

Comparing lithium and valproate in lowering suicide risks: a territory-wide retrospective cohort study and a meta-analysis of 126368 individuals



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INTRODUCTION

- Lithium and valproate are mood-stabilisers commonly prescribed for treating affective disorder, which both **showed some evidence in suicidal prevention**¹⁻³
- Recent studies suggested the superiority of the anti-suicidal effect of lithium in comparison with the class of anticonvulsants⁴⁻⁵
- However, little research **directly compares** the reduction in suicidal risks during monotherapy of lithium or valproate

OBJECTIVES

To **compare the effectiveness** of lithium and valproate in reducing any suicidal ideation and/or suicidal attempts after taking either of these medications

METHODS

A **retrospective cohort study** and **systematic review** were conducted, and observational data were aggregated in subsequent **meta-analysis**

COHORT STUDY

Data source

Electronic health records from the Clinical Data Analysis and Reporting System (CDARS)

Study population

Patient diagnosed with bipolar disorder (ICD-9 CM 296.0, 296.1, 296.4-296.8) who started on lithium or valproate therapy after 2003

Exclusion criteria

- Patients who aged under 18 during initiation/ without valid birth dates, or
- initiated lithium and valproate concurrently, or
- used other mood stabilisers before (i.e haloperidol, chlorpromazine, olanzapine, quetiapine, risperidone), or
- attempted suicide before index date, or had an observational period less than 365 days

Exposure and comparator

- Lithium (BNF code: 0402030K0) was the primary exposure while sodium valproate (0408010W0) was the comparator

Outcome and measurement

- Suicide attempts recorded in CDARs, coded by ICD-9-CM (E958.9)
- Balance baseline characteristic by inverse probability of treatment weighting (IPTW) before estimation of hazard ratios (HR) by weighted Cox proportional hazard model

SYSTEMATIC REVIEW AND META - ANALYSIS

Data source

Electronic databases, namely PubMed, Embase, APA PsycINFO and Cochrane Library

Selection criteria

- All published RCTs and observational studies in English investigating the same objective
- Studies with different comparators (i.e. other drugs or no drug use) and studies measuring non-suicidal outcomes were excluded

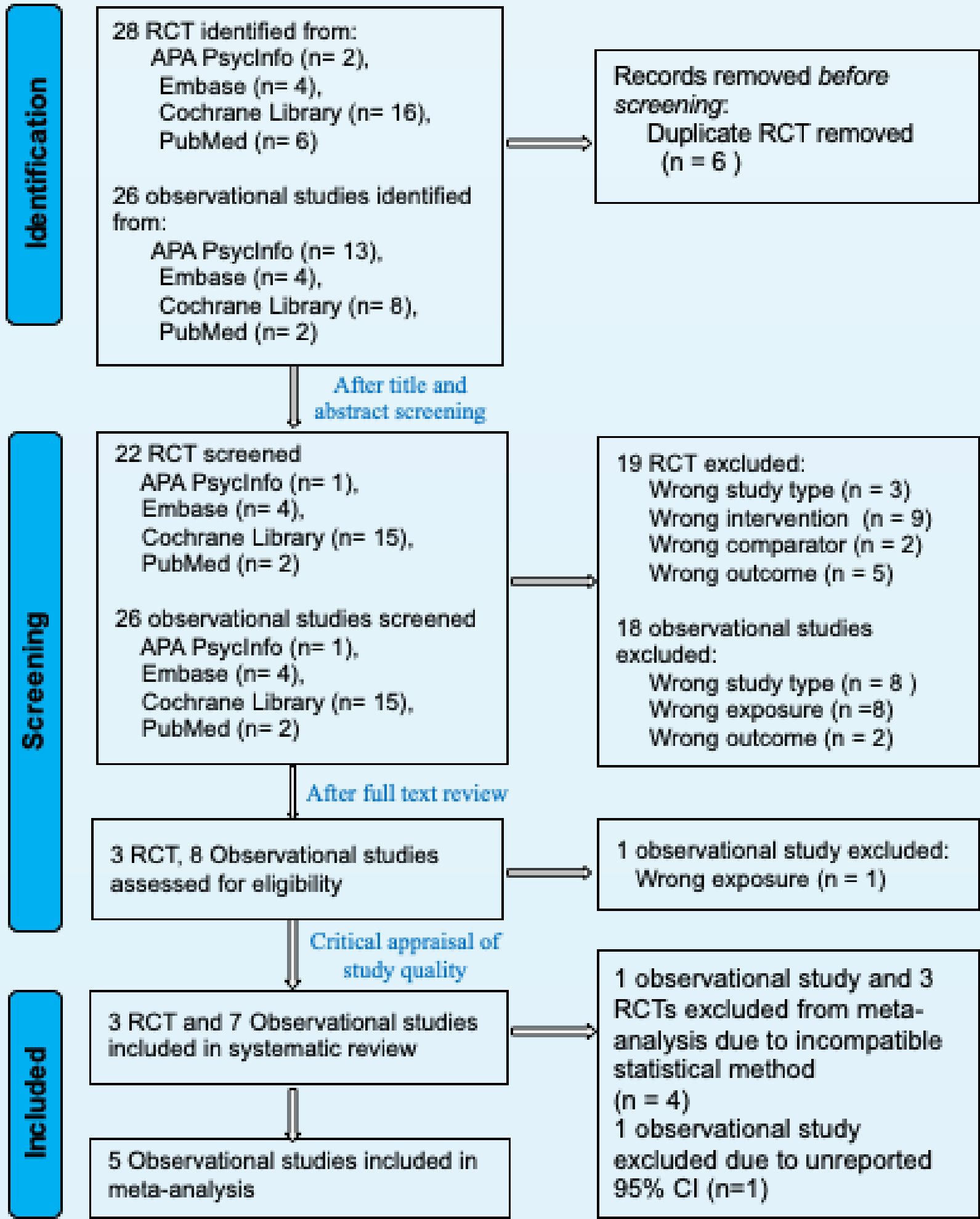


Fig. 1 Prisma Flow Chart

Statistical analysis

- Given the unstandardized outcomes and the incompatible statistical method, a meta-analysis of RCTs was not conducted
- Observational data were pooled using a random effects model, while inverse variance weighting method was applied to determine the relative significance among studies

- Exposure was binarily operationalized, comparing lithium to valproate use
- Heterogeneity between studies was examined by I² statistic
- The Egger's regression test was not conducted due to limited number of observational studies

RESULTS

COHORT STUDY

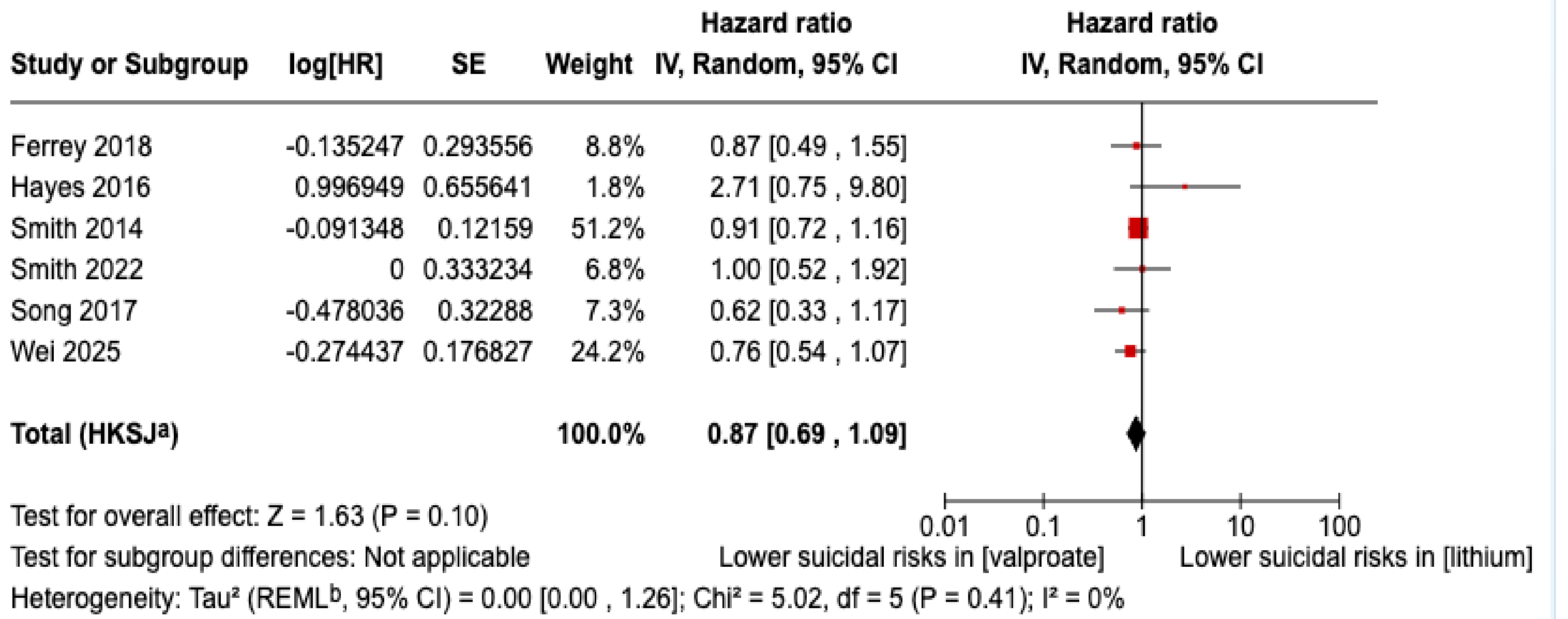
- 1379 valproate and 5556 lithium users were included in our cohort study
- No significant difference** in suicidal risks reduction were reported, comparing valproate to lithium (**adjusted HR 0.76, 95% CI 0.54 – 1.08**)

Table 1. Effect sizes for risk of suicide attempt using Cox regression.

	N (%)		Crude HR (95% CI)	Adjusted HR (95% CI)
	Lithium (ref)	Valproate		
Overall	44 (3.19)	165 (2.97)	0.75 (0.54, 1.04)	0.76 (0.54, 1.08)
Sex				
Female	25 (1.81)	90 (1.62)	0.68 (0.44, 1.06)	0.67 (0.42, 1.07)
Male	19 (1.38)	75 (1.35)	0.85 (0.51, 1.40)	0.89 (0.53, 1.48)
Age				
Age >= 65	2 (0.15)	4 (0.07)	0.08 (0.01, 0.43)	0.06 (0.02, 0.20)
Age < 65	42 (3.05)	161 (2.90)	0.82 (0.59, 1.16)	0.84 (0.60, 1.19)
Severity of comorbidity at baseline				
CCI = 0	40 (2.90)	144 (2.59)	0.75 (0.53, 1.07)	0.77 (0.54, 1.11)
CCI = 1	4 (0.29)	21 (0.38)	0.69 (0.24, 2.01)	0.68 (0.21, 2.15)
Mental disorder at baseline				
Depression	10 (0.73)	50 (0.90)	0.85 (0.43, 1.68)	0.67 (0.30, 1.53)
No depression	34 (2.47)	115 (2.07)	0.70 (0.48, 1.02)	0.72 (0.48, 1.07)
Medicine history				
Anti-depressants	18 (1.31)	67 (1.21)	0.63 (0.37, 1.06)	0.64 (0.37, 1.10)
No anti-depressants	26 (1.89)	98 (1.76)	0.80 (0.52, 1.24)	0.91 (0.59, 1.40)
Anti-psychotics	21 (1.52)	75 (1.35)	0.77 (0.48, 1.25)	0.74 (0.45, 1.23)
No anti-psychotics	23 (1.67)	90 (1.62)	0.73 (0.46, 1.16)	0.81 (0.51, 1.30)

SYSTEMATIC REVIEW AND META - ANALYSIS

- The **RCTs showed no clear evidence** that lithium has better efficacy in preventing suicide than valproate
- The results of 1 case-control and 5 cohort studies were aggregated and generated a **pooled estimates HR of 0.87 (95% CI 0.69 – 1.09)** in meta-analysis



Footnotes

^aCI calculated by Hartung-Knapp-Sidik-Jonkman method.

^bTau² calculated by Restricted Maximum-Likelihood method.

Fig 2. Forest plot of 6 observational study HRs for lithium and valproate use and suicidal risk

DISCUSSION

- Our research filled the literature gap by **directly comparing the suicidal risk reduction of the two commonly used drugs**
- Our findings suggested that **lithium is not superior in reducing suicidal risks** than valproate for patients with different affective disorders
- The key strength of our study was the use of **a large, real-world cohort from a territory-wide database** with high generalisability
- A recent study showed that valproate users had a reduced adverse effects than lithium users, **risks and benefits should be weighed comprehensively** before prescribing lithium⁶

CONCLUSION

To provide individualised psychopharmacotherapy, the **efficacy and safety of lithium should be balanced** when making decision together with patients, considering that **lithium is not better than valproate in terms of anti-suicidal effect**

ACKNOWLEDGEMENTS

I would like to express my deep gratitude to Professor Francisco T. T. Lai, my research supervisor, for his continuous guidance, unwavering support, and constructive suggestions. I wish, also to extend my gratitude to Ms. Cuiling Wei for providing professional assistance in conducting the cohort study.

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