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Research paper

Divalproex and its effect on suicide risk in bipolar disorder: A systematic review and meta-analysis of multinational observational studies

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ABSTRACT

Background: Divalproex has become the most prevalent mood stabilizer for bipolar disorder. However, little is known its effects in the prevention of suicide in patients with bipolar disorder, and recent FDA announcement indicated an increased risk of suicidality when using anti-epileptic agents such as divalproex. The aim of this study is to investigate the effect of divalproex on suicide risk in patients with bipolar disorder.

Methods: A search strategy was used for the PubMed, Embase, ProQuest, ScienceDirect, Cochrane Library, ClinicalKey, Web of Science, and ClinicalTrials.gov until June 13th, 2018. Peer-reviewed observationally clinical studies in humans, investigating the association of divalproex and suicidality in patients with bipolar disorder were included. A random-effects meta-analysis was implemented to calculate the relative risk (RR) and 95% confidence intervals (CIs) for suicidality among patients receiving divalproex and those without.

Results: Total 6 studies were included in the final meta-analysis. There was no significant difference in the incidence rates (reported as [RR]; 95% CI) of suicide attempts (0.921; 0.383–2.215) or completed suicides (0.607; 0.180–2.043) between participants receiving divalproex vs. no medication. There was no significant difference in the incidence rates of suicide attempts (0.815; 0.453–1.466) or completed suicides (1.009; 0.410–2.484) between participants receiving divalproex and carbamazepine.

Limitations: The significantly heterogeneous sample sources and study design amount the included trials.

Conclusions: Treatment with divalproex did not reduce or increase the incidence of suicide-related events in patients with bipolar disorder.

1. Introduction

Bipolar disorder is a major psychiatric disorder defined by periods of depression and mania or hypomania, with a worldwide prevalence of approximately 1–2% (Ferrari et al., 2011, 2016). The risk of suicide attempts averages approximately 31.1% in the patients with bipolar disorder (Tondo et al., 2016), and the lifetime risk of suicide is approximately 14.5 times greater than in the general population (Hayes et al., 2015). Thus, it is important to determine how different treatments are associated with changes in suicide-related events (SREs) in such a high-risk group (Bellivier et al., 2017; de Toffol, 2017).

According to the latest guideline (Yatham et al., 2018), lithium is recommended as a useful medication in bipolar disorder and is considered to have an anti-suicidal effect based upon the recently

Abbreviation: CIs, confidence intervals; GHC, Group Health Cooperative datasets; KP, Kaiser Permanente database; RR, relative risk

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published systematic review and meta-analysis (Smith and Cipriani, 2017; Tondo and Baldessarini, 2018). However, lithium has a narrow therapeutic window and easily causes toxicity (McKnight et al., 2012). In the past decades, divalproex is becoming one of the most commonly used mood stabilizers worldwide (Baldessarini et al., 2008; Blanco et al., 2002). However, divalproex was only approved for acute manic stage by Food and Drug Administration (FDA). In recent guidelines (National Institute for Health and Care Excellence., 2014; Goodwin et al., 2016; Jeong et al., 2015; Kanba et al., 2013; Yatham et al., 2018), divalproex is suggested to use alone or in combination with other medications, as a first- or second-line treatment for bipolar depression, acute manic state, and for long-term maintenance. Although lithium is considered to have a better ability of anti-suicidality than divalproex (Smith and Cipriani, 2017; Tondo and Baldessarini, 2018), the actual effect of divalproex on suicide risk in bipolar patients were rarely addressed.

Studies on the effect of divalproex on suicide risk in patients with bipolar disorder have shown inconsistent results. A nationwide cohort study from Finland (Toffol et al., 2015) found that the use of divalproex might increase the risk of suicide attempts in patients with bipolar disorder, and another nationwide cohort study from Taiwan (Tsai et al., 2016) found a contrary result. Furthermore, the US FDA indicated that antiepileptic drugs (including divalproex) may increase the risk of suicidal thoughts and behavior (US FD Administration, 2009). Nevertheless, the finding could not be replicated when the participants included only those with bipolar disorder (Arana et al., 2010; Leon et al., 2012).

Taken together, we hypothesized that divalproex may influence the risk of suicide in patients with bipolar disorder. However, the evidence for this issue is limited and no meta-analysis focused on divalproex and suicidality in bipolar patients was performed in the past. In addition, several important studies related to this topic were published in recent 5 years (Ahearn et al., 2013; Hayes et al., 2016; Toffol et al., 2015; Tsai et al., 2016). Thus, we performed this comprehensive systematic review and meta-analysis to clarify the effect of divalproex on the risk of suicide in patients with bipolar disorder.

2. Method and materials

This systematic review and meta-analysis were conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Liberati et al., 2009) (see supplemental Table 1 and supplemental figure 1). The current meta-analysis fulfilled the requirements of the Institutional Review Board of the Tri-Service General Hospital (TSGHIRB: B-105-12).

2.1. Search strategy

Two independent authors (TY Chen and PT Tseng) searched the PubMed, Embase, ProQuest, ScienceDirect, Cochrane Library, ClinicalKey, Web of Science, and ClinicalTrials.gov databases until June 13th, 2018 with the following keywords: (divalproex OR valproic acid OR depakine OR valproate) AND (suicide) AND (bipolar disorder). In addition, our search strategy was augmented by hand searching the reference lists of specific review/original articles relevant to the current topic (Goodwin et al., 2016; Redden et al., 2011; Smith and Cipriani, 2017; Tondo and Baldessarini, 2018; Yatham et al., 2018).

Two independent authors (TY Chen and PT Tseng) screened the titles/abstracts of retrieved references. The full-text articles of potentially eligible articles were then retrieved and independently verified for eligibility by the same authors. Disagreements were resolved through discussion. When a consensus could not be reached, a third reviewer (CY Hsu) was consulted.

2.2. Eligibility criteria

The inclusion criteria were as follows: (1) observational clinical studies of humans, (2) peer-reviewed articles investigating the association of divalproex and suicidality (including suicidal ideation, suicide attempts, and completed suicides), and (3) studies that recruited subjects with a diagnosis of bipolar disorder only (included bipolar I disorder, bipolar II disorder, and bipolar disorder, not otherwise specified). To broaden the potentially eligible studies, we did not set any language restrictions during the current study.

The exclusion criteria were as follows: (1) non-human clinical trials; (2) studies in which the association between suicidality and divalproex was not investigated; (3) review/case reports; and (4) studies recruiting subjects with diagnoses other than bipolar disorder. (5) Studies which only compared the effect on suicidality between divalproex and lithium were recruited, because previous meta-analyses had well addressed this issue (Cipriani et al., 2013; Tondo and Baldessarini, 2018).

2.3. Methodological quality appraisal

The quality of individual studies was evaluated by using the Downs and Black quality checklist, which is a widely used scale of 27 items that evaluate both randomized and nonrandomized studies (Downs and Black, 1998). This checklist consists of five subscales measuring reporting, external validity, internal validity (i.e., bias and confounders), and power. As has been done in previous reviews that used the Downs and Black scale (Deady et al., 2017; Samoocha et al., 2010), minor modifications were made to the scale for use in this study. The scoring for question 27 regarding statistical power was simplified to either 1 or 0 points, depending on whether there was sufficient power to detect a clinically significant effect. The set criterion held that studies presenting the power of less than 0.80, with an alpha of 0.05, would be scored as 0 points. The maximum score for the modified checklist was 28, and each individual item was rated as either 1 or 0 points, with the exception of item 5, which reported on principal confounders and was rated up to 2. The final scores of this scale were grouped into the following 4 categories based on different ranges: excellent (26–28), good (20–25), fair (15–19), and poor (14 and less).

Two independent authors (TY Chen and PT Tseng) assessed the quality of the included studies. Any disagreements were discussed and resolved.

2.4. Outcome measures and data extraction

The primary outcome was the difference in the incidence rates [reported as the relative risk (RR)] of SREs, either in suicide attempts or completed suicides, in participants receiving divalproex vs. those without divalproex or those with another mood stabilizers.

The clinical variables of interest were extracted from each study according to a predetermined list. When data were not available in the articles, we tried to contact the authors, up to two times per month, to request additional data.

2.5. Statistical analysis

Due to anticipated heterogeneity, a random-effects meta-analysis rather than a fixed-effects meta-analysis was chosen. Random-effects modeling is more stringent than fixed-effects modeling and incorporates a between-study variance in the calculations (Borenstein et al., 2010) on the platform of the Comprehensive Meta-Analysis software, version 3 (Biostat, Englewood, NJ). We calculated the relative risk (RR) and 95% confidence intervals (CIs) for the incidence rates of suicidal risk among patients receiving divalproex and those without divalproex. Statistical significance was considered at a p value less than 0.05.

2.6. Heterogeneity, publication bias, and sensitivity test

Heterogeneity was assessed using the Q statistic, with a corresponding Q statistic p value of less than 0.05 reflecting high heterogeneity (Higgins et al., 2003) and the I^2 statistic representing the proportion of heterogeneity among the study estimates (Borenstein et al., 2017). Furthermore, we examined any potential publication bias using visual inspection of funnel plots and did not use Egger's regression tests since no data set was more than 10 (Egger et al., 1997; Higgins and Green, 2011). If there was evidence of any publication bias, we used the Duval and Tweedie's trim and fill test to adjust effect size estimates (Duval and Tweedie, 2000). Sensitivity analysis with one study removal test, which has been widely used in the meta-analysis, was performed by removing one study at a time to detect changes in the statistical results. This indicates whether a single study could be biasing the summary of the effect size estimates (Tobias, 1999).

2.7. Subgroup meta-analysis and meta-regression

To determine the potential sources of heterogeneity and confounding effects, we conducted subgroup meta-analyses if the number of studies was three or more. In addition, when there were at least 5 datasets available, we performed meta-regression with the restricted maximum likelihood method to detect potential confounding effects from the clinical variables of interest on the effect sizes (Davey et al., 2011).

3. Results

3.1. Study selection

Fig. 1 provides a flowchart of the study selection process. In brief, 50 full-text articles were reviewed. Among them, 44 were excluded (the reasons for exclusion are provided in supplemental Table 2). Several datasets were not used for further analysis because there were fewer than 3 datasets to compare (Davey et al., 2011), such as those comparing divalproex to other mood stabilizers [gabapentin (Collins and McFarland, 2008; Gibbons et al., 2009) and topiramate (Gibbons et al., 2009; Patorno et al., 2010)] and other atypical antipsychotics [olanzapine and quetiapine (Hayes et al., 2016)]. Ultimately, 6 articles were included into the current meta-analysis (Table 1) (Ahearn et al., 2013; Collins and McFarland, 2008; Gibbons et al., 2009; Goodwin et al., 2003; Toffol et al., 2015; Tsai et al., 2016).

Regarding the chosen studies, in brief, 4 studies compared the suicidal risks between treatment with divalproex and no medication treatment (Ahearn et al., 2013; Goodwin et al., 2003; Toffol et al., 2015; Tsai et al., 2016) (participants treated with divalproex = 3268, participants not treated with medication = 2870, total mean age = 41.7, total mean female proportion = 37.1%), and 4 studies compared the suicidal risks between divalproex and carbamazepine (Collins and McFarland, 2008; Gibbons et al., 2009; Goodwin et al., 2003; Tsai et al., 2016) (participants with divalproex = 10,676, participants with carbamazepine = 1381, total mean age = 38.5, total mean female proportion = 60.9%).

3.2. Methodological quality of included studies

The modified version of the Downs and Black quality checklist was used to evaluate the quality of the selected studies. The quality ranged from “fair” to “good”, and the median score of included studies was 21 with quantile range of 17–21. The details of the methodological quality assessment of the included studies are provided in supplemental Table 3.

3.3. Meta-analysis investigating the differences in suicidal risk in participants receiving divalproex and those without medication treatment

A total of 4 eligible articles with 5 datasets compared the incidence rates of suicide attempts (Ahearn et al., 2013; Goodwin et al., 2003; Toffol et al., 2015; Tsai et al., 2016), and 3 articles with 4 datasets compared the incidence rates of completed suicides (Goodwin et al., 2003; Toffol et al., 2015; Tsai et al., 2016). The results of the meta-analysis comparing different incidence rates of suicide attempts revealed that there were no significant differences in the incidence rates of suicide attempts between patients treated with divalproex and those not treated with medication ($k = 5$, RR = 0.921, 95% CI = 0.383–2.215, $p = 0.855$) (Fig. 2A). In addition, though there was significant heterogeneity (Q value = 212.211, df = 4, p value < 0.001, $I^2 = 98.115\%$), no publication bias was observed via inspection of the funnel plot (supplemental figure 2A). Similarly, there were no

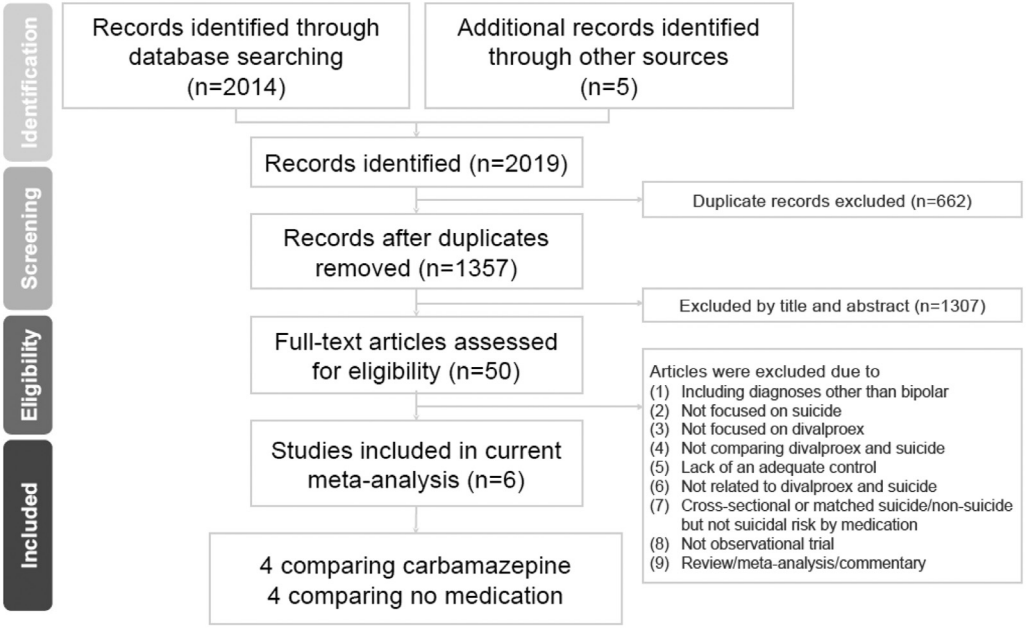


Fig. 1. Flowchart of the selection strategy of the current meta-analysis.

Table 1
Characteristics of recruited studies.

Author (year)	Study design	Comparison	Subjects	Person-year	Mean age	Female (%)	F/U (m)	Country
Tsai et al. (2016)	Nationwide cohort study (NHID)	Divalproex	1953	15342.1	38.0 ± 13.3	51.82	72	Taiwan
		Carbamazepine	615	4787.6	39.0 ± 14.0	53.66		
		No medication	1373	5917.0	46.9 ± 17.4	42.1		
Toffol et al. (2015)	Nationwide cohort study (HDR)	Divalproex	494	807.0	41.7 ± 12.8	55.1	96	Finland
		No medication	332	2143.0		53.9		
Ahearn et al. (2013)	Retrospective cohort study (5 VA Hospitals)	Divalproex	821		53.8	11.9	72	USA
		No medication	1165					
Gibbons et al. (2009)	Retrospective cohort study (PharMetrics)	Divalproex	4581	4169.0	n/a	n/a	84	USA
		Carbamazepine	346	306.0				
Collins and McFarland (2008)	Retrospective cohort study (OSMMHD)	Divalproex	4142	2214.0	38.7 ± 14.2	65.8	72	USA
		Carbamazepine	420	242.0				
Goodwin et al., (2003)	Retrospective cohort study (KP and GHC)	Valproate		(KP) 8722.0	(KP) 38.7 ± 14.6	(KP) 64.0	84	USA
		Carbamazepine		1762.0				
		No medication		23428.0				
				(GHC) 1946.0				
				754.0	(GHC) 37.9 ± 14.7	(GHC) 67.0		
				5014.0				

Abbreviation: F/U: follow up; THIN: The Health Improvement Network; NHID: The National Health Insurance database; HDR: hospital discharge register; VA: Veterans Administration; OSMMHD: Oregon state Medicaid and mental health databases; KP: Kaiser Permanente; GHC: Group Health Cooperative

significant differences in the incidence rates of completed suicides between participants treated with divalproex and those not treated with medication ($k = 4$, RR = 0.607, 95% CI = 0.180–2.043, $p = 0.420$) (Fig. 2A). There was also significant heterogeneity in this case (Q value = 21.538, df = 3, p value < 0.001, $I^2 = 86.071\%$), and again, no publication bias was observed via inspection of the funnel plot (supplemental figure 2B).

3.3.1. Sensitivity test

The sensitivity analysis with one study removal test did not change the results of the meta-analyses of the suicide attempts or of the completed suicides. That is, the insignificant result of the current meta-analysis was not contributed by any single study.

3.3.2. Meta-regression

There was a significant positive association between the incidence rate of suicide attempts and follow-up duration (slope = 0.070, $k = 5$, $p = 0.036$), but there was no significant association between the incidence rate of suicide attempts and the proportion of females ($p = 0.223$). The meta-regression was not performed due to less than 5 datasets available for completed suicides.

3.4. Meta-analysis investigating the differences in the suicidal risks in participants receiving divalproex and those receiving carbamazepine

A total of 4 eligible articles with 5 datasets compared the different incidence rates of suicide attempts and that of completed suicides (Collins and McFarland, 2008; Gibbons et al., 2009; Goodwin et al., 2003; Tsai et al., 2016). The meta-analysis comparing the incidence rates of suicide attempts revealed no significant differences in the incidence rates of suicide attempts between participants treated with divalproex and those treated with carbamazepine ($k = 5$, RR = 0.815, 95% CI = 0.453–1.466, $p = 0.494$) (Fig. 2B). These results were found to be with significant heterogeneity (Q value = 18.859, df = 4, p value = 0.001, $I^2 = 78.790\%$) and significant publication bias, as observed via inspection of the funnel plot (supplemental figure 2C). The adjusted estimated ES via the Duval and Tweedie's trim and fill test revealed a similar non-significant result (RR = 1.047, 95% CI = 0.564–1.942). Similarly, there was no significant difference in the incidence rates of completed suicides between participants treated with divalproex and those treated with carbamazepine ($k = 4$, RR = 1.009, 95% CI = 0.410–2.484, $p = 0.985$) (Fig. 2B). This result was also without significant heterogeneity (Q value = 0.530, df = 3, p value = 0.912, $I^2 < 0.001\%$), but with significant publication bias via inspection of the funnel plot (supplemental figure 2D). The adjusted estimated ES via the Duval and Tweedie's trim and fill test revealed a similar non-significant result (RR = 0.942, 95% CI = 0.397–2.235).

3.4.1. Sensitivity test

The sensitivity analysis with one study removal test showed that there were no changes in the meta-analysis of suicide attempts and completed suicides after the removal of any one of the selected studies.

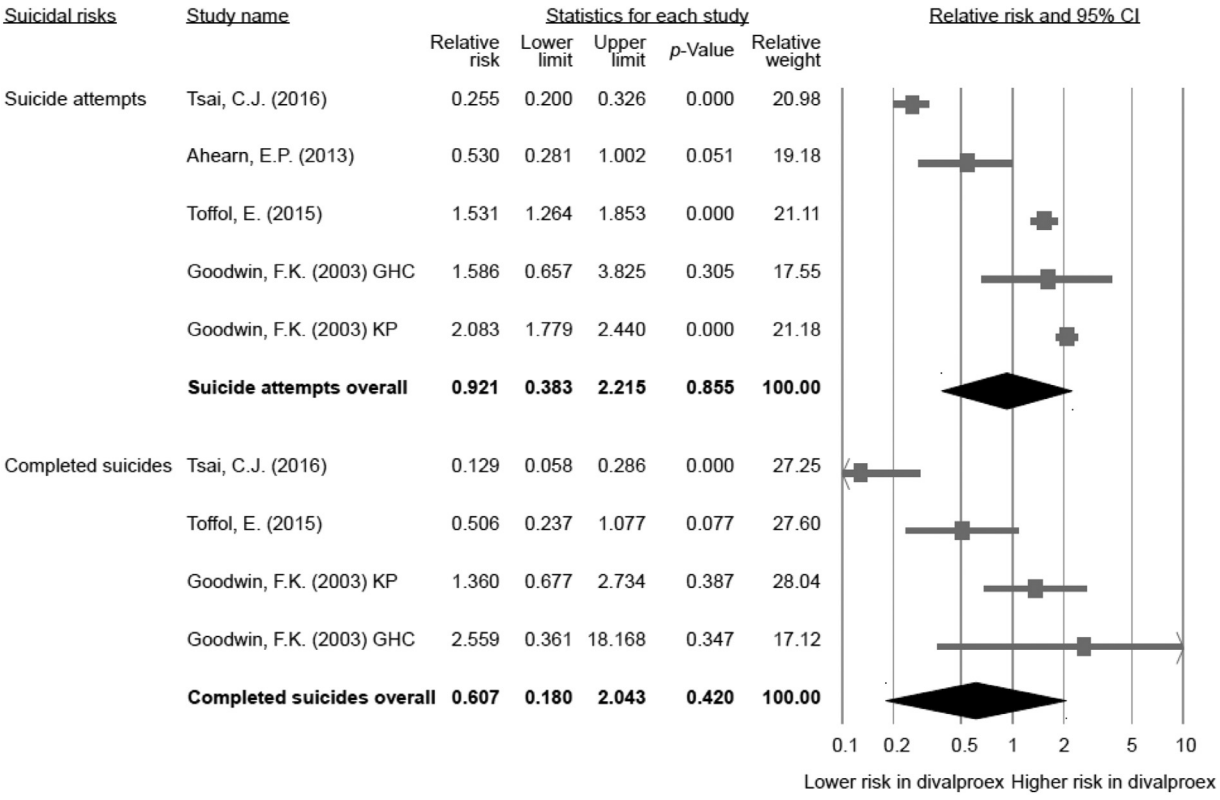
3.4.2. Meta-regression

There was no significant association between the incidence rates of suicide attempts and follow-up duration ($p = 0.300$).

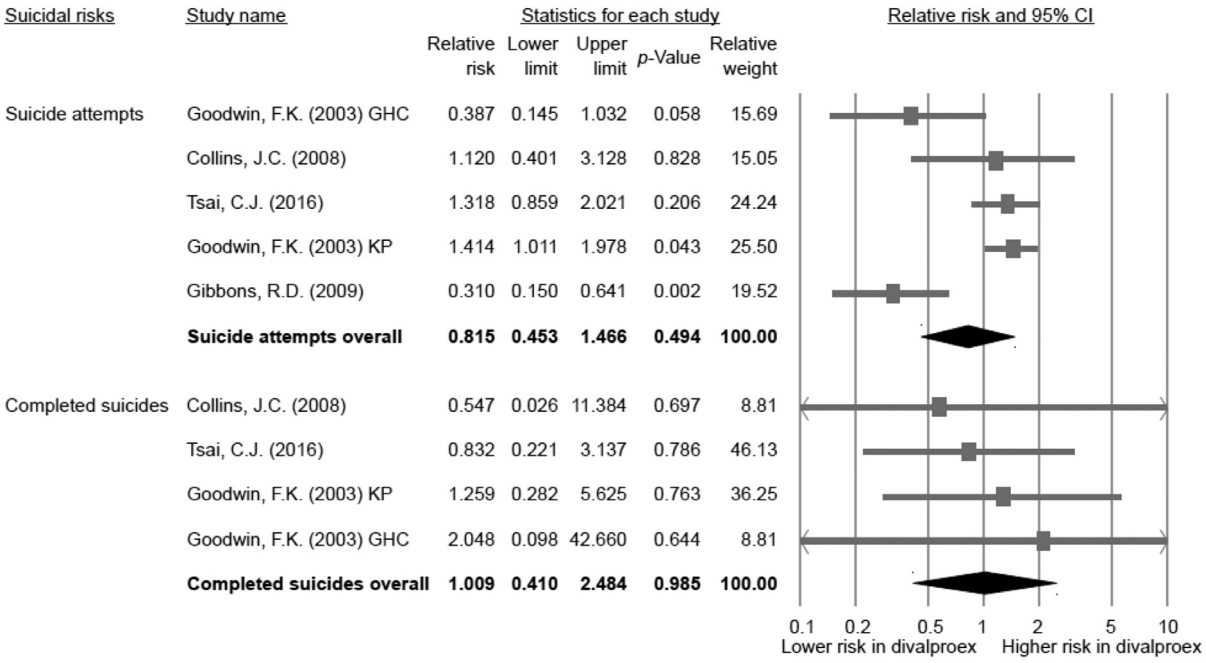
4. Discussion

To the best of our knowledge, this updated synthesis of the current evidence is the first meta-analysis of studies examining the effects of divalproex on the incidence of suicide attempts and completed suicides in patients with bipolar disorder. We also compared the risk of suicidality in bipolar patients treated with divalproex and those treated with carbamazepine. In general, we did not find a protective effect, reducing the incidence rates of suicide attempts or completed suicides with the use of divalproex in patients with bipolar disorder and no significant difference was found between divalproex and carbamazepine.

The current meta-analysis suggests that divalproex may not decrease the incidence of suicidality in bipolar patients. Although this result may be explained by the heterogeneity of the studies we included, it still suggests that divalproex may have no benefit in preventing new cases of SREs in bipolar patients. One recent study showed similar results regarding this topic (Song et al., 2017). The study enrolled more than 50,000 patients diagnosed with bipolar disorder or schizoaffective disorder and found that divalproex had no advantage in suicide prevention for those who had used it for less or longer than 30 days. However, after controlling for various covariates, the risk of SREs was significantly increased when off divalproex for less than 30 days. Another retrospective chart review study found a similar protective benefit of using divalproex, and carbamazepine against non-lethal suicidal behavior in bipolar patients (Yerevanian et al., 2007). A significant increase in suicidal behavior was noted after discontinuation of these medications. We did not include the above two studies in our analysis because they enrolled patients with schizoaffective disorder. However, the rebound phenomenon may suggest a role for divalproex in bipolar disorder maintenance and a benefit in decreasing long-term prevalence of SREs.



A Meta-analysis of the incidence rates of suicidal risks in patients treated with divalproex or not treated with medication



B Meta-analysis of the incidence rates of suicidal risks in patients treated with divalproex or carbamazepine

Fig. 2. (A) Forest plot of the meta-analysis of the incidence rates of suicidal risks in patients treated with divalproex or not treated with medication; (B) forest plot of the meta-analysis of the incidence rates of suicidal risks in patients treated with divalproex or carbamazepine.

Fig. 2A indicates that there were no significant differences in the incidence rates of suicide attempts ($p = 0.855$) or completed suicides ($p = 0.420$) between the divalproex group and the no medication group; Fig. 2B reveals that there were no significant differences in the incidence rates of suicide attempts ($p = 0.494$) or completed suicide ($p = 0.985$) between the divalproex and the carbamazepine groups.

In addition, we found that there was no difference between divalproex and carbamazepine in preventing SREs in patients with bipolar disorder. Compared to a placebo, divalproex and carbamazepine are considered effective in reducing aggression; however, a solid conclusion on their anti-aggressive effects could not be made due to inconsistent study results (Huband et al., 2010). The direct evidence comparing the anti-aggressive effect of divalproex and carbamazepine is limited. Further studies are needed to address this issue.

The controversial anti-suicidal effects of divalproex and carbamazepine could be explained by their insufficient treatment of bipolar depression. Bipolar depression is a leading cause of suicide (Balazs et al., 2006; Sanchez-Gistau et al., 2009), and divalproex and carbamazepine monotherapies are sequentially considered as the second- and third-line treatment options in the latest guideline (Yatham et al., 2018). Although there are two meta-analyses (Bond et al., 2010; Smith et al., 2010) showing that divalproex is effective in bipolar depression, the limited strength of the treatment effect should be considered. There is even less evidence for the effect of carbamazepine in bipolar depression (El-Mallakh et al., 2010). Therefore, we hypothesize that the controversial treatment effects of divalproex and carbamazepine on aggression and bipolar depression may mediate the controversial anti-suicidal results in bipolar patients.

Importantly, our results align with previous findings showing that divalproex does not increase the risk of SREs in bipolar patients. Many of these studies were performed after the announcement from the FDA stating that antiepileptic drugs might increase the risk of suicide (Administration, 2009). Some studies using nationwide or local databases also found that people who use divalproex may have an increased risk of SREs (Olesen et al., 2010; Patorno et al., 2010; Pugh et al., 2012). However, the latest meta-analysis of controlled studies did not find an elevated risk of SREs for divalproex (Redden et al., 2011). Another study evaluated the SREs in patients treated with antiepileptic drugs (included divalproex) and found that antiepileptic drugs did not increase the risk of SREs in patients with bipolar disorder (Arana et al., 2010). In addition, a multi-center, 30-year observational study also reported that divalproex did not increase the risk of SREs in patients with depressive, bipolar, or schizoaffective disorder (Leon et al., 2012). The conclusion we can reach is that although divalproex may not reduce the risk of suicide in bipolar disorder, it is unlikely to increase the risk.

5. Limitations

Several limitations of the current study should be addressed. First, we are unable to explain the exact reasonsbehind the observed difference in suicidal risks, using meta-analysis alone. However, we go over several possible mechanisms in the discussion section. Second, some results show significant publication bias. Nevertheless, we found consistent results by correcting with the trim and fill test (Duval and Tweedie, 2000). Third, several results contained significant heterogeneity. Due to the limited datasets, we could only perform meta-regression on some of the results, and the subgroup analyses like gender and race difference, disease severity, medication compliance, and the amount of time on the medication could not be performed. Fourth, the definitions and measurements of suicidal events and mortality records varied from the source articles and might bias the results and limited the power of the analysis. Fifth, even though the total number of participants was relatively large, the total number of included studies was still small (only 6 studies), which could potentially lead to a type II error. Sixth, some of the included studies were not designed or powered specifically to evaluate the effects of divalproex on suicide, but rather to focus on symptom-based and clinical outcomes. Finally, we could not perform analysis based on different mood states of bipolar disorder due to limited datasets, which may be a concern in clinical practice.

6. Conclusion

In summary, this meta-analysis adds to the current knowledge on divalproex and its comparison between carbamazepine on SREs in bipolar patients. Our results show that divalproex did not increase or decrease the incidence rates of SREs in patients with bipolar disorder. Furthermore, no significant difference was found between divalproex and carbamazepine on the effects of SREs in patients with bipolar disorder.

Declaration of conflict of interest

The authors state that there are no any competing interests in the current study.

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Author contribution

Tien-Yu Chen, the first author, took the responsibility of writing the whole manuscript. Masoud Kamali, the native English speaker, took the responsibility of concept formation and grammar correction. Che-Sheng Chu, Chin-Bin Yeh, San-Yuan Huang, Wei-Chung Mao, Pao-Yen Lin, and Yen-Wen Chen contributed numerously in the study design and concept formation. Ping-Tao Tseng and Chung-Yao Hsu, the corresponding authors, took the responsibility of collection of the manuscript and submitting the manuscript.

IRB

The current meta-analysis fulfilled the requirements of the Institutional Review Board of the Tri-Service General Hospital (TSGHIRB: B-105-12).

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jad.2018.11.093.

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