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Review

# The influence of sertraline on depressive disorder after traumatic brain injury: A meta-analysis of randomized controlled studies

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## ARTICLE INFO

## ABSTRACT

Background: Sertraline showed some potential in alleviating depressive disorder after traumatic brain injury. This systematic review and meta-analysis was conducted to investigate the efficacy of sertraline on the treatment of depressive disorder after traumatic brain injury.
Methods: The databases including PubMed, EMbase, Web of science, EBSCO, and Cochrane library databases were systematically searched for collecting the randomized controlled trials (RCTs) regarding the efficacy of sertraline for traumatic brain injury.
Results: This meta-analysis included five RCTs. The initial use of sertraline was within 8 weeks after traumatic brain injury. Compared with control group for traumatic brain injury, sertraline treatment showed no significant improvement on Hamilton Depression Rating Scale (HAM-D) (standard mean difference (Std. MD) = −0.08; 95% confidence interval (CI) = −0.45 to 0.28; P = 0.65), anxiety score (Std. MD = 0.08; 95% CI = −0.32 to 0.48; P = 0.69), aggression score (Std. MD = −0.12; 95% CI = -0.56 to 0.32; P = 0.59), or quality of life (QOL) score (Std. MD = −0.06; 95% CI = −0.49 to 0.37; P = 0.78). There was no statistical difference of diarrhea (risk ratio (RR) = 0.85; 95% CI = 0.92 to 3.71; P = 0.08), dizziness (RR = 1.15; 95% CI = 0.57 to 2.31; P = 0.70), dry mouth (RR = 2.44; 95% CI = 0.43 to 13.89; P = 0.32), nausea or vomiting (RR = 1.17; 95% CI = 0.37 to 3.70; P = 0.79) between sertraline group and control group.
Conclusions: Sertraline showed no obvious benefits for the relief of depressive disorder after traumatic brain injury.

## 1. Introduction

Patients with traumatic brain injury commonly suffer from major depressive disorder which mostly occurs within the first year after the injury [1-3]. Major depressive disorders result in significant comorbid anxiety and decreased quality of life [4-6]. However, less than half of those patients obtain the medication or psychotherapeutic treatment for their depression [1,7,8].

Selective serotonin reuptake inhibitors have been considered to treat major depressive disorder following traumatic brain injury. For instance, two preliminary studies revealed the evidence for the efficacy and tolerability of sertraline in these patients, and the results showed the favorable influence on anger, aggression, functional status, subjective and objective cognitive functioning [9-11]. The indications include

(1) age 18 years or older, (2) a history of traumatic brain injury or other evidence of traumatic brain injury. The contraindications are as follows: (1) a history of current or past psychosis or mania, (2) to be pregnant or breast-feeding, (3) a history of clinically significant liver or renal disease [12-14].

Recently, several studies on the effect of sertraline on depressive disorder after traumatic brain injury have been published, but the results have been conflicting [12,13,15]. Considering these inconsistent effects, we therefore conducted a systematic review and meta-analysis of randomized controlled trials (RCTs) to evaluate the efficacy of sertraline for depressive disorder in these patients.

## 2. Materials and methods

This systematic review and meta-analysis was conducted based on Preferred Reporting Items for Systematic Reviews and Meta-analysis statement [16] and the Cochrane Handbook for Systematic Reviews of Interventions [17]. Two investigators independently searched articles, extracted data, and assessed the quality of included studies.

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## 2.1. Literature search and selection criteria

Several databases including PubMed, EMbase, Web of science, EBSCO, and the Cochrane library were systematically searched using the keywords: brain injury, and sertraline. Studies published between January 1990 and February 2019 were included. The inclusion criteria were as follows: (1) study design was RCT, (2) patients were diagnosed as traumatic brain injury, (3) intervention treatments are sertraline versus placebo.

## 2.2. Data extraction and outcome measures

Some baseline characteristics of patients were extracted from each included RCT, and they included first author, publication year, sample size, age, the number of female, time since the injury, Glasgow Coma Scale score and detail methods of two groups.

The primary outcome was Hamilton Depression Rating Scale (HAM-D). Secondary outcomes included anxiety score, aggression score, quality of life (QOL) score, diarrhea, dizziness, dry mouth, nausea and vomiting.

## 2.3. Quality assessment in individual studies

The methodological quality of included RCTs was evaluated using the Jadad Scale, which consisted of three evaluation elements including randomization (0–2 points), blinding (0–2 points), dropouts and withdrawals (0–1 points) [18]. One point would be allocated to each element based on the description, randomization and/or blinding of the included RCTs. The score of Jadad Scale ranged from 0 to 5 points, and one study with Jadad score ≥ 3 was thought to have the high quality [19].

## 2.4. Statistical analysis

Review Manager Version 5.3 (The Cochrane Collaboration, Software Update, Oxford, UK) was used for the all statistical analyses. We have assessed the standard mean differences (Std. MDs) with 95% confidence intervals (CIs) for continuous outcomes (HAM-D, anxiety score, aggression score, and QOL score) and risk ratios (RRs) with 95% CIs for dichotomous outcomes (diarrhea, dizziness, dry mouth, nausea and vomiting). Heterogeneity was quantified with the $I^2$ statistic, and the $I^2$ value >50% represented the significant heterogeneity. The random-effect model with DerSimonian and Laird weights was applied for the meta-analyses regardless of the heterogeneity. When the significant heterogeneity presented, sensitivity analysis was conducted to detect the influence of a single study on the overall estimate or perform the subgroup analysis. Publication bias was not evaluated because of the limited number (<10). $P < 0.05$ was thought to be statistically significant.

## 3. Results

### 3.1. Literature search, study characteristics and quality assessment

Fig. 1 demonstrated the flow chart for the selection process and detailed identification. 465 publications were searched after the initial
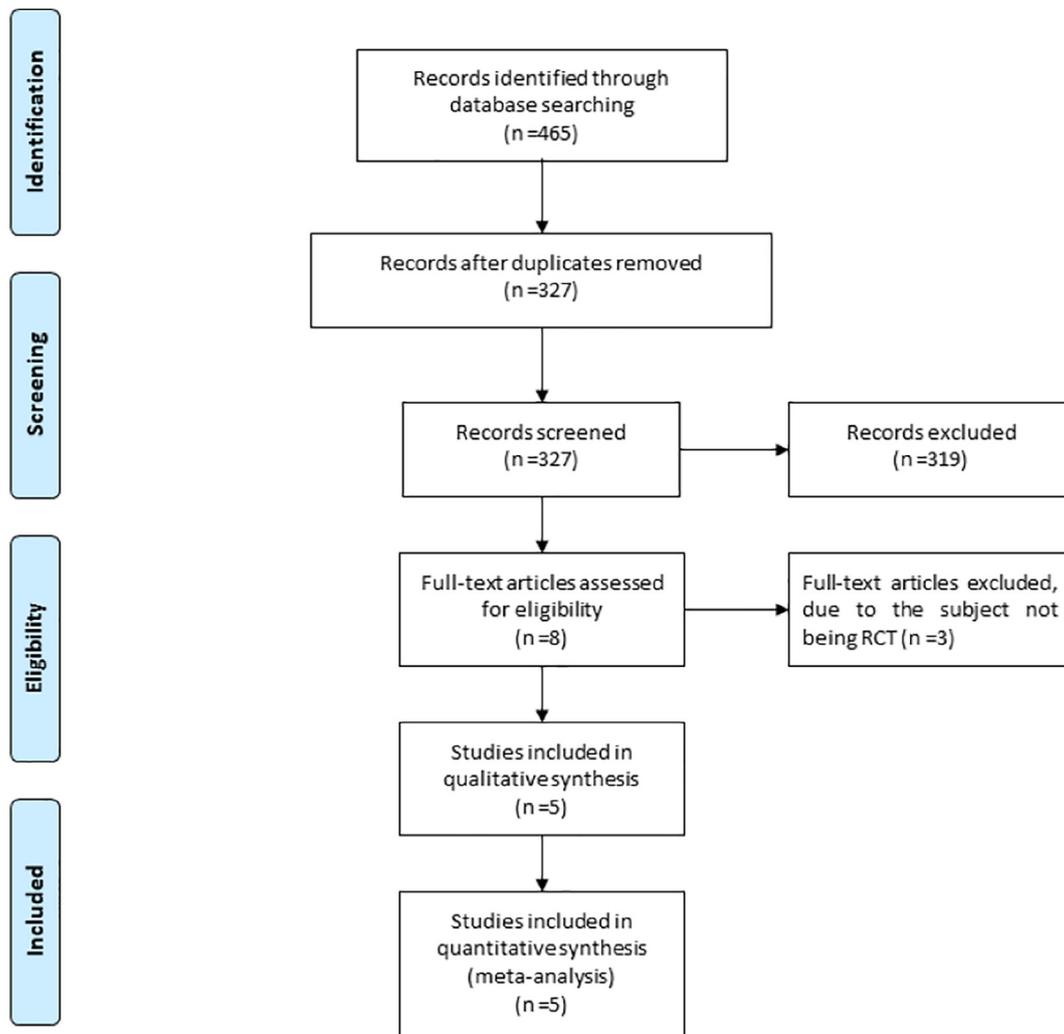


**Fig. 1.** Flow diagram of study searching and selection process.

**Table 1**
Characteristics of included studies.

| No. | Author | Sertraline group | | | | | | Control group | | | | | | Jada scores |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Number | Age (years) | Female (n) | Time since the injury (d) | Glasgow Coma Scale score | Methods | Number | Age (years) | Female (n) | Time since the injury (d) | Glasgow Coma Scale score | Methods | |
| 1 | Fann 2017 | 31 | 38 ± 12.3 | 8 | – | 10.7 ± 4.4 | 25 mg sertraline qd, and gradual increase up to 200 mg/day | 31 | 36.9 ± 12.9 | 7 | – | 10.4 ± 4 | Placebo | 5 |
| 2 | Jorge 2016 | 48 | 49.98 ± 20.05 | 22 | – | – | 100 mg/d sertraline for 24 weeks | 46 | 54.91 ± 18.24 | 16 | – | – | Placebo | 4 |
| 3 | Banos 2010 | 49 | 35.3 ± 16.7 | 10 | 21.5 ± 11.5 | 5.8 ± 3.5 | Sertraline 50 mg for 3 months | 50 | 34.5 ± 15.6 | 17 | 19.2 ± 10.4 | 5.8 ± 2.4 | Placebo | 4 |
| 4 | Ashman 2009 | 22 | 46.8 ± 12.8 | 12 | 18.6 ± 13.8 | – | Sertraline starting at 25 mg and increasing to therapeutic levels (up to 200 mg) for 10 weeks | 19 | 51.5 ± 8.2 | 7 | 16.6 ± 13.9 | – | Placebo | 4 |
| 5 | Lee 2005 | 10 | 33.6 ± 12.3 | 2 | 31.9 ± 5.8 | – | Sertraline starting at 25 mg/day and increasing to 100 mg/day in a week | 10 | 35.5 ± 7.2 | 2 | 30.0 ± 6.5 | – | Placebo | 4 |

search of databases. 138 duplicates and 319 papers were excluded after checking the titles/abstracts. Three studies were removed because of the study design and five RCTs were ultimately included in this meta-analysis [12-15,20].

Table 1 showed the baseline characteristics of five eligible RCTs. The five studies were published between 2005 and 2017, and total sample size was 316. The detail methods of sertraline for traumatic brain injury were summarized in Table 1, and the doses ranged from 25 mg/day to 200 mg/day.

Among the five RCTs, three studies reported HAM-D [12,14,20], two studies reported anxiety score [12,14], two studies reported aggression score [12,15], two studies reported QOL score [12,20], two studies reported diarrhea, dizziness, dry mouth, nausea and vomiting [12,13]. Jadad scores of the five eligible studies varied from 3 to 5, and thus this quality assessment confirmed these studies with high-quality.

### 3.2. Primary outcome: HAM-D

The random-effect model was used for the analysis of primary outcome. The results found that compared to control intervention for traumatic brain injury, sertraline showed no substantial influence on HAM-D (Std. MD = −0.08; 95% CI = −0.45 to 0.28; P = 0.65), and there was low heterogeneity among the studies ($I^2$ = 4%, heterogeneity P = 0.35, Fig. 2).

### 3.3. Sensitivity analysis

The meta-analysis of primary outcome had low heterogeneity among the included studies, and thus we did not perform sensitivity analysis by omitting one study in each turn or conduct the subgroup analysis.

### 3.4. Secondary outcomes

In comparison with control intervention for traumatic brain injury, sertraline resulted in no obvious impact on anxiety score (Std. MD = 0.08; 95% CI = −0.32 to 0.48; P = 0.69; Fig. 3), aggression score (Std. MD = −0.12; 95% CI = −0.56 to 0.32; P = 0.59; Fig. 4), QOL score (Std. MD = −0.06; 95% CI = −0.49 to 0.37; P = 0.78; Fig. 5), diarrhea (RR = 0.85; 95% CI = 0.92 to 3.71; P = 0.08; Fig. 6), dizziness (RR = 1.15; 95% CI = 0.57 to 2.31; P = 0.70; Fig. 7), dry mouth (RR = 2.44; 95% CI = 0.43 to 13.89; P = 0.32; Fig. 8), nausea or vomiting (RR = 1.17; 95% CI = 0.37 to 3.70; P = 0.79; Fig. 9).

## 4. Discussion

Two studies have reported that 58 of 157 patients (36.9%) had the depressive disorder after traumatic brain injury [21,22]. One-year frequency of major depression was estimated as 29.4%~53.1% in patients with traumatic brain injury [1,23]. The incidence of depression was high in the chronic stage of traumatic brain injury, but only a few patients obtained the recovery from depression at 2 years of follow-up [24].

Major depressive disorder was the frequent complication of traumatic brain injury [25-27]. Prevention was more effective than treatment [28,29]. Previous studies have confirmed the efficacy of antidepressants to prevent depression after stroke [30]. 100 mg/d sertraline for 24 weeks were reported to prevent depression after traumatic brain injury [13]. However, several studies reported the opposite results. In one RCT involving 62 participants, all patients had pre-post improvement in depression severity, but 12 weeks of sertraline treatment was associated with no improvement in HAM-D, Maier subscale, SCL-20 self-report, anxiety, post-concussive symptoms, pain, functioning, or health-related quality of life compared to placebo [12]. Ashman and colleagues also revealed no significant differences of depression between sertraline and placebo after traumatic brain injury [14].
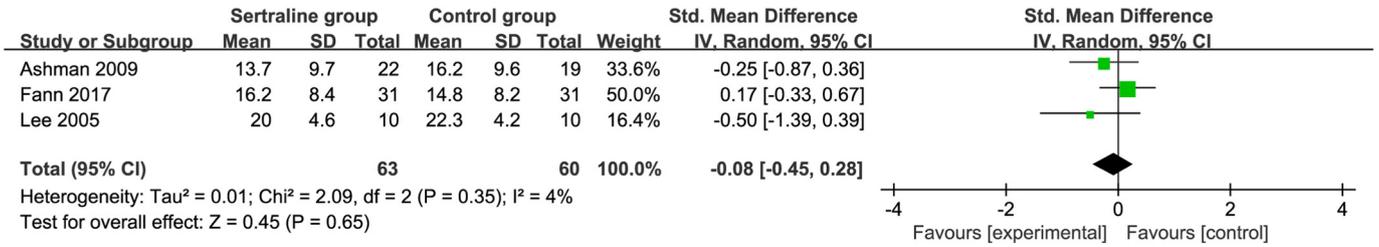
| Study or Subgroup | Sertraline group | | | Control group | | | Weight | Std. Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| | Mean | SD | Total | Mean | SD | Total | | |
| Ashman 2009 | 13.7 | 9.7 | 22 | 16.2 | 9.6 | 19 | 33.6% | -0.25 [-0.87, 0.36] |
| Fann 2017 | 16.2 | 8.4 | 31 | 14.8 | 8.2 | 31 | 50.0% | 0.17 [-0.33, 0.67] |
| Lee 2005 | 20 | 4.6 | 10 | 22.3 | 4.2 | 10 | 16.4% | -0.50 [-1.39, 0.39] |
| **Total (95% CI)** | | | **63** | | | **60** | **100.0%** | **-0.08 [-0.45, 0.28]** |

Heterogeneity: Tau² = 0.01; Chi² = 2.09, df = 2 (P = 0.35); I² = 4%
Test for overall effect: Z = 0.45 (P = 0.65)

**Fig. 2.** Forest plot for the meta-analysis of HAM-D.

| Study or Subgroup | Sertraline group | | | Control group | | | Weight | Std. Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| | Mean | SD | Total | Mean | SD | Total | | |
| Ashman 2009 | 11.1 | 11.9 | 22 | 13.1 | 11.6 | 19 | 40.2% | -0.17 [-0.78, 0.45] |
| Fann 2017 | 19 | 10.9 | 31 | 16.5 | 9 | 31 | 59.8% | 0.25 [-0.25, 0.75] |
| **Total (95% CI)** | | | **53** | | | **50** | **100.0%** | **0.08 [-0.32, 0.48]** |

Heterogeneity: Tau² = 0.00; Chi² = 1.05, df = 1 (P = 0.31); I² = 4%
Test for overall effect: Z = 0.40 (P = 0.69)
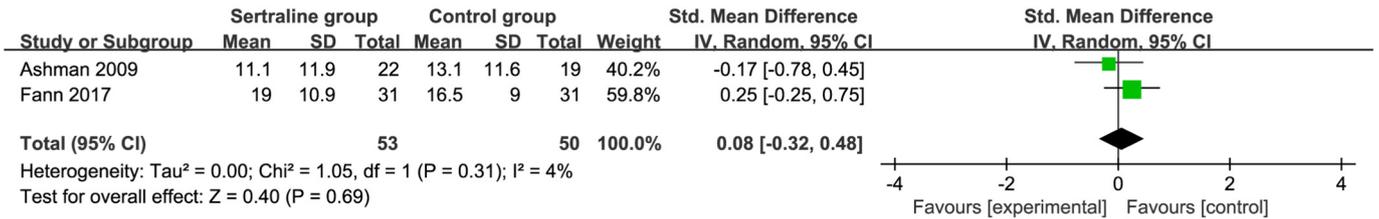
**Fig. 3.** Forest plot for the meta-analysis of anxiety score.

| Study or Subgroup | Sertraline group | | | Control group | | | Weight | Std. Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| | Mean | SD | Total | Mean | SD | Total | | |
| Banos 2010 | 100.5 | 17.2 | 27 | 98.8 | 13.3 | 31 | 49.1% | 0.11 [-0.41, 0.63] |
| Fann 2017 | 7.9 | 5.3 | 31 | 9.9 | 6.2 | 31 | 50.9% | -0.34 [-0.84, 0.16] |
| **Total (95% CI)** | | | **58** | | | **62** | **100.0%** | **-0.12 [-0.56, 0.32]** |

Heterogeneity: Tau² = 0.03; Chi² = 1.52, df = 1 (P = 0.22); I² = 34%
Test for overall effect: Z = 0.53 (P = 0.59)
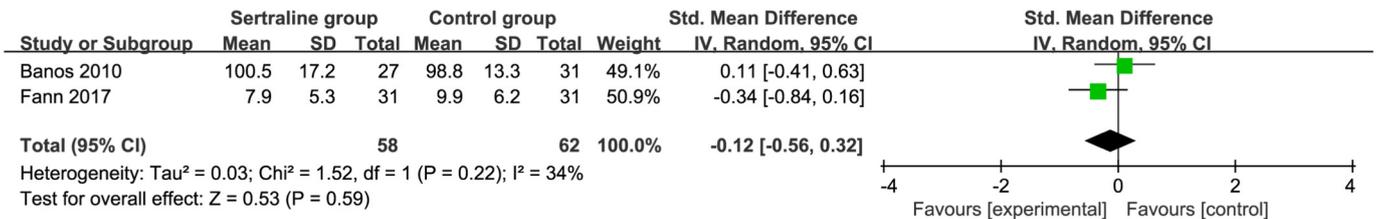
**Fig. 4.** Forest plot for the meta-analysis of aggression score.

| Study or Subgroup | Sertraline group | | | Control group | | | Weight | Std. Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| | Mean | SD | Total | Mean | SD | Total | | |
| Fann 2017 | 36.9 | 27.7 | 31 | 40 | 22.5 | 31 | 75.6% | -0.12 [-0.62, 0.38] |
| Lee 2005 | 112.9 | 10.9 | 10 | 109.8 | 31.9 | 10 | 24.4% | 0.12 [-0.75, 1.00] |
| **Total (95% CI)** | | | **41** | | | **41** | **100.0%** | **-0.06 [-0.49, 0.37]** |

Heterogeneity: Tau² = 0.00; Chi² = 0.23, df = 1 (P = 0.63); I² = 0%
Test for overall effect: Z = 0.28 (P = 0.78)
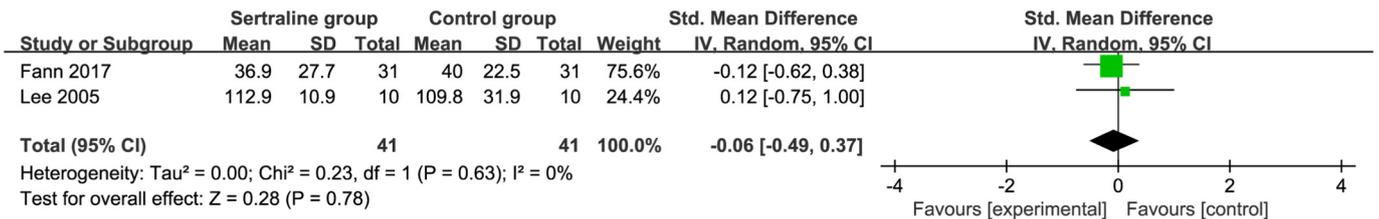
**Fig. 5.** Forest plot for the meta-analysis of QOL score.

| Study or Subgroup | Sertraline group | | Control group | | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| | Events | Total | Events | Total | | |
| Fann 2017 | 4 | 30 | 3 | 30 | 24.4% | 1.33 [0.33, 5.45] |
| Jorge 2016 | 15 | 48 | 7 | 46 | 75.6% | 2.05 [0.92, 4.57] |
| **Total (95% CI)** | | **78** | | **76** | **100.0%** | **1.85 [0.92, 3.71]** |
| Total events | 19 | | 10 | | | |

Heterogeneity: Tau² = 0.00; Chi² = 0.27, df = 1 (P = 0.60); I² = 0%
Test for overall effect: Z = 1.73 (P = 0.08)
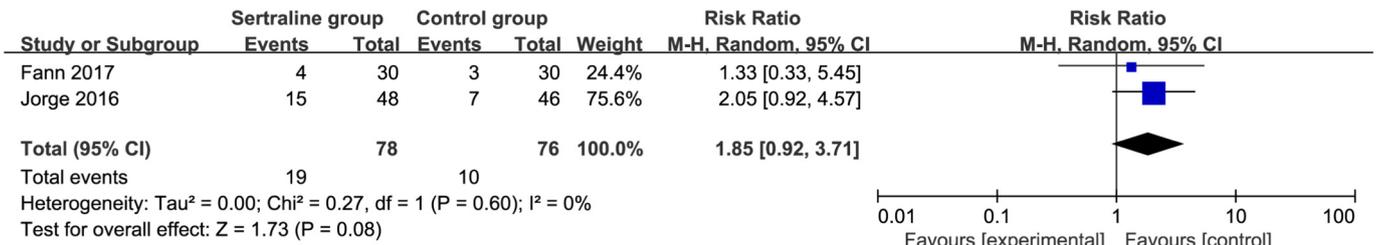
**Fig. 6.** Forest plot for the meta-analysis of diarrhea.

| Study or Subgroup | Sertraline group | | Control group | | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| | Events | Total | Events | Total | | |
| Fann 2017 | 2 | 30 | 3 | 30 | 16.5% | 0.67 [0.12, 3.71] |
| Jorge 2016 | 12 | 48 | 9 | 46 | 83.5% | 1.28 [0.60, 2.74] |
| **Total (95% CI)** | | **78** | | **76** | **100.0%** | **1.15 [0.57, 2.31]** |
| Total events | 14 | | 12 | | | |

Heterogeneity: Tau² = 0.00; Chi² = 0.46, df = 1 (P = 0.50); I² = 0%
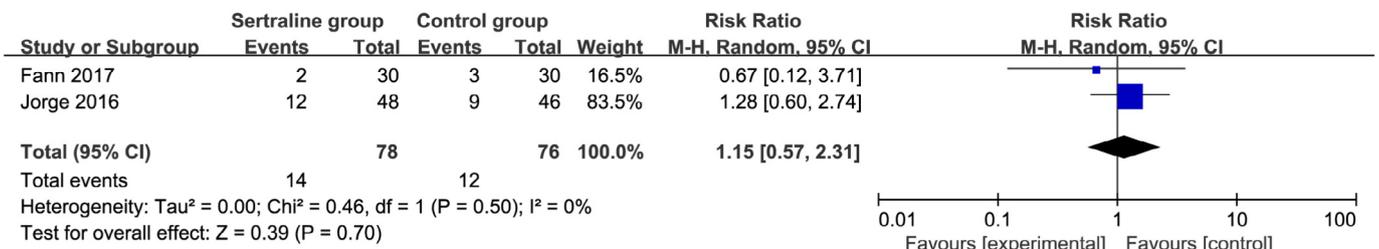Test for overall effect: Z = 0.39 (P = 0.70)

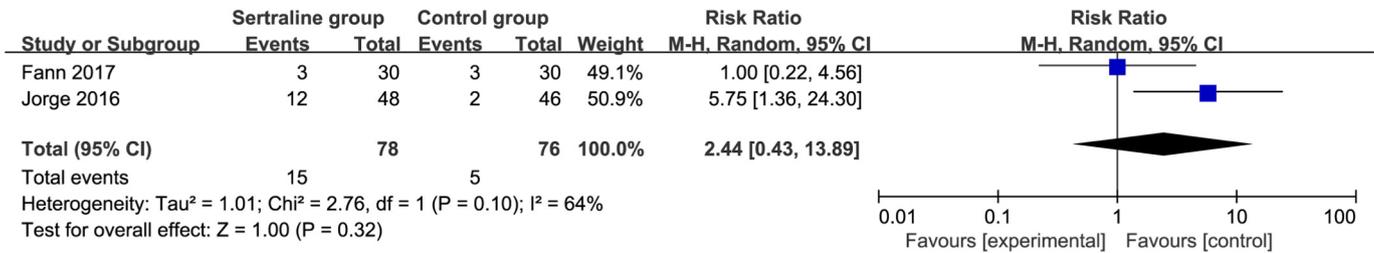**Fig. 7.** Forest plot for the meta-analysis of dizziness.

**Fig. 8.** Forest plot for the meta-analysis of dry mouth.
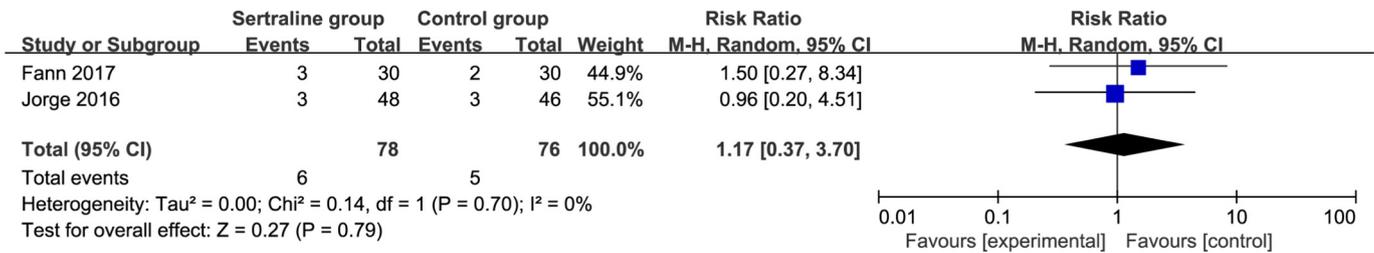


**Fig. 9.** Forest plot for the meta-analysis of nausea and vomiting.

Consistently, our meta-analysis also demonstrates no significant benefits of sertraline treatment for traumatic brain injury in terms of HAM-D, anxiety score, aggression score, and QOL score. Several possibilities may account for the lack of efficacy difference between sertraline and placebo. Firstly, patient samples exhibit high rates of psychiatric comorbidity including current anxiety and history of depression and substance dependence, which may result in resistance to depression treatment [31]. Secondly, early administration of sertraline is associated with better efficacy for traumatic brain injury. One meta-analysis aimed to explore the efficacy of antidepressants to treat depression after traumatic brain injury, and the results revealed that the pre-use of sertraline was effective to alleviate the depression ($P < 0.001$) [32].

Generally, sertraline treatment is well tolerated in the doses ranging from 25 mg qd to 200 mg qd, and there is no statistical difference of diarrhea, dizziness, dry mouth, nausea or vomiting between two groups in our meta-analysis. There are still several limitations. Firstly, only five RCTs are included in this meta-analysis, and all of them have a relatively small sample size ($n < 100$). These may lead to overestimation of the treatment effect in smaller trials. Secondly, although there is only low heterogeneity among the included studies, different doses and methods of sertraline treatment may affect the pooled results. Finally, early administration of sertraline may produce better efficacy for traumatic brain injury, and future studies should explore this issue.

## 5. Conclusion

Sertraline treatment has no obvious benefits to the depressive disorder following traumatic brain injury.

## Acknowledgements

None.

## Disclosure of Competing Interest

The authors declare no conflict of interest.

## Research involving human participants and/or animals

Not applicable.

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