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Systematic Review

Efficacy of Fluoxetine Combined with Cognitive Behavior Therapy in Treating Non-Suicidal Self-Injury in Adolescents: A Systematic Review

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Abstract

Background and Objective: Depression is a long-term mood condition that produces sorrow, loss of pleasure and interest, frequently with cognitive impairment. The incidence and lifetime prevalence of depression in children and adolescents are rising across all patient categories. According to statistics, 20% of teens experience significant depression. This study conducted a comprehensive review to analyse the impact of combining fluoxetine with cognitive behaviour therapy in the treatment of non-suicidal self-injury in adolescents. **Materials and Methods:** The Cochrane Library, PubMed, Embase and Web of Science were searched for controlled trials of fluoxetine and cognitive behaviour therapy for depressed adolescents. Screening and extracting material for systematic review occurred between database inception and May, 2023. **Results:** Seven trials included 893 participants. The systematic review found that the intervention group had a significantly higher rate of remission (OR: 1.11; 95% CI: 1.03, 1.20; $p < 0.01$) than the untreated group. The two groups of patients had similar rates of recurrence, self-injury adverse events and overall adverse events (OR: 0.96; 95% CI: 0.57, 1.61; $p = 0.868$). **Conclusion:** This study demonstrated the stability and reliability of fluoxetine and cognitive behaviour therapy for depressed teenagers. The findings showed that fluoxetine and cognitive behaviour therapy may help depressed teenagers remit.

Key words: Fluoxetine, cognitive behavior therapy, non-suicidal self-injury, depression, treatment approach

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Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Depression is a complex mood disorder that can cause a prolonged sense of sadness, diminished pleasure and a lack of interest, often accompanied by cognitive difficulties^{1,2}. Among all groups of patients with depression, the incidence rate and lifetime prevalence of depression among children and adolescents are increasing. Statistics show that the prevalence of serious depression among adolescents is as high as 20%. Especially since the outbreak of a novel Coronavirus infection, the rate of occurrence of depression among children and adolescents aged 9-15 years has increased from 18.5 to 31.8%³⁻⁵. Adolescent depression patients often have atypical symptoms such as destructive mood and irritability and unstable emotional states can easily lead to extreme behaviors such as non-suicidal self-injury and suicide. Compared to suicidal behavior, non-suicidal self-injury and suicidal ideation (SI) are more prominent depressive disorders in adolescents^{6,7}. At the same time, non-suicidal self-injury and SI are also powerful suicide predictors and even non-suicidal self-injury is more closely related to future suicides^{8,9}. The SI and non-suicidal self-injury usually start in adolescence and often recur in adolescent patients with a high incidence of complications, often accompanied by adverse outcomes such as persistent psychopathological changes and suicidal deaths¹⁰. Non-suicidal self-injury usually indicates the intentional and spontaneous act of directly harming individual body tissue devoid of suicidal intent or attempts. This self-harm behavior is often not accepted by society. Common ways of self-injury include intentionally cutting one's skin, scratching oneself, biting oneself and burning oneself¹¹. Non-suicidal self-injury can enable teenagers to temporarily regulate their emotions and alleviate self-guilt by sensing physical pain. In addition, non-suicidal self-injury has also been proven to have the function of improving interpersonal relationships and gaining attention from others¹². Therefore, the occurrence of adolescent non-suicidal self-injury is no longer a rare phenomenon and adolescents are recognized as a high-risk group.

Currently, research related to treatment mainly focuses on adolescent depression disorder or non-suicidal self-injury behavior. There are three main directions for the treatment of adolescent depression: Drug therapy, psychological therapy and physical therapy. Most drug treatments have adverse risk-benefit characteristics for adolescent depression and their use is often controversial due to the potential increase in suicide risk. When using drugs, clinical doctors should pay attention to balancing clinical needs with suicide risk¹³. Therefore, psychotherapy is usually the first choice for treating

adolescent depression disorders. Cognitive behavior therapy is usually considered a specialized psychological intervention method formed by the organic combination of cognitive therapy and behavior therapy^{14,15}, which gradually eliminates negative emotions by transforming unreasonable concepts or behaviors, thereby improving patients' emotional problems. It emphasises increasing the flexibility of thinking processes and behaviors to better respond to challenges. For a long time, cognitive-behavioral therapy has been problem-oriented, providing personalised interventions for emotional or behavioral disorders faced by different patients, such as cognitive reconstruction, exposure therapy and daily relaxation activities. Research has found that cognitive behavior therapy can have significant therapeutic effects on anxiety and depression symptoms caused by various reasons and has a particularly significant improvement effect on the depressive disorders faced by patients¹⁶. Most adolescent non-suicidal self-injury patients are comorbid with anxiety and depression and depression and anxiety are grievance factors for adolescent non-suicidal self-injury. Traditional antidepressants are represented by Tricyclic Antidepressants (TCAs) and Monoamine Oxidase Inhibitors (MAOIs). With the continuous emergence of new selective antidepressants, serious side effects such as hypertension crises and severe cardiac toxicity have gradually led to the withdrawal of these drugs from the forefront of medication. At present, traditional antidepressants are only applied to some patients with refractory or severe depressive disorders. Selective Serotonin (5-HT) reuptake inhibitors (SSRIs) are currently the first-line drugs for antidepressant treatment due to their good pharmacodynamic and pharmacokinetic characteristics, good efficacy, high safety and ease of use. Fluoxetine is a commonly used first-line antidepressant treatment drug in clinical practice, belonging to the SSRIs class of drugs. A large body of research has exhibited that the use of fluoxetine in depression patient's treatment has good clinical effects and can reduce the patient's family's economic burden with good adherence to drug use. This study carried out a systematic review to analyse the effect of fluoxetine combined with cognitive behavior therapy in treating non-suicidal self-injury in adolescents.

MATERIALS AND METHODS

Study area: The present study was performed at the Fourth Affiliated Hospital of the School of Medicine, International School of Medicine, International Institutes of Medicine, Zhejiang University, from January to February, 2024.

Study type: The study type included in this meta-analysis is controlled trials on fluoxetine combined with cognitive behavior therapy in treating depressed adolescents.

Object of study: In this meta-analysis, a total of 829 research articles were involved with the depressed adolescents who accepted fluoxetine combined with cognitive behavior therapy.

Interventions types: The intervention group was treated with fluoxetine combined with cognitive behavior therapy for treating depressed adolescents, while the untreated group was treated separately with fluoxetine or cognitive behavior therapy.

Types of resultant measures: Inclusion in the study requires a minimum of one of the following resultant indicators: (1) Rate of remission, (2) Rate of recurrence, (3) Self-injury adverse events and (4) Total adverse events. The safety-related outcome indicators mainly include adverse reactions and complications.

Search strategy: Computer searches of EMbase, Cochrane Library, PubMed, Web of Science and databases were performed with a search deadline of May, 2023 in English. The search was carried out by using free words and subject-word combinations and corresponding search strategies were developed based on different databases. English search terms include "fluoxetine", "cognitive behavior" and "adolescent".

Extraction of data and qualitative assessment: The literature was screened separately by two researchers, depending on inclusion and exclusion criteria. If there are differences, they will discuss them and consult with a third party for resolution. When choosing a piece of literature, initially read the title and abstract. Then unrelated literature was exempted and the whole text was read to find out whether to include it. Based on

the above screening, the final inclusion in the literature was determined. Two researchers independently extracted relevant literature data using Excel and, in cases of differences, discussed and negotiated with a third party for resolution. Literature extraction information includes: First author, publication year, size of sample, gender ratio, average age, intervention measures, outcome indicators, etc.

Statistical analysis: This study used Stata software for meta-analysis. For binary variables, odds ratio (OR) is used to represent intergroup differences; for weighted mean difference (WMD), continuous variables or standardised mean difference (SMD) are employed to represent intergroup differences. The 95% confidence interval (CI) is employed to represent the research results and then the heterogeneity level is referred as the I^2 test. Fixed effects model (FEM) analysis or random effects model (REM) analysis is employed based on the heterogeneity of each study. And use Egger's and Begg's tests to determine the overall publication bias of the study.

RESULTS

Search results: According to the search approach, 829 references were recognized. Further exempting duplicate studies, 32 studies were screened depending on title and abstract. Then, 12 articles were assessed in the whole text. After whole-text assessment, five records were exempted for the following reasons: Incomplete data ($n = 5$). Ultimately, 7 studies were added to this systematic review (Table 1). The PRISMA statement flow chart shows this process (Fig. 1).

Remission rate: Five studies confirmed the remission rates of the intervention group and the untreated group. A systematic review showed that the rate of remission in the intervention group was remarkably greater (OR: 1.11; 95% CI: 1.03, 1.20; $p < 0.01$) than in the untreated group (Fig. 2a). The funnel plot

Table 1: Basic characteristics of the included studies

References	Sample size (T/C)	Man/woman	Age (years) (Mean $\pm$ SD (T/C))	T	C	Main outcomes
Emslie <i>et al.</i> ¹⁷	75/69	67/77	13.8 $\pm$ 2.6	Fluoxetine+CBT	Fluoxetine	①②④
March <i>et al.</i> ¹⁸	107/109	NR	14.6 $\pm$ 1.5	Fluoxetine+CBT	Fluoxetine	①③④
Curry <i>et al.</i> ¹⁹	50/48	NR	14.3 $\pm$ 1.5	Fluoxetine+CBT	Fluoxetine	②
Kennard <i>et al.</i> ²⁰	107/109	97/119	14.60 $\pm$ 1.48/14.50 $\pm$ 1.57	Fluoxetine+CBT	Fluoxetine	①
Riggs <i>et al.</i> ²¹	63/63	85/41	17.16 $\pm$ 1.66	Fluoxetine+CBT	Fluoxetine	①
Davey <i>et al.</i> ²²	76/77	63/90	19.7 $\pm$ 2.8/19.4 $\pm$ 2.6	Fluoxetine+CBT	Fluoxetine	①③④
Melvin <i>et al.</i> ²³	20/20	NR	13.59 $\pm$ 1.08	Fluoxetine+CBT	CBT	③

NR: Not reported, T: Trial group, C: Control group, CBT: Cognitive behavior therapy, remission rate, recurrence rate, self-injury adverse events and total adverse events

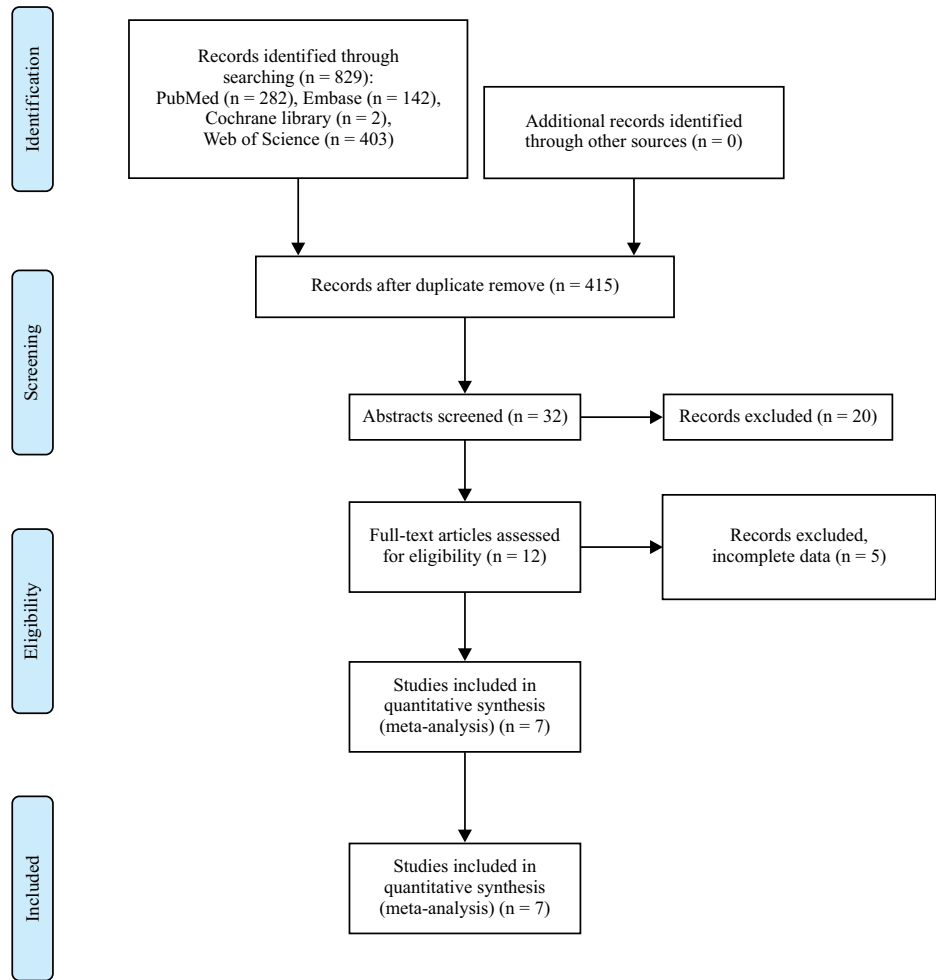


Fig. 1: Flowchart for screening of inclusion in the literature of meta-analyses (PRISMA)

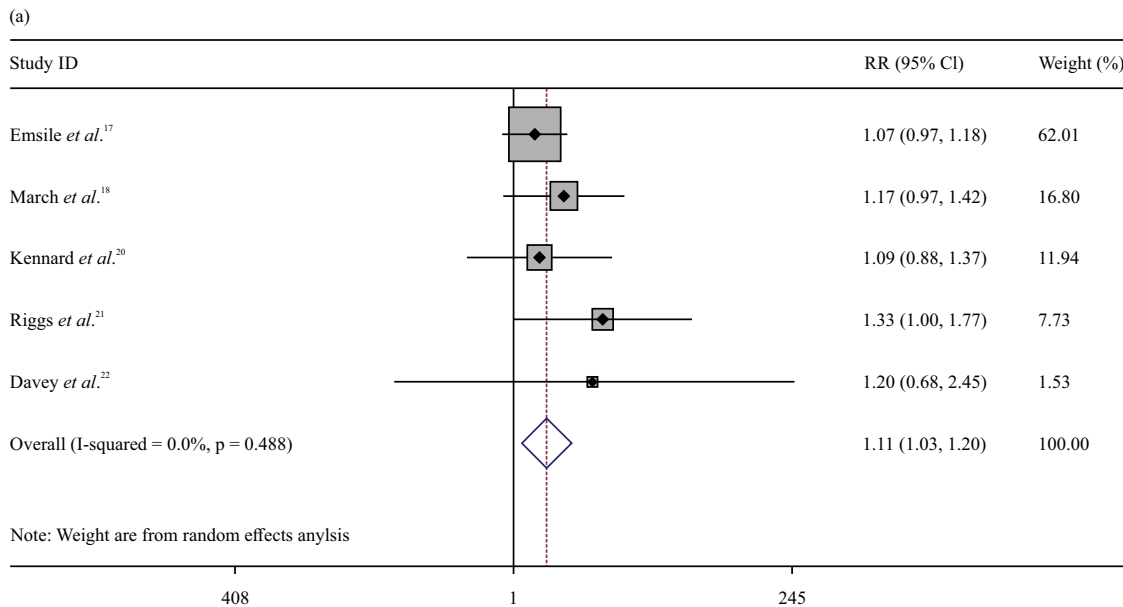


Fig. 2(a-b): Continue

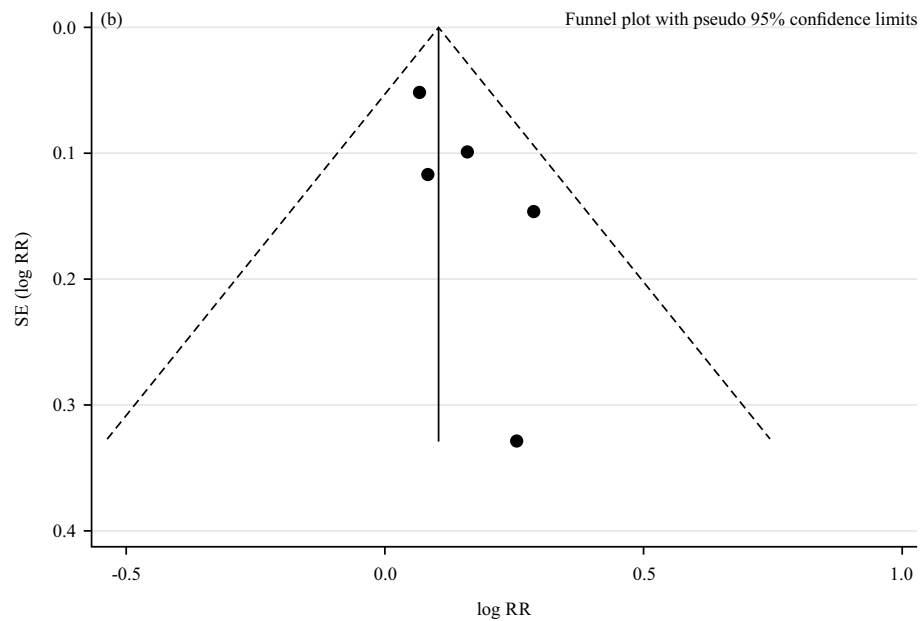


Fig. 2(a-b): (a) Display the forest plot illustrating the remission rate of the selected literature and (b) Demonstrate the funnel plot illustrating the remission rate of the selected literature

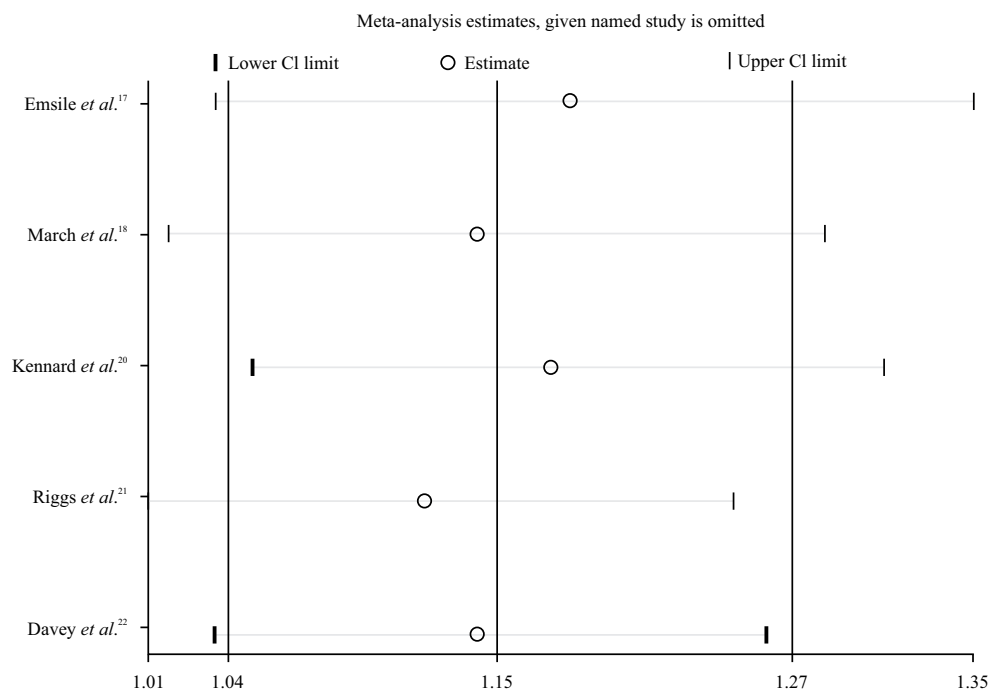


Fig. 3: Sensitivity analysis of the remission rate

is closely symmetrical (Fig. 2b). The trial results showed low heterogeneity and a what-if analysis was carried out (Fig. 3). In comparison to the untreated group, fluoxetine combined with cognitive behavior therapy in treating depressed

adolescents increases the remission rate. The Begg's test is 1.000 and the Egger's test is 0.549, so these research results are relatively stable and there is no obvious publication bias.

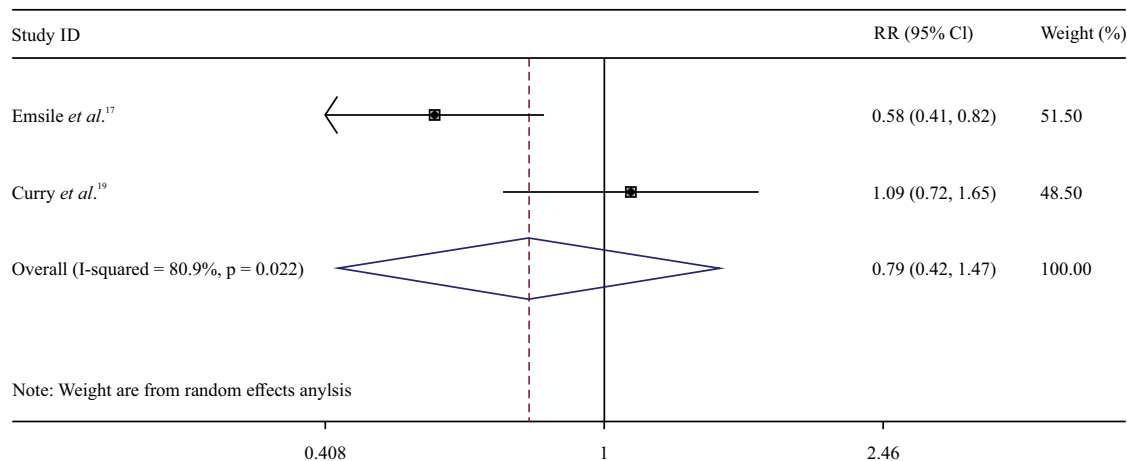


Fig. 4: Forest illustration of the recurrence rate

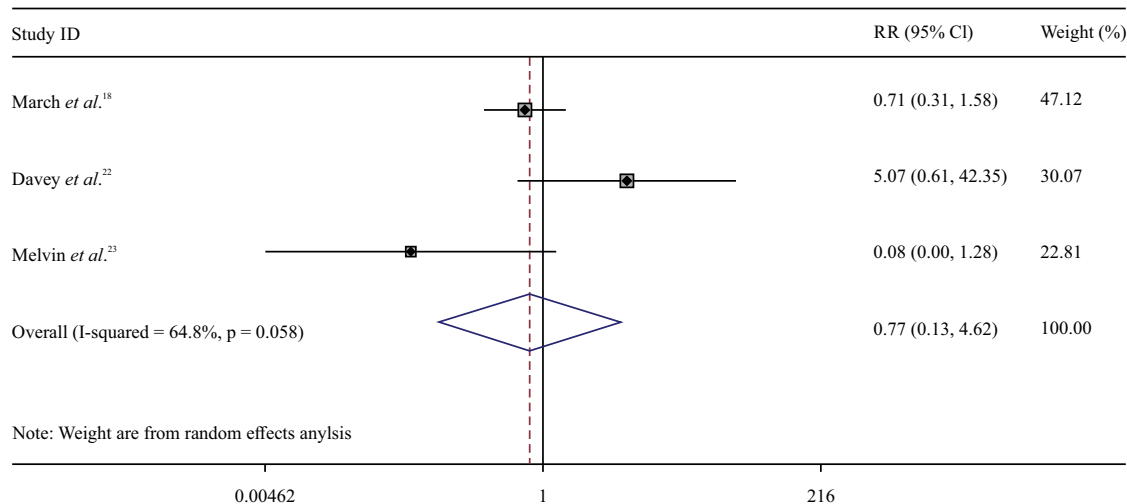


Fig. 5: Forest illustration of the self-injury adverse events

Recurrence rate: Two studies confirmed the rate of recurrence between the intervention group and the untreated group. A systematic review showed that the recurrence rate of the experimental group was of no statistical significance compared to the untreated group (OR: 0.79; 95% CI: 0.42-1.47; $p = 0.449$) (Fig. 4). In comparison to the untreated group, fluoxetine combined with cognitive behavior therapy in treating depressed adolescents did not increase the remission rate.

Self-injury adverse events: Three studies confirmed self-injury adverse events in the treatment group and the untreated group. The systematic review exhibited that the self-injury adverse events of the intervention group had no

significant statistical significance compared to the untreated group (OR: 0.77; 95% CI: 0.13, 4.62; $p = 0.775$) (Fig. 5). In comparison to the untreated group, fluoxetine combined with cognitive behavior therapy in treating depressed adolescents did not decrease the level of self-injury adverse events.

Total adverse events: A systematic review showed that the overall adverse events of the intervention group had no significant statistical significance compared to the untreated group (OR: 0.96; 95% CI: 0.57, 1.61; $p = 0.868$) (Fig. 6). In comparison to the untreated group, fluoxetine combined with cognitive behavior therapy in treating depressed adolescents did not decrease the level of total adverse events.

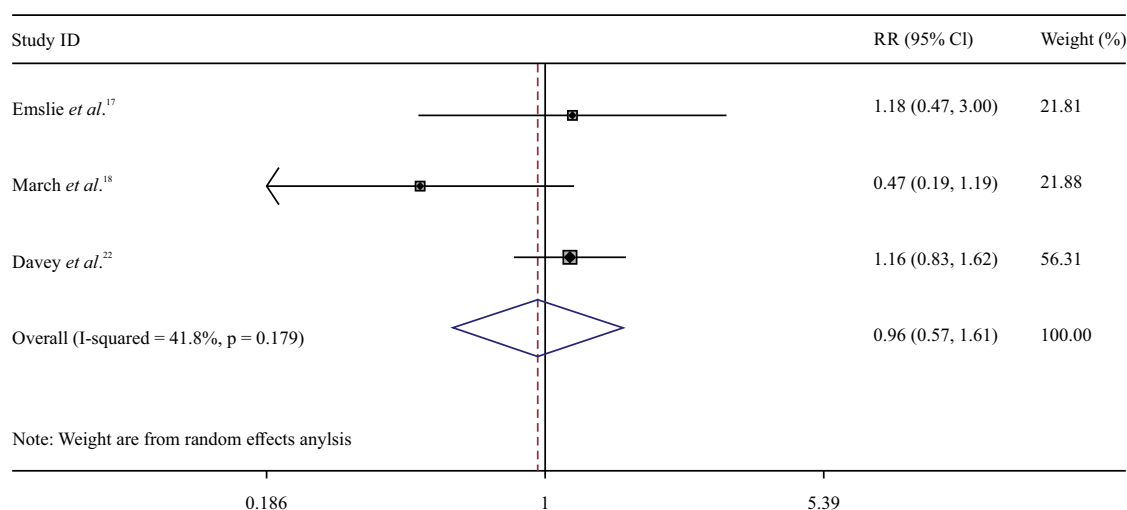


Fig. 6: Forest illustration of the total adverse events

DISCUSSION

After screening, an overall total of 893 patients were added in 7 studies, comprising 498 in the intervention group and 495 in the untreated group. There were five literature reports on the remission rate of depressed adolescents and the integration results showed low heterogeneity. The variation was statistically significant ($p < 0.01$, OR: 1.11; 95% CI: 1.03, 1.20), indicating that the remission rate of depressed adolescents receiving fluoxetine combined with cognitive behavior therapy was higher than that of the conventional group. There were two literature reports on the recurrence rate of depressed adolescents and the variation was not statistically significant ($p = 0.449$, OR: 0.79, 95% CI: 0.42, 1.47), indicating that the recurrence rate of depressed adolescents receiving fluoxetine combined with cognitive behavior therapy was not greater compared to the standard group. For the systematic review reports of self-injury adverse events and total adverse events, compared to the untreated group, a meta-analysis showed that self-injury adverse events and overall adverse events of the test group had no significant statistical significance compared to the control group.

Depression is a very common mental illness in psychiatric clinical practice and with the acceleration of people's pace of life, it has become the primary cause of mental disability worldwide. In the adolescent population, non-suicidal self-harm behavior often occurs simultaneously with depressive disorders. Depression is an emotional disorder characterised by continuous low mood, loss of interest, eating disorders and sleep disorders as its core symptoms. Data released by the World Health Organization shows that the

incidence of depression is directly proportional to age. The occurrence of depression in the adolescent population is twice that of childhood and adolescent patients are more likely to develop impulsive disruption^{24,25}. Hankin followed up on 103 adolescents over a 2 years period and found that depression is a proximal crisis factor in non-suicidal self-injury, playing a major role in predicting self-injury²⁶. There is a positive and negative reinforcement association between non-suicidal self-injury behavior and depressive disorder. Negative emotions require patients to alleviate them through self-injurious behavior. After patients obtain a sense of pleasure through self-injurious behavior, this happiness will further encourage them to meet their needs through repeated self-injury. This explanation has also been confirmed by relevant biological mechanism studies. The decrease in endogenous opioid peptide levels in adolescents with depression requires the release of opioid peptides through non-suicidal self-injury behavior, thereby altering the dysregulation of the endogenous opioid peptide system and increasing pleasure. Moreover, the pain caused by self-injury behavior can be alleviated by the release of opioid peptides²⁷. A meta-analysis based on clinical non-suicidal self-injury individuals found that among individuals admitted to the hospital due to non-suicidal self-injury, the probability of developing depression was approximately 50%²⁸.

In addition, in a longitudinal study carried out by Zhu *et al.*²⁹ an 18 month follow-up study found that depression significantly increases the risk of non-suicidal self-injury in adolescents and this risk is often difficult to reduce before the symptoms of depression and depression are relieved. Baker *et al.*³⁰ found that the rise of negative emotions

(such as depression) is one of the main reasons why individuals suffer from self-harm. This approach can help individuals break free from negative emotions such as self-blame, despair and sadness in a short period of time and restore a calm psychological state. Similarly, the relationship between depression and suicidal ideation has also been confirmed by scholars in multiple fields. According to data from social and public health, about 50% of individuals with depression have obvious suicidal thoughts or even plans and about 10-15% will eventually engage in suicidal behavior to end their lives, accounting for 1/2 to 2/3 of all suicides. In addition, Grossberg and Rice's³¹ study on American high school students also found that adolescent depression is an important risk factor for suicide, accounting for more than one-third of adolescent deaths in the United States.

The intervention plan for cognitive behavior therapy for self-injury is based on the cognitive-emotional model and it is believed that the reason for adolescent self-injury is the existence of negative thinking and emotional regulation ability defects. Therefore, cognitive behavior therapy alleviates individual bad behavior by changing unreasonable cognitive thinking and establishing new reasonable cognitive patterns. Taylor *et al.*³² developed the first cognitive behavior therapy treatment manual for non-suicidal self-injury behavior in adolescents. According to the manual, 25 adolescents underwent a 6-month cognitive behavior therapy intervention and the results exhibited that adolescents had remarkably decreased self-injury behavior after the intervention in the 3 months follow-up results³². Subsequently, the intervention of cognitive behavior therapy in adolescent self-injury gradually enriched and two recent literature reviews with a three-year interval confirmed the significant effect of cognitive behavior therapy^{33,34}. Fluoxetine, as a selective SSRIs, easily penetrates the blood-brain barrier and is a first-line drug for treating depression and anxiety. Pre-clinical studies have shown that fluoxetine can enhance depression-like behavior in mice, regulate the levels of 5-HT, BDNF and TrkB in the hippocampus and thereby enhance neuronal plasticity. Zeng *et al.*³⁵ have shown through *in vitro* studies that fluoxetine has a significant relieving effect on corticosterone-induced neuronal damage, thereby increasing cell survival rates. Clinical experimental data shows that fluoxetine can significantly improve patients' depressive mood and their quality of life³⁶⁻³⁸. In summary, psychotherapy is the main means of non-suicidal self-injury treatment in adolescents. The study outcomes show that cognitive behavior therapy combined with fluoxetine can alleviate the related adverse symptoms in depressed adolescents. However, this study only had three outcome indicators related to

non-suicidal self-injury behavior, so more studies may need to be included in the future to demonstrate whether non-suicidal self-injury behavior can be improved.

The number of included studies is nearly small and there may be significant heterogeneity among different studies, including differences in study design, participant characteristics, intervention measures, measurement tools, etc. This heterogeneity may lead to incompatible results in meta-analysis, increasing the uncertainty of the results.

CONCLUSION

This study conducted a thorough analysis to examine the effects of combining fluoxetine with cognitive behavior therapy in treating non-suicidal self-injury in adolescents. The study findings validate the effectiveness and consistency of combining fluoxetine with cognitive behavior therapy in treating depressed adolescents. The findings suggested that the combination of fluoxetine and cognitive behavior therapy has the potential to enhance the rate of remission in adolescents suffering from depression.

SIGNIFICANCE STATEMENT

This study conducted a thorough analysis to examine the effects of combining fluoxetine with cognitive behaviour therapy in treating non-suicidal self-injury in adolescents. This study provides strong evidence supporting the effectiveness of combining fluoxetine with cognitive behaviour therapy in treating depression in adolescents. The findings highlight the stability and reliability of this treatment approach, offering hope for improved outcomes in this population. The findings suggest that the combination of fluoxetine and cognitive behaviour therapy has the potential to enhance the rate of remission in adolescents suffering from depression.

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