

Valproic acid's effects on visual acuity in retinitis pigmentosa: a systemic review and Meta-analysis

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Received: 2018-06-02 Accepted: 2018-09-18

Abstract

- **AIM:** To gain a better understanding of the overall efficacy of valproic acid (VPA) treatment for retinitis pigmentosa (RP).
- **METHODS:** Publications in PubMed, EMBASE, Cochrane Library, Web of Science and Clinicaltrials.gov were searched for clinical trials of patients with RP assigned to treatment with VPA. Patients' pre- and post-treatment visual field (VF) and best-corrected visual acuity (BCVA) scores were extracted and compared to assess changes.
- **RESULTS:** A total of 78 reports were retrieved and 6 studies involving 116 patients were included in the Meta-analysis. The combined results showed a significant decrease in logarithm of minimal angle of resolution (logMAR) scores, calculated using baseline and post-treatment BCVA ($P < 0.00001$, mean difference = -0.05, 95%CI: -0.05, -0.04, $I^2 = 36%$) scores, which means there was considerable improvement in visual acuity. Meanwhile, more BCVA changes were observed in short-term (≤ 6 mo) treatment studies ($P < 0.00001$, mean difference = -0.05, 95%CI: -0.05, -0.04, $I^2 = 38%$), studies conducted in Asia ($P < 0.00001$, mean difference = -0.05, 95%CI: -0.05, -0.04, $I^2 = 4%$), studies with a sample size of 30 or fewer patients ($P < 0.00001$, mean difference = -0.05, 95%CI: -0.05, -0.04, $I^2 = 38%$) and prospective studies ($P < 0.00001$, mean difference = -0.05, 95%CI: -0.05, -0.04, $I^2 = 0%$). However, VPA's effect on VF was inconsistent across studies ($P = 0.75$, mean difference = -22.76, 95%CI: -160.56, 115.05, $I^2 = 68%$).
- **CONCLUSION:** This Meta-analysis reveals that most RP patients who were treated with VPA showed improvement in BCVA. However, its effect on VF remains inconsistent. VPA may be a promising treatment for RP.
- **KEYWORDS:** retinitis pigmentosa; valproic acid; visual acuity; Meta-analysis

DOI:10.18240/ijo.2019.01.20

Citation: Chen WJ, Ma L, Li MS, Ma X. Valproic acid's effects on visual acuity in retinitis pigmentosa: a systemic review and Meta-analysis. *Int J Ophthalmol* 2019;12(1):129-134

INTRODUCTION

Retinitis pigmentosa (RP) refers to a disease about progressive degeneration of retina. Usually, RP begins from the mid periphery and spreads to macula and fovea. It presents as blindness at night and then develop to be the narrowing of visual fields (VF), causing tunnel vision and the legal blindness or complete blindness at last^[1]. RP can lead to gradual dysfunction as well as the loss of rod photoreceptors in cells. It firstly impacts the night vision in mid-peripheral retina rich in rods and then impacts the night vision in central retina rich with cones. As a result, the cones will be eventually lost due to the disease process or following the loss of rods^[2]. The prevalence of RP is about 1:4000^[1]. RP itself exhibits a high heterogeneity as over 50 genes have mutations which can lead to non-syndromic RP. As reported, there are about 3100 kinds of mutations in these genes by now^[3].

At present, RP cannot be treated as it is impossible to hinder the loss of photoreceptors as well as function. The use of neuroprotectors is a basal treatment mode, which adopts many trials to evaluate their curative effects in the treatment of RP, including neurotrophic factors, vitamin A, DHA, and lutein^[4]. In recent years, the valproic acid (VPA) has drawn people's attention as it has the potential to treat RP. Functioning as an emotional and anticonvulsant stabilizer, VPA, to our knowledge, can lead to the inhibitory effects against gamma-aminobutyric acid (GABA) in central nervous system^[5]. Based on empirical evidence, VPA is likely to effectively treat people suffering retinal dystrophies due to its inhibitory effect on histone deacetylase^[6] and inflammatory response pathway through microglial cell apoptosis^[7-8]. However, its therapeutic benefits in RP remain inconclusive and controversial. According to Clemson *et al*^[9], an average four-month VPA treatment will contribute to the improvement on best-corrected visual acuity (BCVA) and VF for 5/7 RP patients. In another study, Bhalla *et al*^[10] retrospectively studied 31 patients suffering various pigmentary retinal dystrophies after

treatment with VPA for an average of 9.8mo. In comparison with publication of Clemson *et al*^[9], Bhalla *et al*^[10] found that the severity of VF kept decreasing in 4/5 patients and averagely, the VF was greatly worsened during the process of being treated with VPA ($P=0.002$). Besides, the VPA could lead to some undesirable side effects. Recently, Iraha *et al*^[11] found that VF level improved during the 6-month follow-up period; however, these reversed to baseline values after discontinuing the drug. Therefore, a systemic review together with a Meta-analysis are conducted aiming at evaluating how VPA contributes to RP treatment.

MATERIALS AND METHODS

Identification and Selection of Studies Literature search was independently performed by two investigators (Chen WJ and Li MS) in the PubMed, EMBASE, Cochrane Library, Web of Science and Clinicaltrials.gov. databases without restricting the publication language. All related studies available as of December 10, 2017 were retrieved. We used the following key words: (“valproic acid” or “propylisopropylacetic acid” or “2-propylpentanoic acid” or “divalproex” or “depakene” or “depakine” or “convulsofin” or “depakote” or “vupral” or “divalproex sodium” or “semisodium valproate” or “ergenyl” or “magnesium valproate” or “valproate” or “valproate sodium” or “sodium valproate” or “calcium valproate” or “valproate calcium” or “dipropyl acetate”) and (“retinitis pigmentosa” or “rod cone dystrophy” or “pigmentary retinopathy” or “retinopathy, pigmentary” or “tapetoretinal degeneration”). In addition, the reference lists of all retrieved studies are involved to determine other appropriate studies.

Integration and Elimination Standard Eligible studies had to satisfy specific standards: 1) research design: randomized controlled trials (RCTs), Non-randomized comparative researches including single-arm researches, cross-over researches and cohort researches; 2) experiment objects: RP patients; 3) intervention: topical and oral VPA; 4) results variables: baseline and post-treatment BCVA and VF was included. Duplications, reviews, case reports, meeting abstract, animal/*in vitro* studies, unrelated topic, and author's response, were not included.

Data Collection Two reviewers (Chen WJ and Li MS) collected the information as follows from the suitable studies: the first author's name, the publication year, the research design, the number of patients/eyes, sex, intervention, mean age, BCVA, VF, the length of treatment, and quality scores. The analysis on only data for the last treatment were conducted on the condition that the researchers reported original data with all stages of follow-up included. Disagreements were resolved by discussing all items with another reviewer (Ma L).

Quality Assessment Through applying a Jadad scale^[12], RCTs were evaluated. Single-arm, cross-over, and cohort studies were assessed applying the Newcastle-Ottawa Scale

(NOS)^[13] at the same time. With the application of the NOS scale, comprehensive research quality was determined as bad (score=0-3), fairly good (score=4-6), or excellent (score=7-9).

Analysis on Data Analysis on data involved is carried out applying Review Manager [RevMan (Computer program), Version 5.3, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014]. The result variables were BCVA and VF. In an authentic publication, if visual acuity (VA) was presented in the form of Snellen VA, the data was changed to logMAR values to make data analysis easier. According to report before, “counting fingers” (CF), “hand motion” (HM), “light perception” (LP), and “no light perception”(NLP) were assigned a logMAR value of 1.85, 2.3, 2.7, and 3.0, respectively^[14-15]. The average variation in VA or VF ranging from baseline to last treatment points were combined and counted applying inverse variance ways. The combined average differences and 95% confidence intervals (CI) were figured out applying the fixed-effect or random-effect model. The data test of Cochran Q for heterogeneity over researches and the I^2 data which quantifies the percentage of total variation attributable to between-study heterogeneity were figured out. The Q data was regarded as with statistical significance if $P<0.1$, and I^2 values higher than 50% demonstrated elevated heterogeneity. When testing the significant heterogeneity outcomes from the random-effect model were employed; otherwise, the fixed-effect model was applied. Analysis on heterogeneity was conducted with the I^2 data and determined as follows: low (25% to 50%), moderate (50% to 75%), or high (>75%)^[16]. Analysis on subgroup were carried out according to the length of treatment, location, and sample size. An I^2 value > 50% was determined as heterogeneity, and a random-effects model was subsequently employed to the statistics. If not, a fixed-effects model was used to pool the statistics. A P value less than 0.05 was regarded as statistical significance.

RESULTS

Overall Characteristics of Eligible Studies Figure 1 shows the study inclusion flow in this Meta-analysis. A total of 78 reports were initially identified. Of these, 13 were excluded based on the exclusion criteria listed above, including 13 duplications, 26 reviews, 12 case reports, 9 animal or *in vitro* studies, 6 authors' responses, 3 unrelated topics, 1 meeting abstract, and 2 studies without posted results. The 6 remaining clinical reports (1 clinical trial and 5 full-text) that met the inclusion criteria were analyzed^[9-11,17-19]. These 6 reports included 1 randomized controlled trial (RCT), 3 retrospective studies, and 2 prospective studies. A total of 203 eyes in 116 patients were included in this Meta-analysis. Additionally, the overall quality scores of the included studies are presented in Table 1.

Table 1 Characteristics of included trails and patients

Author (Publication year)	Design	Location	VPA dose (mg/d)	Length of treatment (mo)	Patients (eyes)	Mean age (y)	Sex (M/F)	Outcomes	Quality scoring
Totan, 2017	Retrospective	Indian	500	9.4±2.7	24 (48)	34.3±10.3	13/11	BCVA	5
Shanmugam, 2012	Prospective	Indian	500	4.0±1.6	10 (20)	42.5±16.1	NR	BCVA	6
Iraha, 2016	Prospective	Japan	400	6	29 (29)	52.5±11.5	12/17	BCVA, VF	6
Bhalla, 2013	Retrospective	USA	562.5±125	21.5±16.0	4 (8)	44.8±19.0	NR	VF	4
Clemson, 2011	Retrospective	USA	643±133	4±1	7 (13/14)	36±16	NR	BCVA, VF	5
Clinicaltrail, 2010	RCT ^a	USA	250-1000	12	40 (80)/42 (84)	NR	NR	BCVA, VF	3

^aThe control group is Placebo. RCT: Randomized controlled trail; NR: Not reported; BCVA: Best-corrected visual acuity; VF: Visual field.

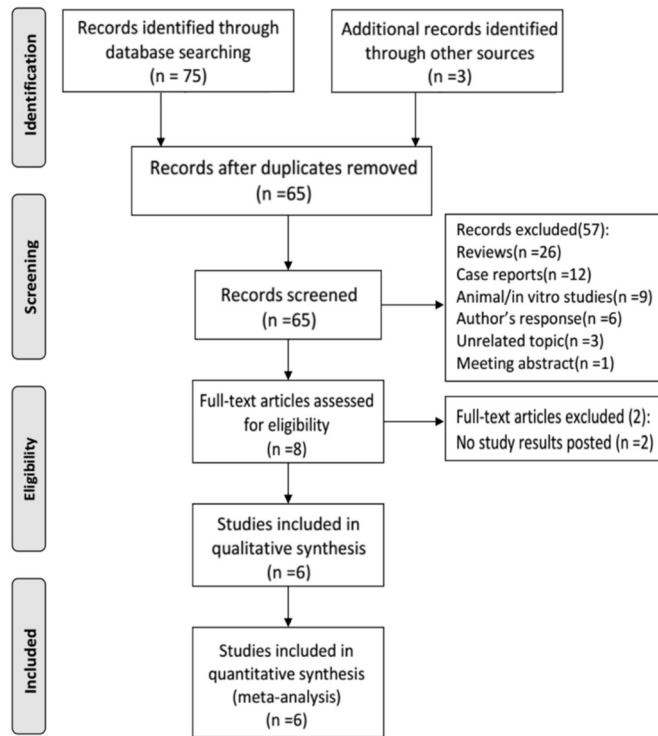


Figure 1 Flow chart of trails included in this Meta-analysis.

Efficacy Analysis Data on the therapeutic effects of treatment with VPA in RP were available for pooled analysis. Short-term treatment with VPA was 2mo, and long-term treatment was 12mo. The raw data with BCVA and VF of the included studies are presented in Table 2. The combined BCVA results showed a reduction based on the logMAR scores. The pooled mean difference in BCVA was -0.05 (95%CI: -0.05, -0.04, $I^2=36\%$) from baseline to the final treatment points (Figure 2), which means a significant improvement in BCVA.

However, when we tried to combine all VF results, there were no statistically differences between scores at the baseline and final treatment points (Figure 3). Altogether, these analyses show that VPA treatment improved BCVA, but the effect on VF was inconsistent across studies.

Sensitivity Analyses We conducted a subgroup analysis to explore the source of heterogeneity in BCVA and VF regarding the length of treatment, location, sample size and study design. More BCVA changes were observed in short-term (≤ 6 mo) treatment studies (Figure 4), studies conducted in Asia (Figure 5),

Table 2 The raw data with BCVA and VF of the included studies

Author (publication year)	BCVA (logMAR)			VF		
	Eyes	MD	SE	Eyes	MD	SE
Totan, 2017	48	0	0.034	NR	NR	NR
Shanmugam, 2012	20	-0.047	0.003	NR	NR	NR
Iraha, 2016	29	-0.056	0.018	NR	NR	NR
Bhalla, 2013	NR	NR	NR	8	64.725	142.031
Clinicaltrail, 2010				38	-150.43	71.37
L	40	0	0.539			
R	40	-1.4	0.824			
Clemson, 2011	14	-0.172	0.072	13	34.923	20.953

MD: Mean difference; SE: Standard error; NR: Not reported; BCVA: Best-corrected visual acuity; VF: Visual field.

studies with 30 patients or fewer (Figure 6) and prospective study (Figure 7).

DISCUSSION

This Meta-analysis analyzed the associations between VPA and RP, with the purpose to draw a conclusion of great significance. As far as we know, it is the first time for the Meta-analysis method to be used for comprehensively discussing how VPA impacts RP. According to the combined BCVA results in this Meta-analysis, logMAR scores declined to a large extent, which implied BCVA improvement in RP patients. However, for VF, difference presented no statistical significance from baseline to final treatment points, and VPA's effect on VF was inconsistent across studies. The clinicaltrials.gov^[17] data suggested that VF decreased after a period of VPA intake. Nevertheless, Clemson *et al*^[9] and Bhalla *et al*^[10] found VF improved significantly with treatment.

The exact mechanism of how VPA improved BCVA in patients suffering RP remains unclear. The VPA functions as an emotional and anticonvulsant stabilizer. It is able to impact the GABA level by decarboxylating glutamic acid and modulating GABA transaminase, which mediate its effect on abovementioned capacities. According to some evidences, due to the strong neuroprotective properties, VPA can well protect cell death and mediate inflammation^[20-21]. In addition, VPA can serve as an inhibitor inflammatory response pathway associated with photoreceptors in virtue of the microglial cell apoptosis^[7-8,22]. Besides, it can effectively subdue HDAC^[6,20,23].

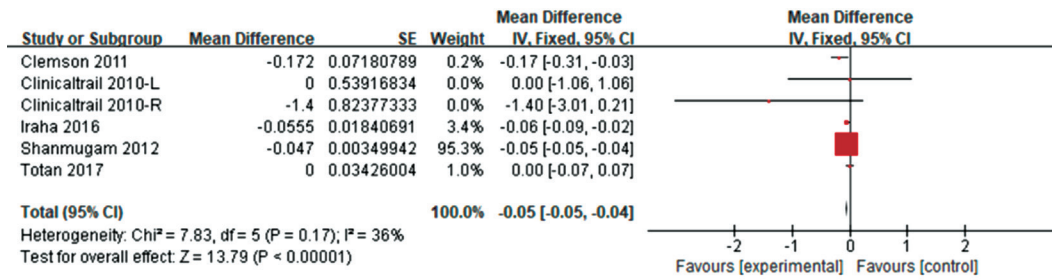


Figure 2 Diagram shows the 95%CI of mean change of BCVA from baseline in each study.

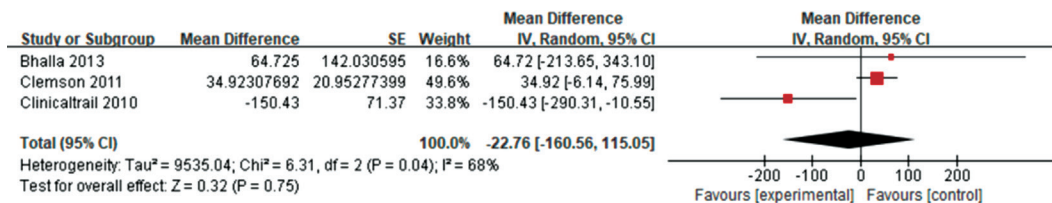


Figure 3 Forest plot shows the mean change of VF from baseline.

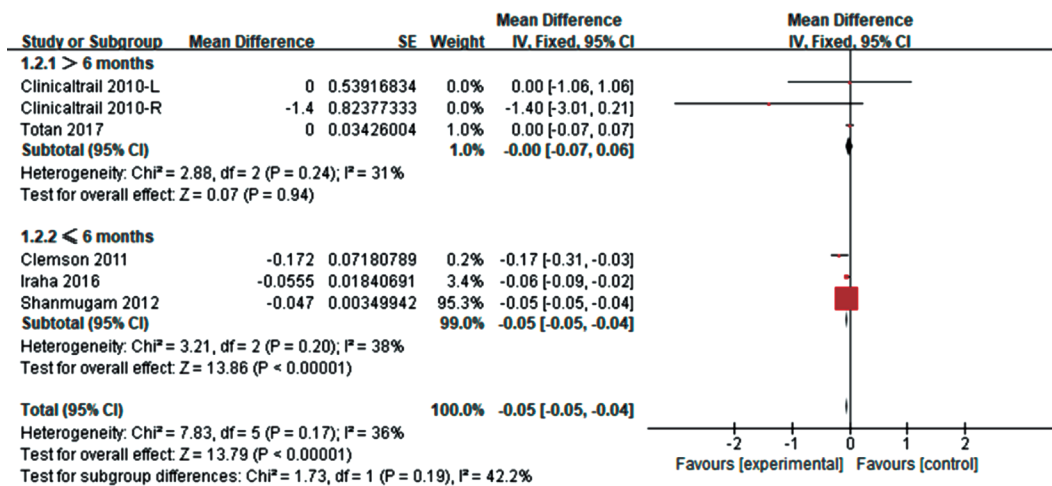


Figure 4 Forest plot shows subgroup analysis of BCVA based on length of treatment.

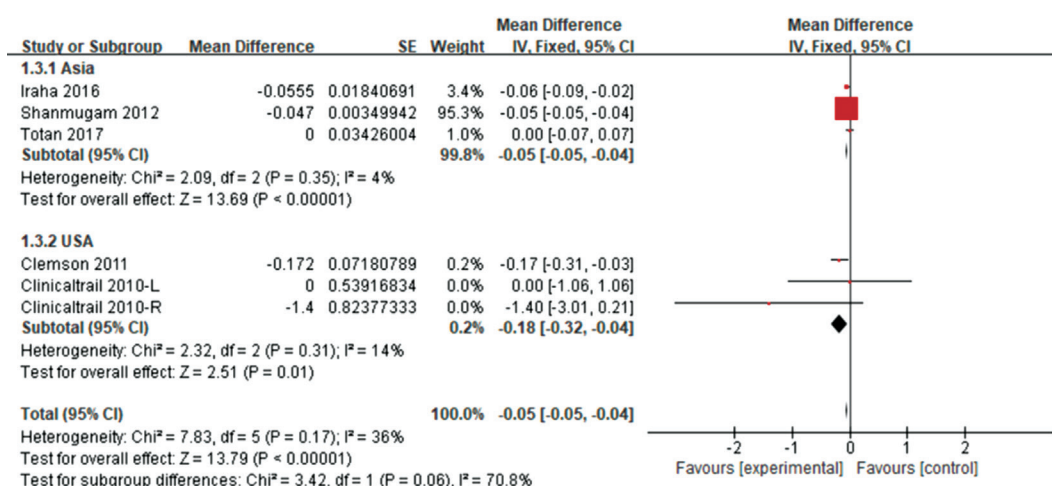


Figure 5 Forest plot shows subgroup analysis of BCVA based on location.

VPA has a special property, which has been reported in recent days, that is the special ability to overthrow damage to photoreceptor. Cells can achieve differentiation in one culture under the induced by VPA^[6]. Also, glial cells can achieve differentiation into the photoreceptor-type cells under the

simulation of VPA^[24], and VPA downregulates complement proteins as well as enhances diverse neurotrophic factors. Together, these VPA properties possibly result in the rescue of some of the borderline photoreceptors (*i.e.* slightly damaged or yet to be damaged), thereby improving visual function.

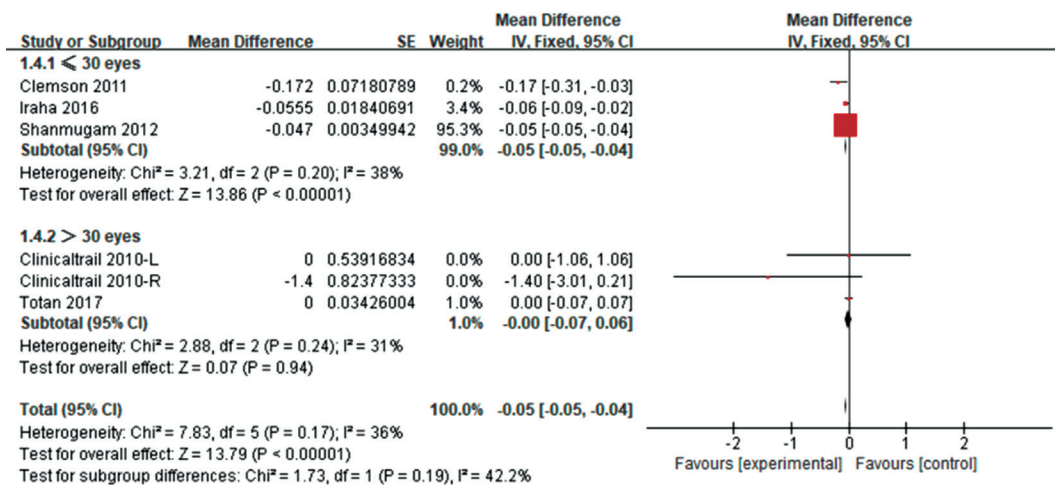


Figure 6 Forest plot shows subgroup analysis of BCVA based on sample size.

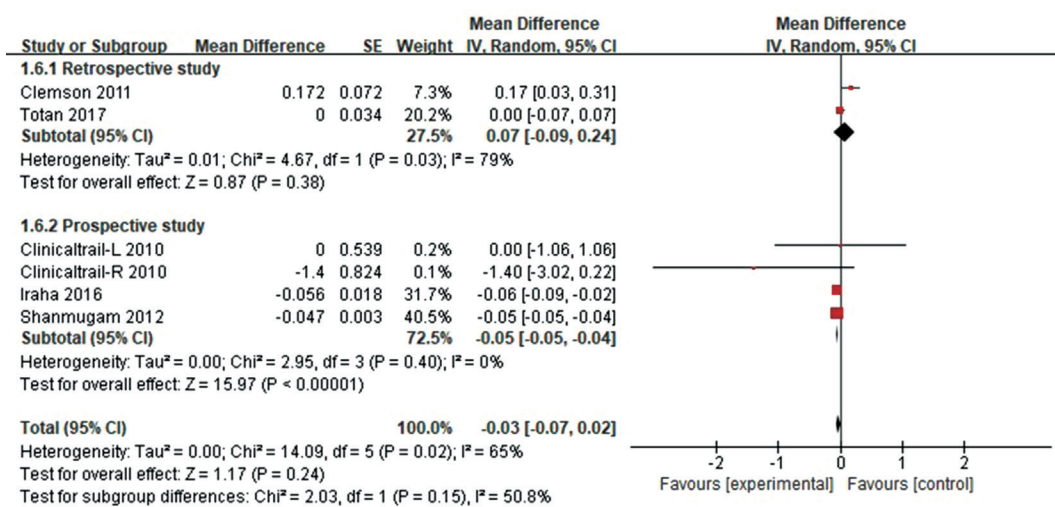


Figure 7 Forest plot shows subgroup analysis of BCVA based on study design.

According to some studies, VPA is able to lead to side effects like the hepatotoxicity as well as the neurological and mitochondrial toxicity^[25]. VPA negatively influence some mitochondrial events such as inhibiting and lowering activity of mitochondrial complexes I and IV, curbing oxygen consumption as well as adenosine triphosphate synthesis, sequestering coenzyme A, damaged structural organization of inner mitochondrial membrane, decreased hepatic cytochrome aa3, damaged oxidative phosphorylation, the subduing mitochondrial β -oxidation, and fragmenting vascular^[11,25-26]. However, these adverse effects were often described in patients at higher dosages used for other indications such as anticonvulsant activity (25-40 mg/kg-day), and it would be reduced when administered at doses which is extremely lower compared with the dose of anticonvulsants.

The work suffers many limitations, which should be taken into account carefully. All the study results are largely dependent on individual studies which covered samples at small size and exhibited some differences involving intervention time, population, routes of administration, as well as follow-up length. Meanwhile, patients did not exhibit a genetic

characteristic and therapeutic effect of VPA is varying due to RP genetic variation. As there are insufficient randomized control trial (RCTs), the review focused on assessing single-arm studies. In addition, since we recruit 3 retrospective studies in this Meta-analysis, there may have some impact on reliability of the data collected and analyzed. The clinical trial included in the Meta-analysis only reported the BCVA scores' mean and standard deviation for right and left eyes in each patient, respectively. Therefore, the data cannot be combined to obtain a total result without the original data, and the inclusion of left and right eye data separately in this paper may also be a source of heterogeneity.

To sum up, according to the Meta-analysis adopted in the paper, treating RP patients with VPA significantly improves BCVA, yet many studies hold controversial opinions about its curing effect on VF. On that account, it is the most proper to adopt prospective trial, multi-center trial and RCT to effectively exam the clinical effect of VF on patients suffering RP.

ACKNOWLEDGEMENTS

We would like to thank Fu-Sheng Tang and Sheng-Yao Chen for their help on statistical methods.

Authors' contributions: Conceptualization: Chen WJ, Ma L, Ma X; Data curation: Chen WJ, Li MS; Formal Analysis: Chen WJ, Li MS, Ma L; Funding Acquisition: Ma X; Investigation: Chen WJ, Li MS; Methodology: Chen WJ, Ma L; Project administration: Chen WJ, Ma L; Resources: Ma X; Software: Chen WJ, Ma L, Li MS; Supervision: Chen WJ, Li MS; Validation: Ma L, Ma X; Visualization: Ma X; Writing - Original Draft Preparation: Chen WJ, Li MS; Writing-Review & Editing: Ma L, Ma X.

Foundations: Supported by the National Natural Science Foundation of China (No.81770970, No.81271022).

Conflicts of Interest: Chen WJ, None; Ma L, None; Li MS, None; Ma X, None.

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