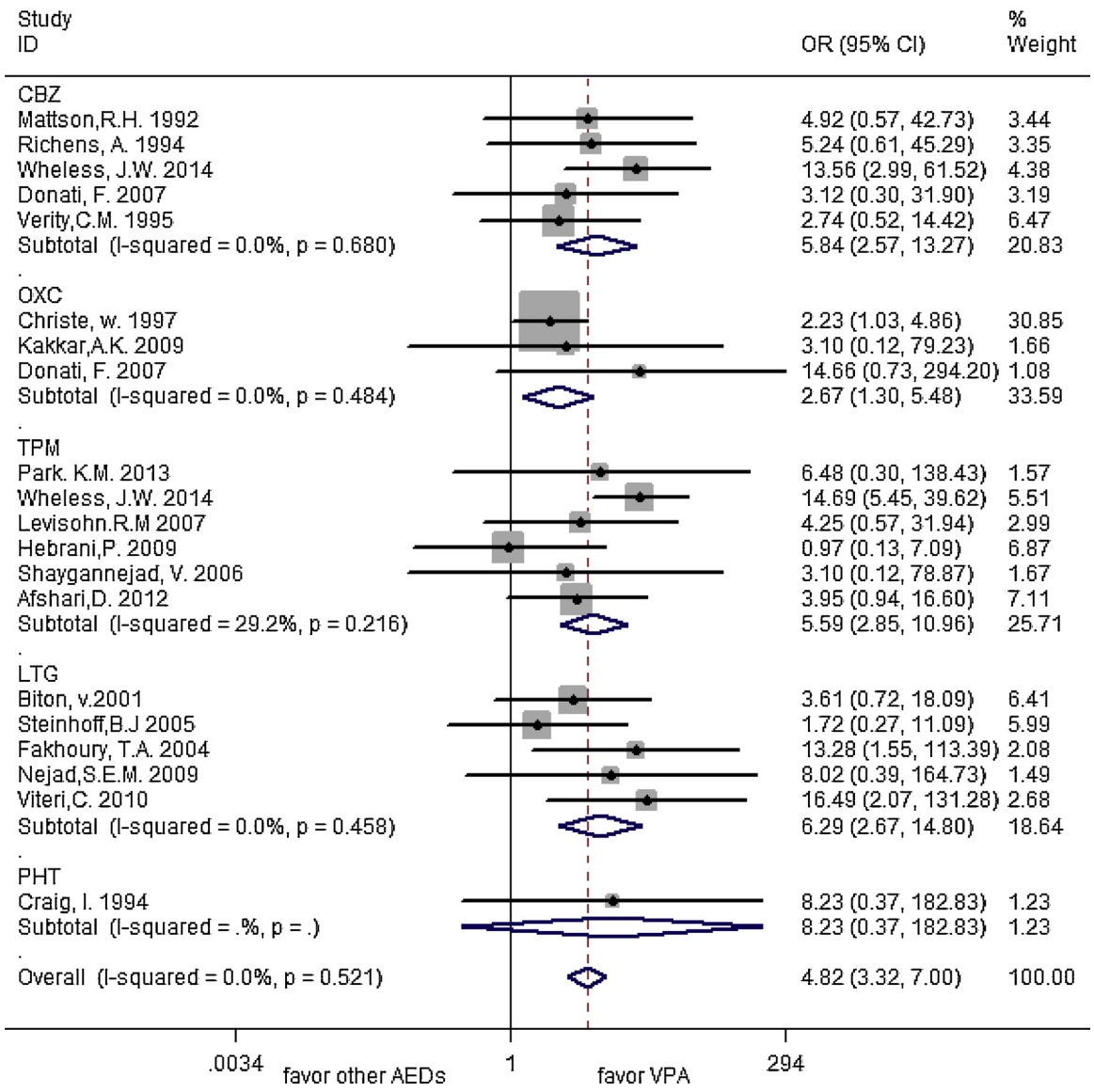

Fig. 4. The pooled OR of VPA-alopecia compared with other AEDs respectively. VPA = Valproic Acid, LTG = Lamotrigine, CBZ = Carbamazepine, OXC = oxcarbazepine, TPM = topiramate, PHT = phenytoin, AEDs = antiepileptic drugs.

of users [49,55–57], and fluoxetine, which was reported to have a higher risk of causing hair loss [58,59]. More female patients were included in studies of MA, and many case reports and studies reported more frequent hair loss in female patients [51,60]. According to the results of our meta-analysis, a higher pooled OR of VPA-associated alopecia was observed among patients with MA than patients with epilepsy, but the result was not significantly different. Women tend to pay more attention to their skin and hair, and therefore they are more likely to complain than men, as reflected in other studies [53,55]. In addition, women are considered more vulnerable to medication-related hypothyroidism, which is a risk factor for hair loss [61,62].

According to case reports, sodium valproate causes alopecia in up to 8%–12% patients in a dose-dependent manner [63]. Patients with high blood valproate concentrations tend to develop adverse effects [64], and a decrease in the dosage reduces the occurrence of some common side effects, including alopecia [65]. One study reported that approximately 28% subjects with blood valproate levels of 80–150 mcg/L experienced hair loss compared to 4% of patients with concentrations between 25 and 50 mcg/L [66]. In contrast, we drew a different conclusion in our meta-analysis of previous related publications. We divided the included studies into two groups according to the 50% daily drug dose (DDD) of VPA, and patients taking a lower dose ($\leq$ 750 mg/d) had a similar risk of developing alopecia to patients who were administered a higher dose ($>$ 750 mg/d). Dose-related alopecia was reported from case studies, but researchers have not completely established whether its impact on hair loss was dose-related, but a dosage reduction usually resulted in the re-growth of hair in individuals with valproate-associated alopecia [67]. Nevertheless, based on our meta-analysis, if a patient experienced VPA-associated hair loss, reducing simple reduction in the VPA dose might fail to reduce the risk of alopecia. Thus, clinicians should be aware that valproate therapy may result in hair loss, even when the dose is within the therapeutic window, and once patients experience hair loss, a wise approach is to withdraw VPA instead of simply reducing the dose. No studies have examined VPA overdoses and hair loss, but these data lay the foundation for further studies, which would be profoundly meaningful [53].

One study reported that hair loss began within 3–6 months after initiating therapy [49], and another found that this effect occurred after 1–4 months of treatment with VPA [68]. Our meta-analysis confirmed this result. When we pooled the results of studies that followed patients for 6 months, the risk of alopecia was even higher than studies that followed patients for more than 6 months. Thus, clinicians should

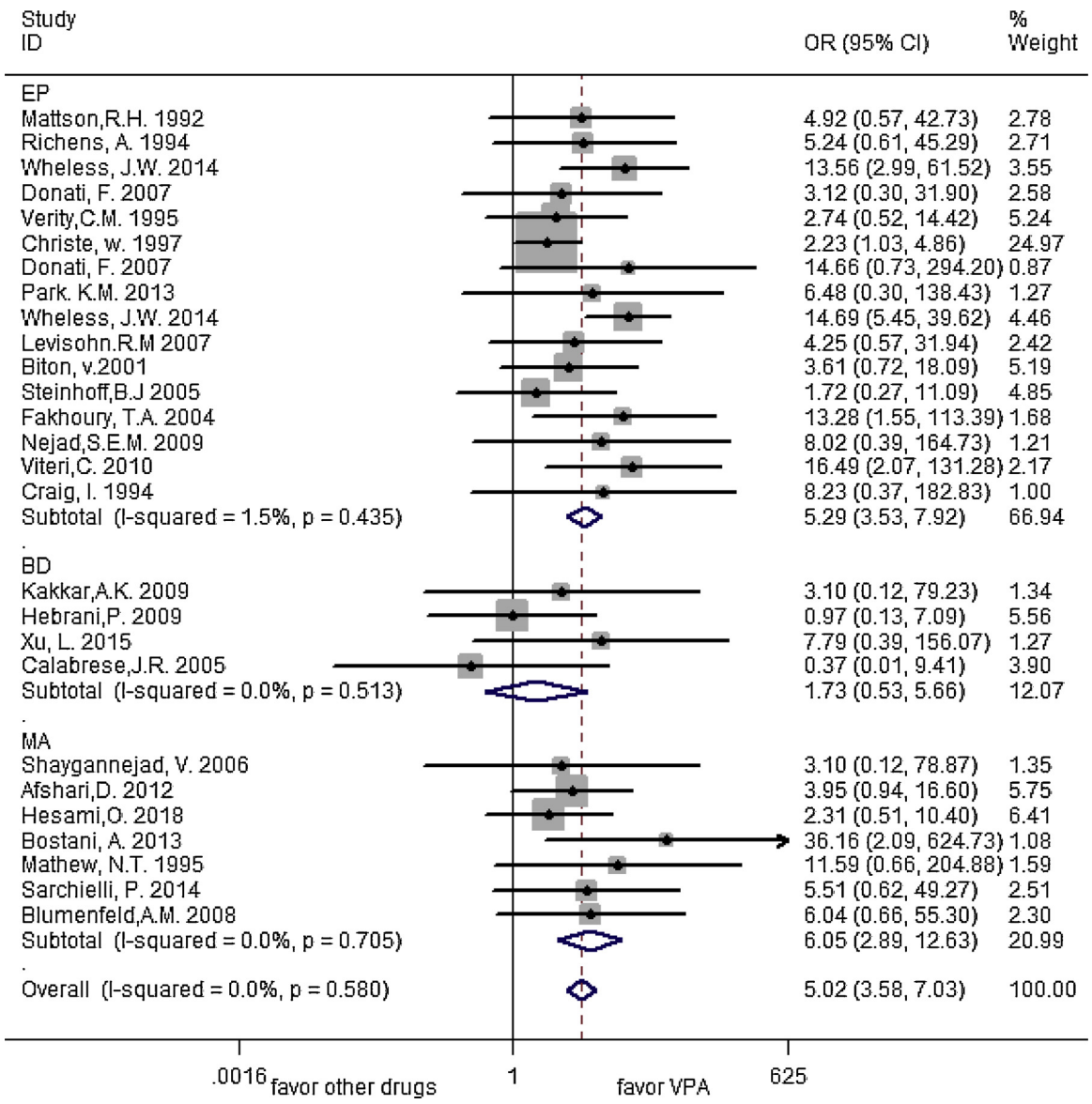

Fig. 5. The pooled OR of VPA-alopecia among different patients groups. VPA = Valproic Acid, EP = epilepsy patients, BD = bipolar disorders, MA = migraine headache.

monitor VPA-induced alopecia within the first 6 months.

However, our study also had some limitations. First, only a small number of patients experienced alopecia after receiving VPA therapy, and only 1587 patients were treated with VPA in the 25 prospective studies. Second, the included studies did not all employ a randomized, double-blinded design, and the quality of some studies was poor. Additionally, women tended to experience VPA- associated hair loss at a higher rate, but the data were unavailable for us to perform a pooled estimation and directly confirm this conclusion. Third, the numbers of included studies and the compared AEDs were small; therefore, we need to be cautious about drawing general conclusions. Finally, one way to semi-quantitatively analyse the severity of hair loss is to determine how often the drug was truly withdrawn due to hair loss; however, only a few studies mentioned this aspect, and the pooled results displayed substantial heterogeneity and were unbelievable.

Nevertheless, our meta-analysis still has some strengths. First, we are the first researchers to clarify the overall incidence of VPA-induced alopecia and quantify the relative risk of VPA compared to other AEDs and non-AEDs, and we illustrated the risks among different patient groups. Second, we discussed the risk of VPA-associated alopecia in patients treated with different VPA doses for different periods. Third, subgroup and sensitivity analyses were also conducted to ensure the robustness of our conclusions. Our study provides a platform for examining vast heterogeneous data from studies exploring the risk of VPA-induced alopecia under a common analysis and provides some important insights.

5. Conclusions

Based on the findings of the present study and the existing literature, VPA-induced hair loss is more common than many clinicians have realized, and its overall incidence is 11%. VPA poses a higher risk of hair loss than other AEDs, and we recommend that VPA should be replaced with LTG if a need occurs, since it has the lowest risk of hair loss compared to VPA. VPA-induced alopecia does not depend on the dose, and reducing the drug dose does not reduce the risk. Patients taking VPA had a higher risk of suffering hair loss within the first 6 months, and patients should be advised about the risk. Taken together, these results support the need for large prospective population-based studies and clinical trials to confirm whether VPA increases the risk of

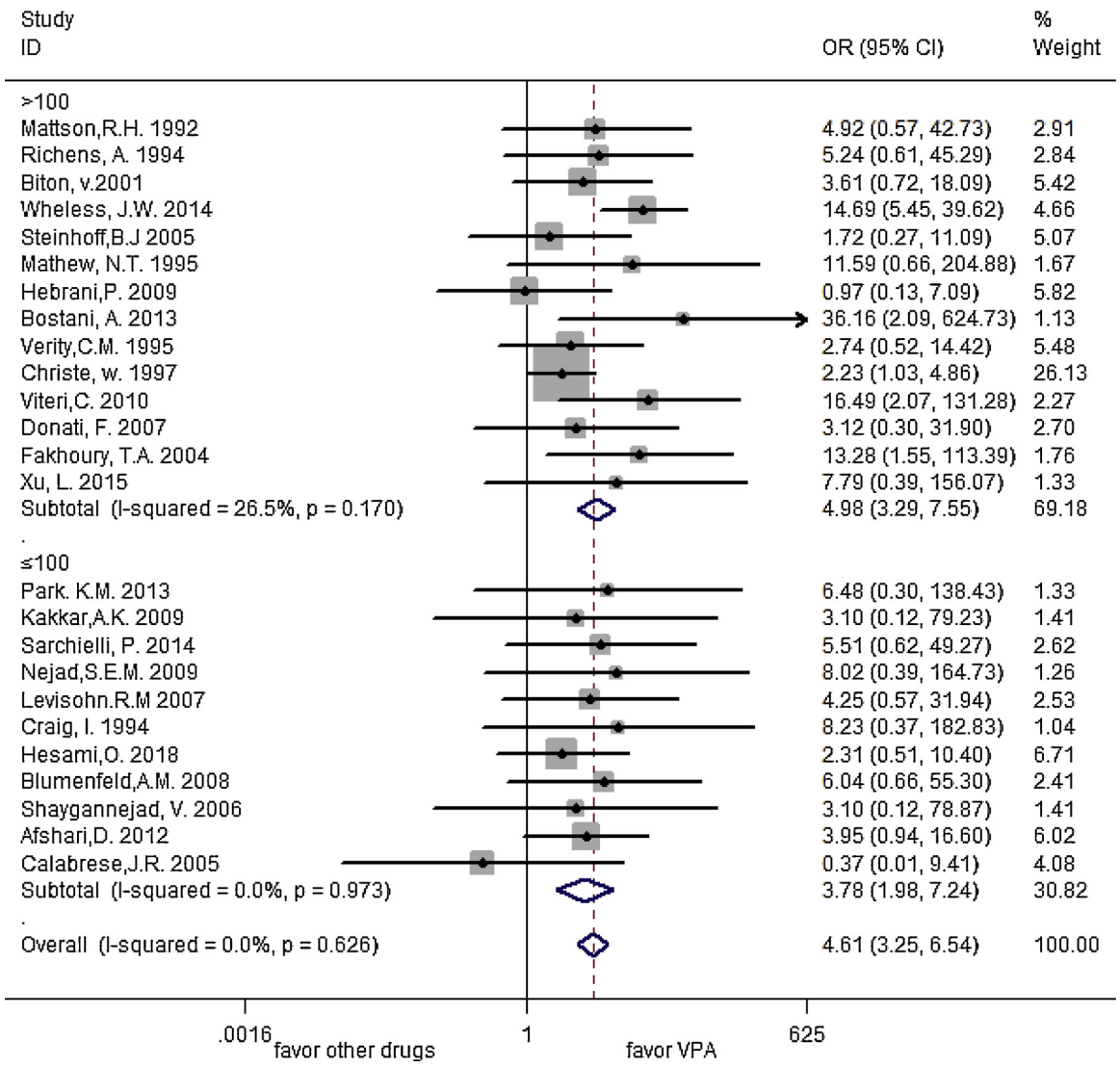

Fig. 6. A. Subgroup analysis of VPA-alopecia compared with other drugs based on the sample size. VPA = Valproic Acid. B. Subgroup analysis of VPA-alopecia compared with other drugs based on the follow up time. VPA = Valproic Acid. C. Subgroup analysis of VPA-alopecia compared with other drugs based on the different drug dose. VPA = Valproic Acid.

developing hair loss compared to other drugs and whether this phenomenon is dose-dependent.

Competing interests

The authors have no competing interests to declare.

Authors' contributions

WXP and LL conceived the study. WXP and WHJ finalized the search strategy. WXP and WHJ primarily screened studies and extracted data with supervision from ZLN and LL. WXP, WHJ and XD analysed the data. All authors participated in data interpretation, writing the manuscript and critically reviewing the manuscript. All authors read and approved the final manuscript.

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