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Comparative efficacy of antidepressant medication for adolescent depression: a network meta-analysis and systematic review

Tianwei Wu[1†], Fan Song[2†], Weili Cao[3], Chengjiang Liu[4*] and Shuangzhen Jia[5*]

Abstract

Purpose To evaluate the success rate of different antidepressants in addressing depression among teenagers, while also offering substantiation for the efficacy and tolerability of these treatments in this demographic.

Methods Participants were adolescents aged 6–18 years diagnosed with major depressive disorder according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) , Chinese Classification of Mental Disorders (CCMD-3) or equivalent diagnostic criteria (e.g., Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition(DSM-4) , International Classification of Diseases, Tenth/Eleventh Revision(ICD10/11)) . We conducted a systematic search of major databases (PubMed, Cochrane Library, and Web of Science) for randomized controlled trials (RCTs) published up to October 2024. The search strategy included the following keywords: "Depression,""Depressive Disorders,""Emotional Disorders,""adolescent,""young adult, ""minors,""fluoxetine,""sertraline,""paroxetine,""agomelatine," "vilazodone,""escitalopram," and "venlafaxine."

Results Our network meta-analysis(NMA) included 15 RCTs involving 12,258 participants. The included studies were assessed using the Cochrane risk of bias tool. The majority of studies had low risk of bias in terms of randomization and allocation concealment, while some studies had unclear implementation of blinding or outcome assessment. The NMA results showed that in several major indicators Children's Depression Rating Scale-Revised (CDRS-R) , Clinical Global Impression-Severity (CGI-S) and Children's Global Assessment Scale (CGAS) , agomelatine (MD = -0.34, 95 % CI = -0.59, -0.09), fluoxetine (MD = -0.31, 95 % CI = -0.42, -0.21), sertraline (MD = -0.27, 95 % CI = -0.47, -0.06) were significantly better than placebo in improving CDRS-R. In terms of CGI-S, sertraline (MD = -4.39, 95 % CI = -4.77, -4.01) was more effective. In contrast to the placebo, escitalopram (MD = 2.08,95 % CI = 1.33,2.84) was more effective in CGAS; Surface Under the Cumulative Ranking Curve (SUCRA) values showed that escitalopram (96.1 % and 86.4 %) could achieve better therapeutic effects in CGAS and Clinical Global Impressions-Improvement (CGI-I) , and agomelatine (86.4 %) was more effective in improving CDRS-R scores than other drugs. Sertraline (100 %) appears to be the most likely strategy to decelerate the increase in CGI-I scores. The effectiveness of paroxetine (99.9%) in the management of Montgomery-Asberg Depression Rating Scale (MADRS) was significantly better than that of several other drugs.

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Conclusion For symptom severity scales, agomelatine (CDRS-R: SUCRA 86.4%) and paroxetine (MADRS: SUCRA 99.9%) demonstrated the greatest efficacy. For functional improvement, escitalopram ranked highest on CGAS (SUCRA 96.1%). Sertraline showed superiority in clinician-rated severity (CGI-S: SUCRA 100%) and improvement (CGI-I: SUCRA 80.2%). Clinical decisions should prioritize escitalopram for functional recovery and sertraline for severe cases requiring rapid symptom reduction.

Trial registration PROSPERO registration number: CRD42024609880.

Keywords Depression, Network meta-analysis, Adolescents, Drug therapy, Drug efficacy

Introduction

Adolescent depression is increasingly becoming a common mental health issue among teenagers worldwide, profoundly affecting their psychological, physiological, and social functioning [1]. In recent years, the incidence of depression during mid-to-late adolescence has been approximately 4% to 5% annually, with an upward trend in prevalence and a downward trend in age of onset. This has led to significant distress for patients, impairment in functioning, reduced quality of life, and substantial burden on their families [2]. Compared to adult depression, adolescent depression is characterized by a longer disease course. The younger the age of onset, the higher the rates of relapse and suicide risk, which severely impact patients' academic performance, family relationships, and social interactions [3]. Moreover, adolescent depression has unique pathophysiological features, such as the immaturity of neurotransmitter systems and heterogeneous treatment responses, which add to the complexity and challenges of treatment [4].

Antidepressants are one of the main methods concerning the management of depression in adolescents [5]. However, adolescents are currently in the phase of development and growth, and the 5-Hydroxytryptamine(5-TH) and norepinephrine neurotransmitter systems in the nervous system are not yet mature. The response to antidepressants is different from that of adults [6, 7]. At present, the commonly used antidepressants in clinical practice mainly include selective 5-HT reuptake inhibitors (SSRIs), Serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic and tetracyclic antidepressants, etc. [8]. Recently, a new type of antidepressant, agomelatine, which belongs to melatonin receptor agonists and 5-HT2 C receptor antagonists, has emerged. Nonetheless, the effectiveness of these medications in addressing adolescent depression requires validation through extensive sample analysis [9, 10]. Some studies have shown that fluoxetine, an SSRIs, demonstrates efficacy and is generally well accepted among adolescents experiencing depression [11], However, certain research has indicated that there exists no substantial distinction between fluoxetine and placebo in the management of depression among kids and teenagers [12]. The effectiveness of 5-HT and norepinephrine reuptake inhibitors, alongside the novel melatonin receptor agonists and 5-HT2 C receptor antagonist antidepressants in addressing depression in teenagers, remains inconclusive at this time [13].

While the majority of published RCTs primarily assess the comparative effectiveness of atypical antipsychotics, physical therapy, and novel pharmacological agents as antidepressants, there are relatively few direct comparisons between different enhancement strategies. Moreover, although treatment outcomes in adolescents are influenced by unique neurobiological and developmental factors, existing reviews often conflate adult and adolescent populations [14]. Therefore, this systematic review and NMA aims to evaluate the relative efficacy of antidepressants in adolescent depression, informing evidence-based clinical practice with multi-dimensional outcome measures.

Approaches and methodologies

We conducted a comprehensive examination and NMA in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Furthermore, this study has been enrolled with International Prospective Register of Systematic Reviews (PROSPERO), bearing the number CRD42024609880.

Literature source and retrieval strategy

A systematic search of PubMed, Web of Science and Cochrane Library was conducted for RCTs published up to October 2024. Following the Cochrane Collaboration and PRISMA recommendations, literature search, literature assessment, extraction of information and analysis of data were carried out. The search strategy is established following several preliminary searches utilizing MeSH terms and free text keywords and is subsequently refined in accordance with a particular database. We manually searched pertinent articles from conferences, scholarly reports, and research papers to augment the search findings and help to lower publication prejudice. These are the search keywords: "depression", "depressive disorder", "emotional disorders", "adolescent", "young adult", "minors", "fluoxetine", "sertraline", "paroxetine", "agomelatine", "vilazodone", " escitalopram", "venlafaxine".

A detailed search strategy can be found in the supplementary materials. Utilize endnote software to eliminate redundant literary works. In accordance with the established criteria for inclusion or exclusion, one should eliminate literature by carefully reviewing its heading and the abstract. Finally, exclude relevant literature through a comprehensive examination of the complete text. The chosen study underwent independent scrutiny and verification by two researchers. In case the two researchers have different opinions; the third researcher will negotiate and reach a consensus.

Criteria for selecting literature

Criteria for inclusion: (1) The research was a randomized controlled clinical trial; (2) The participants in the research were adolescents aged 6–18 years who had been diagnosed with Diagnostic and Statistical Manual of Mental Disorders (DSM-5), Chinese Classification of Mental Disorders (CCMD-3) or equivalent diagnostic criteria (e.g., Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-4), International Classification of Diseases, Tenth/Eleventh Revision (ICD10/11)); (3) The study was a RCT comparing one of the following antidepressants—fluoxetine, sertraline, escitalopram, agomelatine, paroxetine, venlafaxine, or vilazodone—against placebo; (4) Outcomes included at least one validated depression rating scale (e.g., CDRS-R, MADRS, CGI-I, or CGAS).

Exclusion criteria were: (1) Studies without required outcome indicators and unreasonable interventions(The use of interventions involving doses exceeding Food and Drug Administration(FDA)/European Medicines Agency(EMA)-recommended ranges for adolescents, unvalidated doses, or measures unrelated to the study objectives.); (2) Research data is missing or cannot be extracted.

Review of literature and extraction of data

The literature obtained from the repository was integrated into EndNote X9 software for manual and automatic review, and the duplicate literature was removed. Subsequently, titles as well as abstracts were examined, leading to the exclusion of literature that clearly failed to satisfy the inclusion criteria. Ultimately, the complete texts of the works that potentially align with the established criteria were procured for in-depth examination, and the pertinent literature was meticulously filtered out. A comprehensive data extraction table was meticulously crafted, encompassing the following contents of data extraction: ① General information of the study: author, publication date, sample size, age, etc.; ② Intervention strategies: the quantity of cases and intervention strategies of the experimental cohort and the control cohort respectively; ③ Outcome indicators: mainly include. The Revised Depression Rating Scale for Children (CDRS-R), Montgomery-Asberg Depression Rating Scale (MADRS), Clinical Overall Impression - Improvement Scale (CGI-I), Clinical Overall Impression - Severity Scale (CGI-S), and Global Assessment Scale for Children (CGAS). The aforementioned procedures of literature evaluation and data extraction were executed separately by two investigators, who subsequently verified their findings with one another. Any differences would be resolved through discussion with the third researcher.

Literature quality evaluation

The caliber of the studies incorporated was evaluated by two researchers utilizing the bias risk assessment tool as prescribed by the Cochrane Manual of Systematic Review 5.1. The Cochrane risk of bias assessment encompassed seven dimensions: random sequence generation, concealment of assignment, blinding of participants and investigators, blinding of evaluators, completeness of outcomes, partial disclosure of results, and additional sources of prejudice. Every single one was assessed according to the criteria of Low risk, High risk, and Unclear.

Quantitative analysis

Employing Stata 17.0 software alongside the network meta package facilitates the construction of an evidence network diagram for the comparative analysis of treatment measures across various outcome indicators in NMA. The assessment of dichotomous variables is conducted through odds ratios (OR), while mean differences (MDs) and 95% CI are utilized for the evaluation of continuous variables. The identification of inconsistency in NMA results entails the examination of closed loops created by studies that encompass both primary and secondary evidence. Each closed loop's inconsistency factor is obtained, and if the inconsistency factor (IF) is close to 0 and the 95% CI includes 0, it suggests that the possibility of inconsistency is relatively small. We employed Stata 17.0 software to compute the SUCRA, facilitating the ranking of various interventions and their respective outcomes. SUCRA is an indicator that reflects the likelihood of the superiority or inferiority of an intervention, with values approaching 100% signify a greater effectiveness of the treatment. Ultimately, funnel plots were employed to examine the influence of small sample sizes on outcome indicators.

Outcomes

Literature review and evaluation procedure

The outcomes of the search of the included literature showed that there was a total of 10624 preliminary research articles. Among them, 1922 articles were

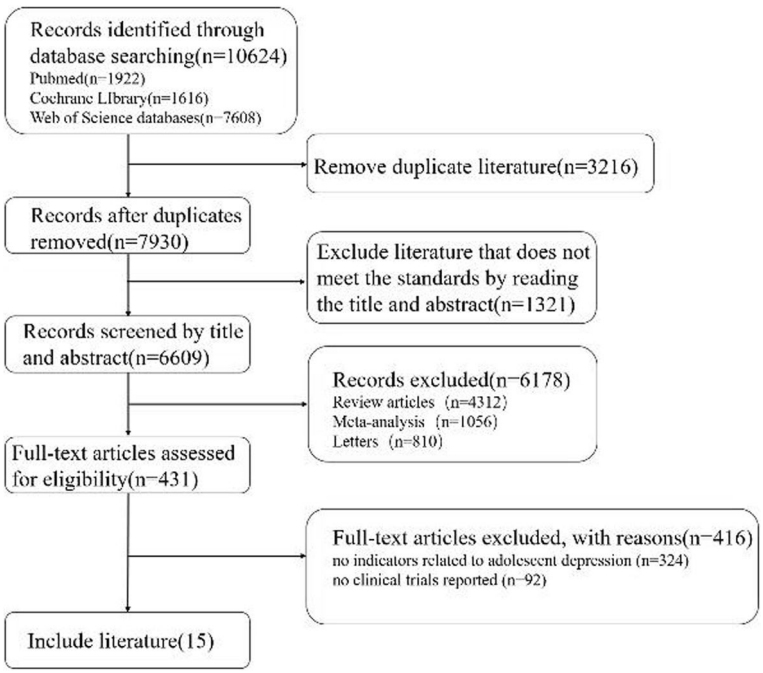

Fig. 1 Flow chart of literature screening for NMA

retrieved from PubMed, 1622 articles from the Cochrane Library, and 7608 articles from Web of Science. Following the elimination of 3216 duplicate articles, we meticulously examined titles as well as abstracts, selecting 431 articles that met the inclusion criteria, while the remaining articles were subjected to a comprehensive review. involving 7 medications for treating adolescent depression (fluoxetine, vilazodone, paroxetine, escitalopram, sertraline, venlafaxine, and agomelatine) and placebo, totaling 8 interventions. The process and rationale for literature screening are shown in Fig. 1.

Fundamental attributes and assessment of methodological rigor in the studies considered

A set of fifteen articles were included. involving 12,258 study subjects and covering 7 medications for treating adolescent depression, including fluoxetine, vilazodone, paroxetine, escitalopram, sertraline, venlafaxine, agomelatine and placebo, totaling 8 interventions. Table 1 summarizes the key characteristics of the studies included in the NMA. Figure 2A and B illustrate the evaluation of the methodical level of the studies that were included.

Outcomes of the NMA

Network structure

This study includes 8 interventions: fluoxetine, vilazodone, paroxetine, escitalopram, sertraline, venlafaxine, agomelatine and placebo. The evidence relationship diagram for all outcome indicators is shown in Fig. 3, with figures A, B, C, D, and E representing the network structures for CDRS-R, CGI-S, CGAS, CGI-I, and MADRS, respectively.

Changes in CDRS-R

The results of the CDRS-R score changes come from 13 RCTs, including 8 treatment plans involving 3,503 subjects. Elevated scores suggest a greater intensity of depressive symptoms. The 8 interventions are fluoxetine, placebo, vilazodone, paroxetine, escitalopram, sertraline, venlafaxine, and agomelatine. A comprehensive total of 28 both direct and indirect contrasts were conducted through NMA, among which agomelatine (MD of −0.34, 95% CI of −0.59, −0.09), fluoxetine (MD of −0.31, 95% CI of −0.42, −0.21), sertraline (MD of −0.27, 95% CI of −0.47, −0.06), and escitalopram (MD of −0.12, 95% CI of −0.28, 0.04), paroxetine (MD of −0.12, 95% CI of −0.39, 0.16), and vilazodone (MD of −0.10, 95% CI of −0.24, 0.05) demonstrated a notable decrease in CDRS-R ratings following treatment in contrast to the placebo group, accompanied by significant distinctions. While the CDRS-R ratings exhibited a decline following therapy using escitalopram, paroxetine, and vilazodone, the variations observed did not reach statistical significance. Venlafaxine (MD of 0.08, 95% CI of −0.11, 0.27) showed an increase in CDRS-R scores compared to the placebo group after treatment.

Based on the SUCRA curve analysis for changes in CDRS-R scores, agomelatine (86.4%) and fluoxetine

Table 1 The trial characteristics and baseline characteristics of the participants of the 11 trials included in the network meta-analysis

Study and Year	Intervention	Treatment Group,NO.	Placebo Group,NO	Disease Severity	Age range (years)	Duration	Measurement
Julia Bondar et al [15]. 2020	Fluoxetine(10–40 mg)	109	110	major depressive disorder	12–17	6 and 12 weeks	CDRS-R
Lorenzo-Luaces et al [16]. 2020	Fluoxetine(10–40 mg)	109	112	major depressive-disorder	12–17	12weeks	CDRS-R
GRAHAM J. EMSLIE et al [17]. 2002	Fluoxetine(10–20 mg)	109	110	major depressive disorder	8–18	8 weeks	CDRS-R, MADRS, CGI-S
Emslie GJ et al [18]. 1997	Fluoxetine 20 mg	48	48	major depressive disorder	7–17	8 weeks	CDRS-R, CGAS
Christopher G Davey et al [19]. 2019	Fluoxetine 20–40 mg	64	59	moderate-to-severe major depressive disorder	15–25	12 weeks	MADRS
Robert L.Findling et al [20]. 2020	Vilazodone 30 mg; fluoxetine(10–40 mg)	Vilazodone (186); fluoxetine(97)	182	major depressive disorder	7–17	8 weeks	CDRS-R, CGI-S
Durgam S et al [21]. 2018	Vilazodone 30 mg	180	170	major depressive disorder	12–17	10 weeks	CDRS-R, CGI-S, CGI-I
EMSLIE GJ et al [22]. 2006	Paroxetine 10-50 mg	101	102	major depressive disorder	7–17	8 weeks	CDRS-R
Berard R et al [23]. 2006	Paroxetine 20-40 mg	177	91	major depressive disorder	13–18	12 weeks	MADRS
EMSLIE GJ et al [24]. 2009	Escitalopram 10-20 mg	154	157	major depressive disorder	12–17	8 weeks	CDRS-R, CGI-S, CGI-I, CGAS
Findling RL et al [25]. 2013	Escitalopram 10-20 mg	154	157	major depressive disorder	12–17	8 weeks	CDRS-R, CGI-I, CGAS
Wagner KD et al [26]. 2003	Sertraline 50-200 mg	185	179	major depressive disorder	6–17	10 weeks	CDRS-R, CGI-S, CGI-I, CGAS
Sarah Atkinson et al [27]. 2017	Desvenlafaxine 35/50 mg	121	120	major depressive disorder	12–17	8 weeks	CDRS-R, CGI-S
Karen L.Weihs et al [28]. 2017	Desvenla-faxin(35/50 mg); Fluoxetine(20 mg)	Desvenlafaxine (72); Fluoxetine(67)	70	major depressive disorder	12–17	8 weeks	CDRS-R
Celso Arango et al [29]. 2021	Agomelatine (20 mg); Fluoxetine(10–20 mg)	Agomelatine (94); Fluoxetine(99)	101	major depressive disorder	12–17	12 weeks	CDRS-R, CGI-S

(84.7%) were the most effective, followed by sertraline (74.7%). The cumulative probability indicates that agomelatine and fluoxetine are associated with the greatest benefit in terms of CDRS-R scores. As shown in Fig. 4A.

Changes in CGI-S

In the CGI-S scores, a total of 7 RCTs were included, involving 2,220 individuals. A greater score indicates a heightened severity of depression. Seven interventions were conducted: fluoxetine, placebo, vilazodone, escitalopram, sertraline, venlafaxine, and agomelatine. NMA produced 21 direct or indirect comparisons, showing that sertraline (MD of −4.39, 95% CI of −4.77, −4.01), escitalopram (MD of −1.53, 95% CI of −1.79, −1.28), fluoxetine (MD of 0.20, 95% CI of −0.17, 0.56), agomelatine (MD of −0.25, 95% CI of −0.63, 0.14), vilazodone (MD of −0.20, 95% CI of −0.56, 0.16), and venlafaxine (MD of −0.17, 95% CI of −0.44, 0.10) all had better efficacy in improving CGI-S scores than the placebo, among which, sertraline (MD of −2.86, 95% CI of −3.31, −2.40) had a more significant effect than escitalopram, with a statistically significant difference.

According to the SUCRA values, sertraline (100%) is the best treatment option for reducing CGI-S scores, followed by escitalopram (83.3%) and fluoxetine (63.2%). The therapeutic effects of vilazodone (30.9%), venlafaxine (30.2%), and agomelatine (36.5%) do not differ significantly. The accumulated likelihood suggests that sertraline correlates with the highest advantage in CGI-S scores. As shown in Fig. 4B.

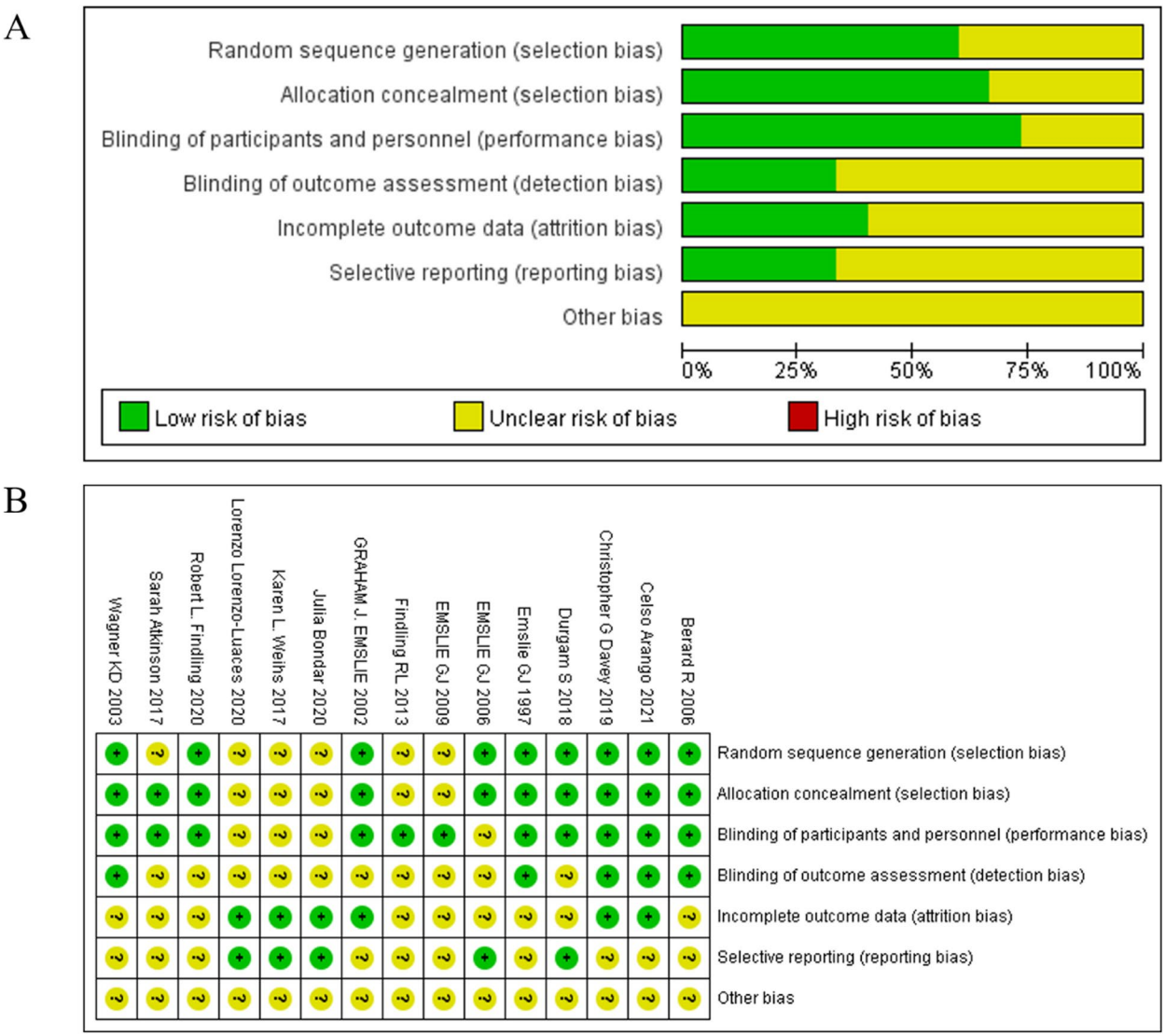

Fig. 2 Risk of bias graph and risk of bias summary

Changes in CGAS

The four included studies encompassing 1,082 participants, reporting changes in CGAS scores for four interventions: fluoxetine, placebo, escitalopram, and sertraline. Lower CGAS scores indicate more severe depression. The NMA yielded six direct or indirect comparisons. According to the CGAS, escitalopram (MD of 2.08, 95% CI of 1.33, 2.84) and sertraline (MD of 1.26, 95% CI of 0.20, 2.32) were more effective than the placebo, with both differences being statistically significant. In contrast, fluoxetine (MD of 0.27, 95% CI of −0.84, 1.38) demonstrated no notable distinction in relation to the placebo.

According to the ranking of SUCRA values, escitalopram (96.1%) showed the highest efficiency on CGAS, followed by sertraline (66.8%), while fluoxetine (26.1%) is the least effective in improving patients' CGAS scores. The cumulative likelihood suggests that escitalopram correlates with the highest advantage in CGAS scores, as illustrated in Fig. 4C.

Changes in CGI-I

The evaluation of alterations from baseline in CGI-I scores encompassed four studies with a collective sample of 1,340 patients. Higher scores indicate more severe depression. There were 4 interventions: placebo,

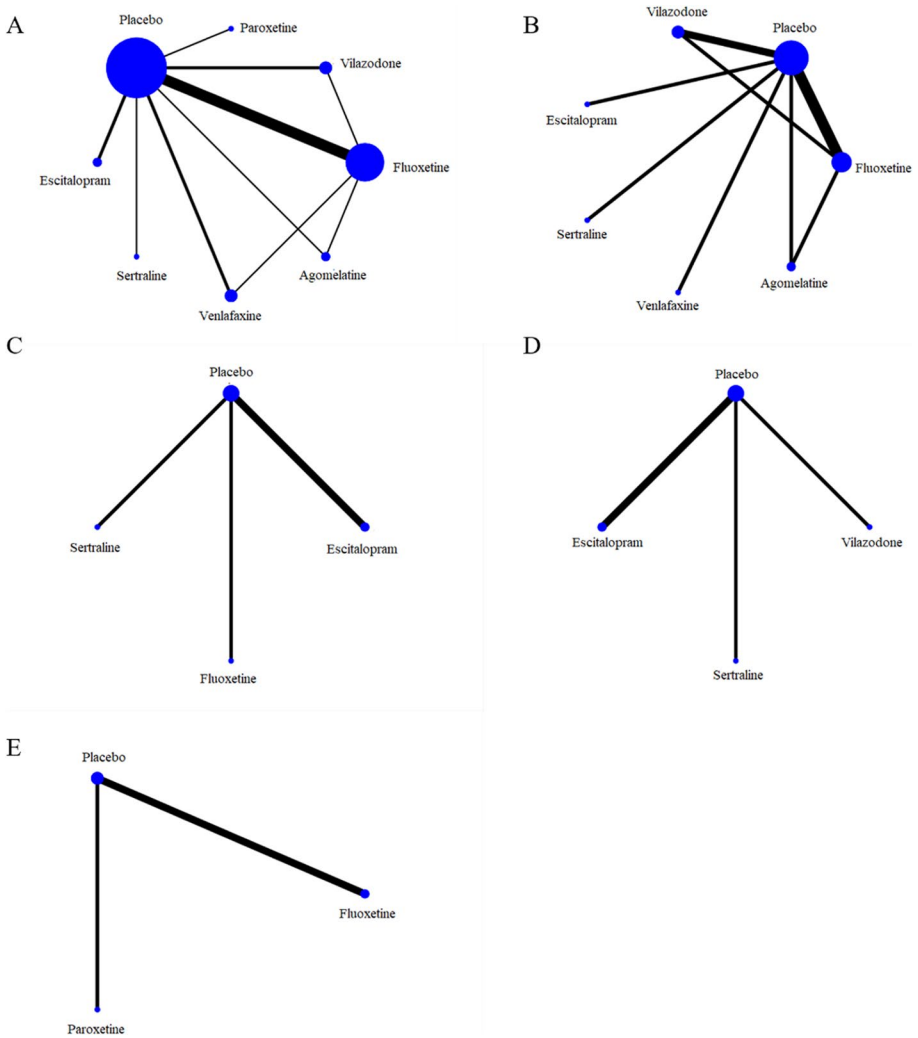

Fig. 3 Evidence relationship comparing the efficacy of fluoxetine, vilazodone, paroxetine, escitalopram, sertraline, venlafaxine, agomelatine, and placebo in the treatment of adolescent depression. **A** Children's Depression Rating Scale-Revised (CDRS-R). **B** Clinical overall impression - Severity (CGI-S). **C** Global Assessment Scale for Children (CGAS). **D** Clinical Overall Impression Improvement Scale (CGI-I). E: Montgomery-Asberg Depression Rating Scale (MADRS)

vilazodone, escitalopram, and sertraline. In terms of CGI-I scores, escitalopram (MD of −3.30, 95% CI of −3.93, −2.68) and sertraline (MD of −3.16, 95% CI of −4.03, −2.29) showed significantly better efficacy than the placebo, with statistically significant differences. In contrast, vilazodone (MD 0, 95% CI-0.84,0.83) showed little difference from placebo.

The results of the ranking based on SUCRA values are as follows: Escitalopram (86.4%) ranks first in the change of CGI-I scores, followed by sertraline (80.2%). The cumulative likelihood suggests that escitalopram is linked to the highest advantage in CGI-I scores, as illustrated in Fig. 4D.

Changes in MADRS

The results of the MADRS score changes come from 3 RCTs, including 3 treatment plans involving 610 individuals. Elevated scores suggest a greater intensity of depressive symptoms. The three interventions are paroxetine, fluoxetine, and placebo. The NMA conducted a total of 3 direct or indirect comparisons, among which paroxetine (MD: −0.75, 95 % CI: −1.01, −0.49) and fluoxetine (MD of −0.25, 95% CI of −0.46, −0.04) showed a reduction in MADRS scores compared to placebo, with the differences being statistically significant.

According to the SUCRA curve analysis, paroxetine (99.9%) is the most effective in improving MADRS scores, followed by fluoxetine (49.6%), as shown in Fig. 4E.

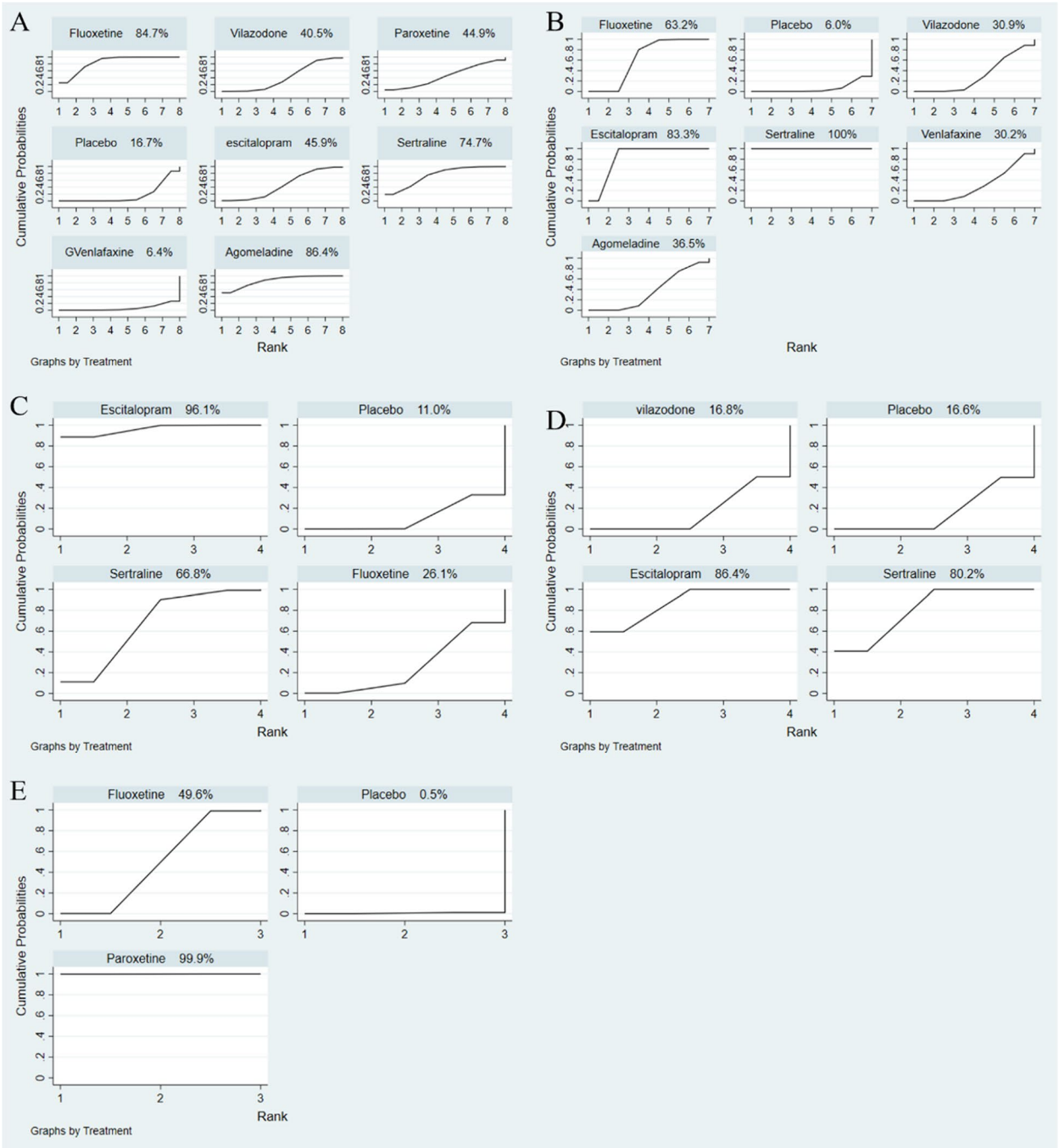

Fig. 4 The SUCRA values of each treatment: **A** Children's Depression Rating Scale-Revised (CDRS-R). **B** Clinical overall impression - Severity (CGI-S). **C** Global Assessment Scale for Children (CGAS). **D** Clinical Overall Impression Improvement Scale (CGI-I). **E** Montgomery-Asberg Depression Rating Scale (MADRS)

Bias in publication

A funnel plot was employed to illustrate the publishing bias associated with the evaluation scales, which encompass CDRS-R, MADRS, CGI-I, CGI-S, and CGAS. This study indicates the possibility of publication bias within the NMA, as illustrated in Fig. 5.

Discussion

This meta-analysis is based on 15 RCTs, including 12,258 adolescents with depression, comparing the efficacy of fluoxetine, vilazodone, paroxetine, escitalopram, sertraline, venlafaxine, agomelatine with placebo, and various drugs in treating depressive disorders in adolescents.

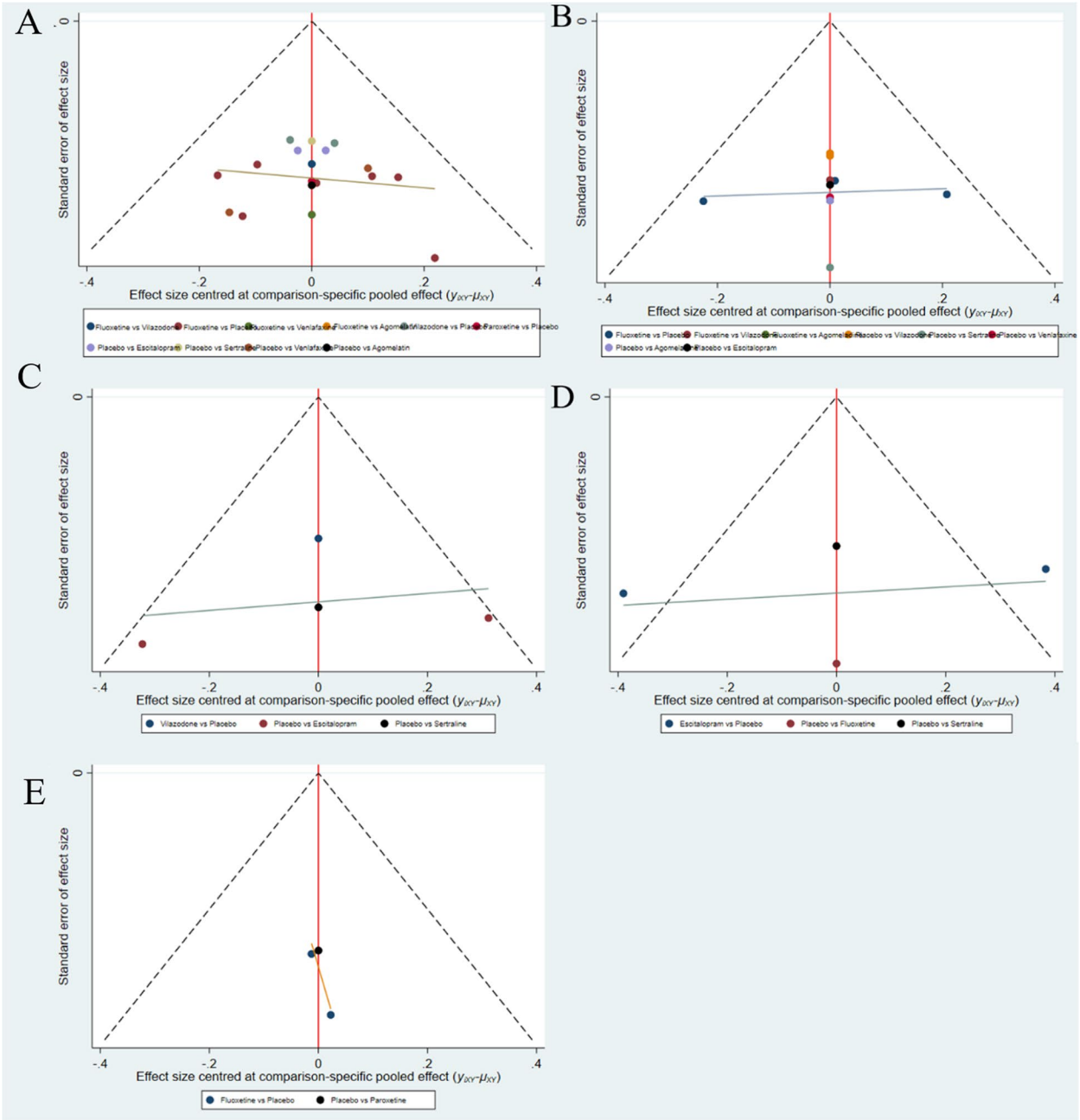

Fig. 5 Funnel plot of efficacy and safety results. **A** Children's Depression Rating Scale-Revised (CDRS-R). **B** Clinical overall impression - Severity (CGI-S). **C** Global Assessment Scale for Children (CGAS). **D** Clinical Overall Impression Improvement Scale (CGI-I). **E** Montgomery-Asberg Depression Rating Scale (MADRS)

The pairwise meta-analysis results found that agomelatine has better efficacy in improving CDRS-R scores compared to other interventions, with a SUCRA value of 86.4%, followed by fluoxetine with a SUCRA value of 84.7%. Sertraline has better efficacy in improving CGI-S scores, with a SUCRA value of 100%. Escitalopram is the most advantageous choice for mitigating the rise in CGAS scores, evidenced by an SUCRA value of 96.1%. Furthermore, sertraline and escitalopram exhibited superior efficacy compared to alternative therapies in enhancing CGI-I scores, achieving SUCRA values of 80.2% and 86.4%, respectively. Paroxetine showed the best effect in improving MADRS scores, with a SUCRA value of 99.9%.

The pathogenesis of adolescent depression is closely related to the monoamine neurotransmitter system, particularly the dysfunction of serotonin, norepinephrine, and dopamine. Based on this, antidepressant drugs work by modulating the concentration of neurotransmitters in the synaptic cleft [30]. SSRIs have become the first-line treatment for adolescent major depressive disorder (MDD) due to their safety and tolerability advantages [31]. Recent research evidence shows that different SSRIs exhibit significant differences in clinical efficacy and safety. Escitalopram, as the S-enantiomer of citalopram, has demonstrated superior clinical characteristics: its serotonin reuptake inhibition strength is 100 times stronger than that of the parent compound [32]. In a double-blind trial involving 380 patients, the drug showed a rapid onset of efficacy from the first week of treatment [33]. Cipriani et al.'s landmark network meta-analysis compared the efficacy of antidepressants in adults with MDD and identified escitalopram as one of the most effective agents. In terms of overall efficacy in adults, escitalopram was ranked higher than sertraline [34]. However, their analysis did not specifically evaluate adolescents. In contrast, our study in adolescents revealed a different profile: while escitalopram ranked first in the CGAS and CGI-I assessments, sertraline outperformed escitalopram in CGI-S. This may be due to developmental differences in the maturation of the serotonin and dopamine systems in adolescents. These findings underscore the necessity for age-specific evaluations when translating antidepressant efficacy data. Meanwhile, Solmi et al.'s safety study confirmed that escitalopram has the lowest incidence of adverse reactions [35]. These dual advantages have established its position as the first-choice drug for adolescent depression.

Sertraline, on the other hand, stands out in improving CGI-S scale scores through its unique binding to σ1 receptors and weak inhibition of dopamine transporters [36]. Although Locher et al. pointed out that SSRIs (such as sertraline) showed no significant difference in efficacy compared to placebo in adolescent depression [37], our study, which included a larger sample size (12,258 cases) and strictly selected high-quality RCTs, found that sertraline was significantly better than placebo in CGI-S and CGI-I. This corrects the early small-sample studies' doubts about its efficacy.

It is worth noting that fluoxetine, with its characteristic activation of 5-HT2 A/2 C receptors, is more targeted for patients with hypersomnia [38]. Its improvement effect on the CDRS-R is comparable to that of the new drug agomelatine, and its safety is second only to escitalopram. Paroxetine, as the most potent SSRI, ranks first in improving the MADRS scores, but its anticholinergic side effects limit its clinical application.

In terms of new drug development, agomelatine has shown unique potential. This drug works through a dual mechanism—melatonin receptor agonism to improve sleep rhythm and 5-HT2 C receptor antagonism to regulate mood [39]. In a 12-week long-term treatment, its CDRS-R improvement effect was significantly better than that of traditional SSRIs. Arango et al.'s Phase III trial confirmed that a 25 mg dose could reduce the CDRS-R score by 5.2 points, with even more significant effects in the adolescent subgroup [29]. However, it should be noted that its clinical application is currently mainly limited to adults, and the long-term safety data for the adolescent population still need to be perfected. In contrast, the SNRI venlafaxine performed poorly in adolescents, with CDRS-R improvement effects not even reaching that of placebo. This may be related to the immature development of the norepinephrine system in adolescents.

Our MNA used indirect comparisons to reveal the efficacy ranking of traditional SSRIs and new drugs. Compared with Hetrick's study [40], not only did it verify the superiority of fluoxetine and escitalopram, but it also found that extending the treatment course to 12 weeks could significantly improve agomelatine's efficacy ranking. However, Dragioti et al.'s [41] cautionary findings cannot be ignored: SSRIs may increase the risk of suicide in adolescents. This requires that clinical decisions must balance efficacy and safety. For example, although escitalopram performs best in functional recovery, high-risk patients still need enhanced monitoring.

Future research needs to focus on solving three key issues: First, head-to-head comparative trials should be conducted to verify the indirect comparison results of NMA, especially the efficacy differences between agomelatine and escitalopram. Second, a safety monitoring system specific to adolescents should be established to assess drug risks at different developmental stages. Finally, predictive models based on biomarkers should be developed to achieve a transition from population efficacy to individualized treatment. Current evidence suggests that combining the rapid onset of efficacy of SSRIs (such as escitalopram) with the specific mechanisms of new drugs (such as the sleep regulation of agomelatine) may open up new pathways for sequential treatment of adolescent depression. However, this hypothesis needs to be verified through adaptive clinical trial designs.

Limitations

This mesh meta-analysis presents certain limitations. First, it is important to note that the limited number of investigations and subjects involved may result in both type I and type II errors. Second, we compared the effects of several drugs on adolescent depression mainly

through clinical measurement scales, but not all studies were evaluated in the corresponding scales. Furthermore, while three direct comparative trials were included in the analysis, the majority of evidence derives from indirect comparisons. The limited number of head-to-head trials restricts the robustness of conclusions regarding the relative efficacy between specific antidepressants. Consequently, the findings are currently in a preliminary stage and must be approached with the utmost caution in their interpretation.

Conclusion

In this study, we found that in terms of SUCRA ranking, for symptom severity scales, agomelatine (CDRS-R: SUCRA 86.4%) and paroxetine (MADRS: SUCRA 99.9%) demonstrated the greatest efficacy. For functional improvement, escitalopram ranked highest on CGAS (SUCRA 96.1%). Sertraline showed superiority in clinician-rated severity (CGI-S: SUCRA 100%) and improvement (CGI-I: SUCRA 80.2%). Clinical decisions should prioritize escitalopram for functional recovery and sertraline for severe cases requiring rapid symptom reduction.

Supplementary Information

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Supplementary Material 1.

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Authors' contributions
Tianwei Wu, Fan Song: Data curation, Formal Analysis, Methodology, Software, Writing – original draft. Weili Cao: Data curation, Software, Writing – original draft. Chengjiang Liu: Formal Analysis, Methodology, Writing – original draft. Shuangzhen Jia: Conceptualization, Supervision, Validation, Visualization, Writing – review & editing. All authors contributed to the manuscript and approved the final version for submission.

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Data availability
All data generated or analysed during this study are included in this published article and its supplementary information files.

Declarations

Ethics approval and consent to participate
This is a systematic review and meta-analysis, ethics approval and consent to participate are not applicable.

Consent for publication
Not applicable. This study does not involve human participants.

Competing interests
The authors declare no competing interests.

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