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ORIGINAL ARTICLE

The efficacy and safety of ganaxolone for the treatment of refractory epilepsy: A meta-analysis from randomized controlled trials

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Abstract

Objective: Epilepsy is one of the most common and refractory neurological disorders globally. Ganaxolone, a neuroactive steroid that enhances GABAergic inhibition, has been tested in many trials for the resolution of refractory epilepsy. Based on these, our study implemented a meta-analysis to evaluate the general benefit of ganaxolone for refractory epilepsy.

Methods: EMBASE, Medline, Scopus, Cochrane Library, and Clinicaltrials.gov were searched for relevant randomized controlled trials (RCTs) up to June 20, 2022. The risk ratio (RR) and standard mean difference (SMD) were analyzed using dichotomous and continuous outcomes, respectively with a random effect model. Trial sequential analysis (TSA) was also performed to judge the reliability of results.

Results: We totally collected 659 patients from four RCTs to evaluate the efficacy and safety of ganaxolone. As results showed, ≥50% reduction in mean seizure frequency has improved significantly compared with placebo (RR = 1.60, 95%CI: 1.02–2.49, $p = 0.04$, $I^2 = 30\%$), which is supported by TSA. However, the percentage of seizure-free days shows no statistical significance ($p = 0.36$). For safety outcomes, adverse events (AEs), serious adverse events, and AE leading to study drug discontinuation all revealed no obvious difference between ganaxolone and placebo ($p > 0.05$).

Significance: Based on our research, we have observed that ganaxolone is safe and has potential efficacy in the treatment of refractory epilepsy, waiting for further studies.

KEYWORDS
GABAergic inhibition, ganaxolone, meta-analysis, refractory epilepsy

Jiahao Meng and Zeya Yan contribute equally to this work.

1 | INTRODUCTION

Epilepsy is one of the most common chronic diseases of the central nervous system, affecting more than 70 million individuals globally.[1,2] The lifetime prevalence of epilepsy is approximately 760 per 100 000 people, while the incidence is 61.44 per 100 000 person-years.[2,3] The prevalence of active epilepsy varies with age and has revealed a bimodal distribution, peaking in children aged 5–9 years and in the elderly above the age of 80.[1] The primary goal of epilepsy treatment is to prevent seizures as soon as possible, and antiseizure medications are the mainstay of epilepsy treatment. Due to mechanisms of enhanced inhibition GABAergic system and sodium channel blockage, dozens of antiepileptic drugs have now been proven effective.[2,4] Despite the fact that about 90% of patients with active epilepsy were using antiseizure medications, only 44% reported that their seizures were under control.[5] Patients on antiseizure medications who continue to suffer seizures should have the drug titrated up to the highest acceptable dose, or an alternative medicine should be utilized. Nevertheless, a non-negligible proportion of patients still present with refractory epilepsy. The International League Against Epilepsy (ILAE) defines refractory epilepsy as the failure of two well-tolerated and appropriately selected antiseizure medications to completely control sustained seizures.[8] The meta-analysis revealed a 13.7%–36.3% prevalence of refractory epilepsy and a 14.6%–25.0% incidence among patients with epilepsy, with a high degree of heterogeneity among included studies.[6] Previous research has yielded similar results.[7] Furthermore, the comorbidities of refractory epilepsy negatively influence the quality of life and result in higher health-care costs.[8] As a result, there is a great demand for medicines that can diminish seizures in people with refractory epilepsy over time.

Ganaxolone is a 3beta-methylated synthetic analogue of the allopregnanolone that belongs to a new class of neuroactive steroids.[9,10] Ganaxolone is not hormonally active because the 3beta-methyl substituent prevents its metabolism and oxidation on the 3alpha-hydroxy moiety, avoiding the related side effects.[11] Compared with benzodiazepines that only bind to GABAA receptors, ganaxolone binds to GABAA receptors and GABAA receptors containing the d-subunits. In theory, ganaxolone might be used to treat seizures.

The ability of ganaxolone to control induced seizures in multiple animal models suggested that it could have a promising application in the treatment of epilepsy.[12–14] The earliest randomized controlled trial (RCT) evaluated the tolerability and efficacy of ganaxolone in patients who had stopped taking other antiseizure medications before surgery.[15] Ganaxolone monotherapy was well-tolerated but had limited efficacy in these patients with complex partial seizures. The drug was dormant for many years due to its limited bioavailability. Sperling et al. altered the formulation of ganaxolone and demonstrated a reduction in mean weekly seizure frequency in adult patients with drug-resistant focal-onset seizures.[16] It also had favorable safety and tolerability. This sparked an interest in further research. A multicenter study further revealed that ganaxolone might be effective in the most drug refractory patient population.[17] Ganaxolone also dramatically reduced the frequency of seizures in patients with CDKL5 deficiency disorder associated with refractory epilepsy.[18] Additionally, ganaxolone was licensed by the US Food and Drug Administration (FDA) this year for the treatment of CDKL5 deficiency disorder, and an application has been submitted to the European Union.[19] In view of the variability among studies, we conducted the systematic review and meta-analysis of all available RCTs to estimate the safety and efficacy of ganaxolone in refractory epilepsy.

Key Points

- Ganaxolone may be an effective antiseizure medication for patients with refractory epilepsy.
- Ganaxolone can reduce the seizure frequency of at least 50%.
- Ganaxolone shares similar safety with the placebo, and the patients tolerate it well.

2 | METHODS

2.1 | Study protocol

In compliance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guideline, this systematic review and meta-analysis were performed elaborately. Moreover, this research has been registered in PROSPERO (CRD42022334522) for rigorously review.

2.2 | Search strategy

From the inception to June 20, 2022, EMBASE, Medline, Scopus, the Cochrane Library databases, and Clinicaltrials.gov were systematically searched using keywords as follows: (epilepsy OR epilep* OR seizure) AND (ganaxolone OR GNX OR CCD-1042 OR 3β-Methyl-5α-pregnan-3α-ol-20-one OR 3α-Hydroxy-3β-methyl-5α-pregnan-20-one).

After removing duplicate studies through Endnote X9 automatically, two investigators read the title, key words, and abstract manually to search out studies that met the predefined eligible criterion. Any disagreement came to a discussion with the third author and reached a consensus ultimately.

2.3 | Eligible criteria

According to Population, Intervention, Comparison, Outcome and Study type (PICOS) question format, the inclusion criteria were declared as follow:(a). Population: enrolled participants diagnosed with refractory epilepsy; (b). Intervention: with the application of ganaxolone; (c). Comparison: with the application of placebo; (d). Outcome: objective indicators to measure the treatment of refractory epilepsy; (e). Study type: RCTs. Exclusion criteria were as follows: (a). Essential data were unavailable; (b). Study types were reviews, protocol, comments, retrospective study, and case report. For duplicate research with overlapping populations, only the most complete report was included in this meta-analysis.

2.4 | Outcomes and data extraction

The primary efficacy outcome was the proportion of patients with a reduced seizure frequency of at least 50% from baseline to the double-blind phase (50% response rate). The percentage of seizure-free days among the trial process was taken into consideration as the secondary efficacy outcome. For the safety of ganaxolone, not only the total number of adverse events (AEs) was included for analysis, but also the serious adverse events (SAEs) and AE leading to study drug discontinuation. The data of all outcomes were extracted by two investigators (ZYY and JHM) after rigorous selections and assessments. Moreover, the basic information of included studies (first authors, the number of countries and centers, publication, treatment group, number of participants, epilepsy types, dosage of drug, gender, race, age, and study period) was extracted in Table 1.

2.5 | Statistical analysis

Review Manager 5.4 software (The Cochrane Collaboration, Oxford, UK) was used to assess the pooled data from included studies. A random-effect model was used to calculate the estimated standard mean difference (SMD) or risk ratio (RR) with 95% confidence interval (95%CI). I^2 was used to estimate the statistical heterogeneity as follows:

TABLE 1 Characteristics of the included studies

Study	Countries (centers)	Publication	Treatment group (No. of participants)	Epilepsy types	Dosage of drug	Female, %	White race, %	Age, years (mean ± SD)	Study period
Knight et al. 2022 (NCT03572933)[18]	8 (39)	Lancet Neurol	Ganaxolone: 50 vs. Placebo: 51	CDD-associated refractory epilepsy	63 mg/kg/day (≤28 kg) 1800 mg/day (>28 kg)	Ganaxolone:78 Placebo:80	Ganaxolone:92 Placebo:92	Ganaxolone: 5.75 ± 1.75 Placebo: 7.25 ± 1.75	Titration: 4 weeks Maintenance: 13 weeks
Lappalainen et al. 2017 (NCT01963208)[17]	6 (71)	Neurology	Ganaxolone: 179 vs. Placebo: 180	Refractory partial-onset seizures	1800 mg/day	NA	NA	NA	Titration: 2 weeks Maintenance: 12 weeks
Sperling et al. 2017 (NCT00465517)[16]	1 (24)	Epilepsia	Ganaxolone: 98 vs. Placebo: 49	Refractory partial-onset seizures	1500 mg/day	Ganaxolone:65.3 Placebo:73.5	Ganaxolone:88.8 Placebo:85.7	Ganaxolone: 39.1 ± 11.7 Placebo: 40.2 ± 11.1	Titration: 2 weeks Maintenance: 8 weeks
Laxer et al. 2000(−)[15]	1 (12)	Epilepsia	Ganaxolone: 24 vs. Placebo: 28	Refractory partial-onset seizures	1875 mg/day	Ganaxolone:33.3 Placebo:50.0	Ganaxolone:87.5 Placebo:71.4	Ganaxolone: 37.9 ± 11.6 Placebo: 31.9 ± 9.5	Titration: 1 day Maintenance: 8 days

Abbreviations: CDD, CDKL5 deficiency disorder; NA, not available.

≥50% means "high heterogeneity," 30%–50% means "moderate heterogeneity," ≤30% means "low heterogeneity." The GRADEpro GDT application was used to calculate the anticipated absolute effects. All tests were two-tailed, and a <0.05 *p*-value was considered for significant.

Type I and II errors of the meta-analysis with a limited number of samples were evaluated by trial sequential analysis (TSA), following the Copenhagen Trial Unit approach. The analysis was performed by TSA viewer software version 0.9.5.10 beta. Required information size (RIS) that estimates the sample size was calculated, and the risk of type I and type II errors was set to 5% and 20%, respectively. If the cumulative Z-curve crosses the TSA boundary or RIS boundary, the conclusion is credible, and no further studies are required.

2.6 | Risk of bias assessment

The risk of bias plot was assessed using Review Manager 5.4 software for individual RCT. The unified standard of the Cochrane Collaboration was applied to assess the risk of bias as follows: selection bias, performance bias, detection bias, attrition bias, reporting bias, and other biases.

3 | RESULTS

3.1 | Search results

Our research has identified a total of 641 studies through an initial search according to our preset search strategy from five databases (110 from MEDLINE, 277 from Embase, 214 from Scopus, 25 from Cochrane Library, and 15 from Clinicaltrial.gov). In total, 363 studies were removed due to duplication through automatic screening by Endnote X9. Then, 139 researches that were not directly relevant with the interest were excluded. On the basis of our eligible criterion, reports were removed as follows: 49 reviews, 48 conference abstracts, 28 animal researches, 6 notes, and 4 RCTs. Finally, four studies were included in our meta-analysis meeting the inclusion criterion.[15–18] Details of flow diagram are available in Figure 1.

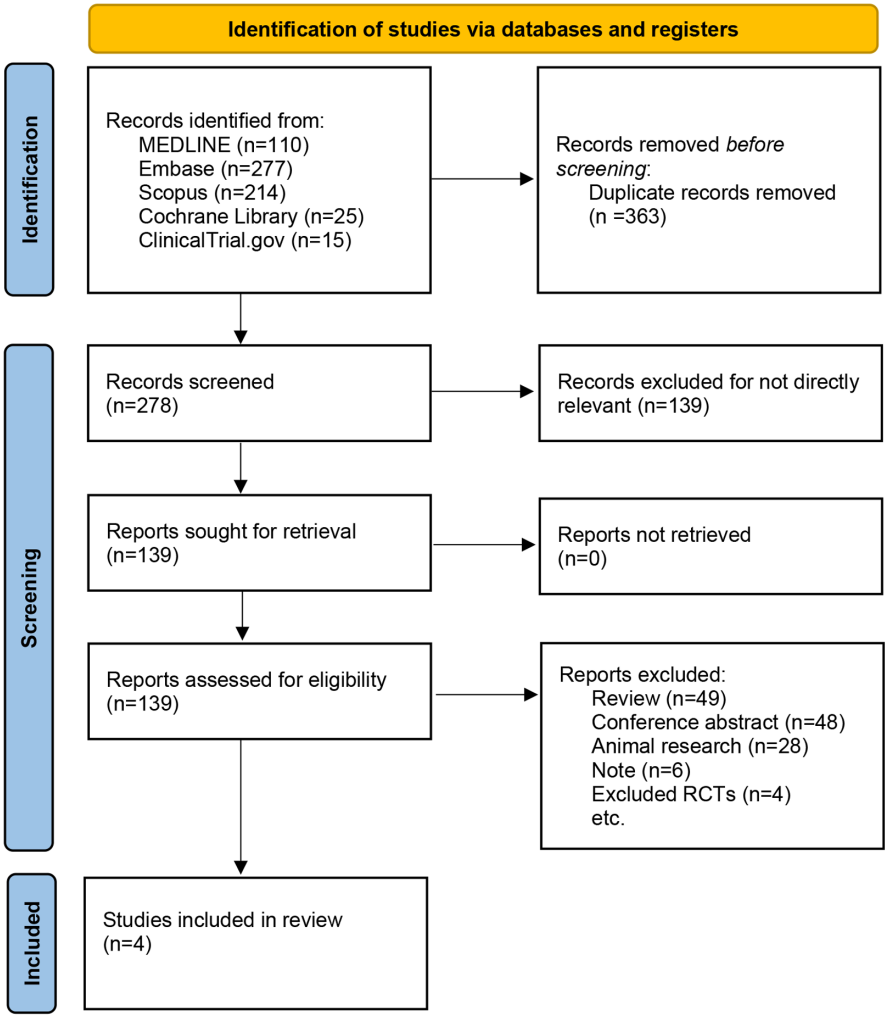

FIGURE 1 The study search, selection, and inclusion process

3.2 | Study characteristics

The four enrolled studies pooled 659 patients, 351 with the application of ganaxolone, and 308 with placebo. The dosage of intervention ranged from 1500 to 1875 mg/day. As for patient gender and race in ganaxolone group, percent of female ranged from 33.3% to 92%, mainly white. The other characteristics such as age and study period are found in Table. It is worth mentioning that part of the research contents conducted by Lappalainen et al. in 2017 cannot be available temporarily. Additional characteristics of included studies, just like inclusion/exclusion criteria, efficacy/safety outcomes, and conclusion, are found in supplementary material (Table S1).

3.3 | Efficacy outcomes

In total, 50% response rate was extracted to evaluate the clinical effect of ganaxolone. Through statistical analysis, ganaxolone group showed a significant difference compared with the placebo group (RR = 1.60, 95%CI: 1.02–2.49, $p = 0.04$, $I^2 = 30\%$), which has been shown in Figure 2A. Moreover, as the result of absolute effect analysis, for every 1000 patients with refractory epilepsy who received ganaxolone, 111 more would have a 50% response rate (range from 4 more to 277 more) (Table S2). To further verify the validity, our research brought the percentage of seizure-free days among the trial process into the research aspect. It is regrettable that no obviously significant difference was found between the two groups, with a high heterogeneity (SMD = 0.40, 95%CI: −0.46 to 1.25, $p = 0.36$, $I^2 = 90\%$) (Figure 2B).

3.4 | Safety outcomes

All the included four RCTs reported adverse events that took place in the process of research. Therefore, this research made a generalized analysis of the data derived from four RCTs, and the result of AE revealed no significant difference between the two groups (RR = 1.42, 95%CI: 0.81–2.49, $p = 0.22$, $I^2 = 96\%$). As for the appearance of SAE, similarly, ganaxolone group showed no difference compared with placebo group (RR = 0.95, 95%CI: 0.44–2.05, $p = 0.90$, $I^2 = 0\%$). Further analysis of AE leading to study drug discontinuation also showed similar result (RR = 0.85, 95%CI: 0.30–2.37, $p = 0.75$, $I^2 = 0\%$). The forest plot of the results above is detailed in Figure 3.

3.5 | Trial sequential analysis

We made a further analysis of 50% response rate because of its preliminary positive result. As shown in Figure 4, the cumulative Z-curve crossed the test statistic that corresponds to $p = 0.05$ ($Z = 1.96$). However, it did not cross the TSA boundary, suggesting that the conclusion was robust while the number of included studies still needed to be more sufficient. However, for AE the cumulative Z-curve did not crosses the TSA boundary or RIS boundary (Figure S1).

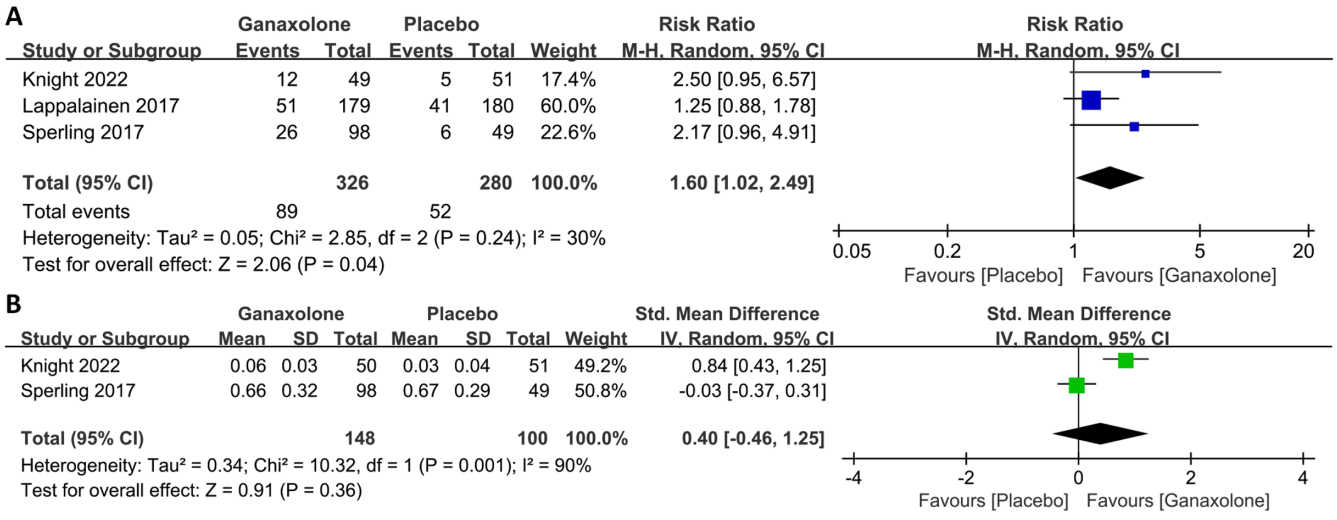

FIGURE 2 Meta-analysis forest plots: (A) the pooled risk ratio (RR) of 50% response rate in ganaxolone compared with placebo, the diamond indicates the estimated RR with 95% confidence interval (CI) for the pooled patients; (B) meta-analysis forest plots: The pooled standard mean difference (SMD) of percentage of seizure-free days in ganaxolone compared with placebo, the diamond indicates the estimated SMD with 95% confidence interval (CI) for the pooled patients

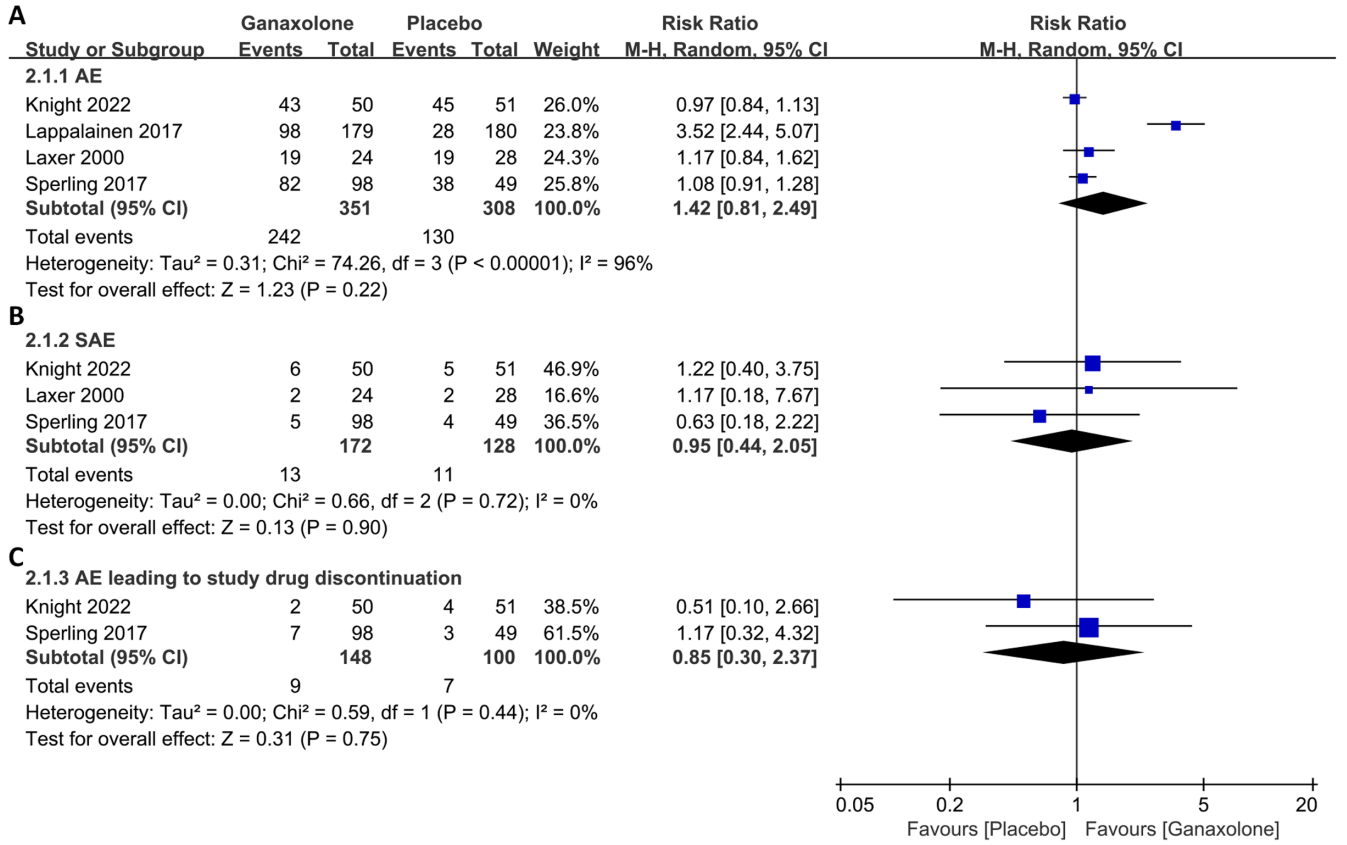

FIGURE 3 Meta-analysis forest plots: The pooled risk ratio (RR) of patients with adverse events (AEs) (A), serious adverse events (SAEs) (B), and AE leading to study drug discontinuation (C) in ganaxolone compared with placebo, the diamond indicates the estimated RR with 95% confidence interval (CI) for the pooled patients

3.6 | Risk of bias

The independent risk of bias for the included trials has been illustrated in Figure 5. The risk of bias appeared in our research was mainly derived from the study conducted by Lappalainen et al. 2017. The risk of reporting bias and other bias in this research was both unclear because of the lack of partial data. Therefore, the risk of incomplete outcome even showed high risk of bias, which was represented by red. Other types of bias in this research were low risk. The risk of bias in remaining studies was all low. The details of risk of bias graph are available in supplementary material (Figure S2).

4 | DISCUSSION

Ganaxolone is a neuroactive steroid to enhance GABAergic inhibition. And our meta-analysis was the first elaborated article summarizing the efficacy and safety of ganaxolone for the treatment of refractory epilepsy. Based on our analysis, ganaxolone seems safe and has potential efficacy in the treatment of refractory epilepsy.

Our findings indicated that ganaxolone was associated with a decrease in the proportion of patients with at least 50% reduction in seizure frequency. And this difference between ganaxolone and placebo seemed more clearly during the maintenance periods. As previous research studies reported, patients were given a new formulation of ganaxolone, and seizure frequency was reduced by a median of 16% in the trial of Sperling et al.[16] Likewise, the median percentage change in 28-day major motor seizure frequency for ganaxolone in the Marigold Trial was −30.7%.[18] Therefore, the treatment effect of ganaxolone was comparable to other antiseizure medications.[20–22] Actually, as TSA revealed, ganaxolone may be proved to have more potential efficacy if the sample size or trials attain an ideal condition.

In our meta-analysis, we detected no significant positive effect of ganaxolone on the percentage of seizure-free days. And the heterogeneity was high for this result. Differences in methodologies, participants, and study designs may contribute to this heterogeneity.[16,18] To be specific, a multicenter, double-blind, add-on trial investigated the safety and efficacy of ganaxolone in adults aged 18–69 years with refractory epilepsy, while another

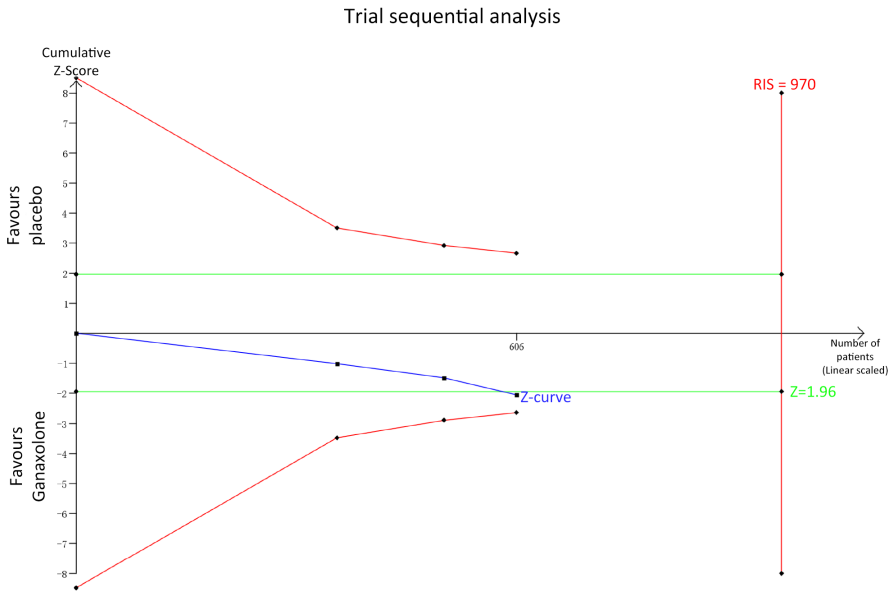

FIGURE 4 Trial sequential analysis of 50% response rate

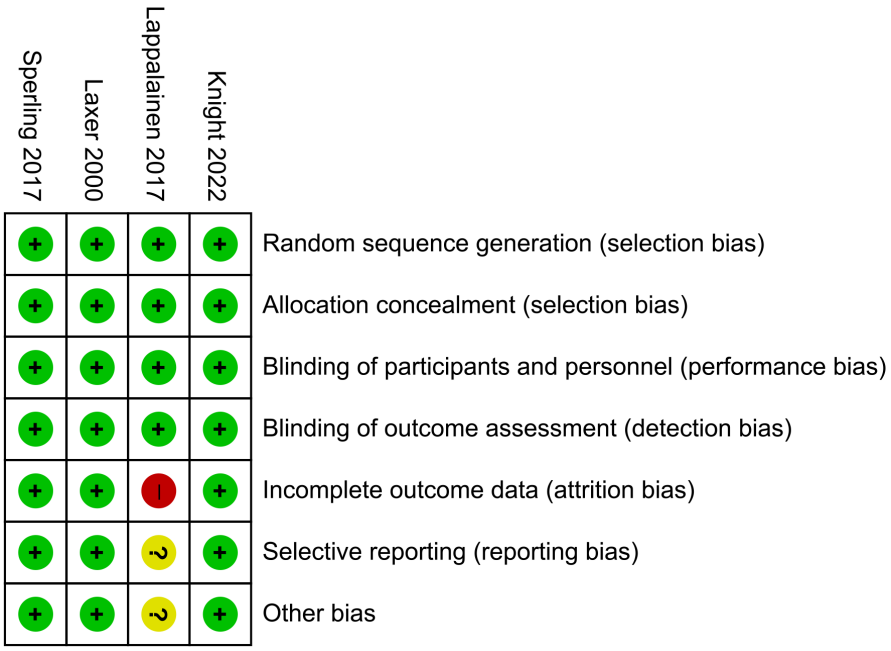

FIGURE 5 Risk of bias summary

trial focused on patients aged 2–21 years with CDKL5 deficiency disorder. Participants in one trial received a maximum dose of 1800 mg per day of enteral adjunctive ganaxolone, and participants in the other trial were given a daily dose of 1500 mg orally.

Actually, the AE of antiseizure drugs was one cause of refractory epilepsy. In our meta-analysis, the incidence of AE, SAE, and AE leading to study drug discontinuation was no difference between ganaxolone and placebo. After further analysis of AE by TSA, we may conclude the lack of difference between interventions due to the small sample size. However, to our knowledge, no research has established that ganaxolone causes cell mutations or carcinogenesis, organ toxicity, or embryo or fetus malformations in animal models presently.[12,23] Furthermore, the rate of discontinuation due to AEs was broadly similar to the results of trials with other antiseizure medications.[24,25] The most frequently reported adverse events in the clinical trials were somnolence, pyrexia, seizure, vomiting, headache, and upper respiratory tract infection. Although patients in the ganaxolone and placebo groups had a high risk of adverse events, ranging from 68% to 88%, the risk of SAE and AE leading to drug discontinuation was low. No patient died from treatment-related AEs among the four RCTs. These meant that most AEs caused by ganaxolone were tolerable and limited. This conclusion may be further confirmed with the expansion of sample size.

Cenobamate, a voltage-gated sodium channel blocker, has recently been proved more effective than other third-generation antiseizure medications for the treatment of

focal-onset seizures in adults.[26] Adjunctive cenobamate is associated with the reduction in seizure frequency compared with placebo, not only 50% response rate but also the percentage of seizure-free days.[27,28] At the meantime, cenobamate may lead to a higher rate of AEs in a dose-related fashion. Nearly 15% of patients discontinue cenobamate due to treatment-emergent adverse events.[27] Whereas we observed that ganaxolone could only increase 50% response rate and had the similar safety with the placebo group. Besides, cenobamate relevant studies have focused on adults, while ganaxolone has been used in patients aged 2–21 years with CDKL5 deficiency disorder.

The broad-spectrum activity of ganaxolone in various animal models suggested its potential utility in epilepsy. Our study observed that ganaxolone could be used in refractory epilepsies. The detailed criteria to define epilepsy in each of the included trials were provided in the Table S3. All of these met the ILAE definition of refractory epilepsy. The differences focused mainly on the different causes and types of seizures. Besides, ganaxolone has also been shown to be useful in other epilepsies. Ganaxolone was assessed in an open-label and add-on trial that included 20 children with refractory infantile spasms. Children were given up to 36 mg/kg/d of ganaxolone, and 66% had at least a 25% reduction in the frequency of seizure.[29] In another open-label trial of ganaxolone up to 1800 mg/d, girls with protocadherin-19 (PCDH19) -related epilepsy had fewer seizures at 6 months.[30] Ganaxolone was also found to control refractory status epilepticus in a small number of clinical studies.[30] There are a number of ongoing, double-blind, RCTs designed to investigate the safety, efficacy, and tolerability of ganaxolone in infantile spasms, catamenial seizures, tuberous sclerosis complex, and PCDH19-related epilepsy. Moreover, interactions between antiseizure medications have been extensively investigated. There was a synergistic effect between ganaxolone and midazolam in seizure models, which might be related to the action of GABAA receptors.[31] The combination of ganaxolone and tiagabine showed a significant antiseizure activity, possibly associated with tiagabine-induced elevation of GABA levels.[31] In all, ganaxolone may have broader applications in the future than just refractory epilepsy.

There is an obvious limitation in this study that the samples incorporated into the study were of a small size. The baseline characteristics of the four RCTs were not completely identical, such as demographic characteristics, the dosage of ganaxolone, the route of drug delivery, the formulation of ganaxolone, study period, etc., which might lead to potential bias. Limited by only four RCTs and inconsistent baseline characteristics, we could not perform subgroup analysis. However, there was low and moderate heterogeneity in most of the outcomes. Besides, the treatment duration was short and ranged from 9 days to 17 weeks. Only Knight et al. 2022 and Lappalainen et al. 2017 had a duration of 12 weeks or longer. The results of long-term follow-up were similarly lacking. Nevertheless, we have seen several open-label trials with long-term follow-up ongoing. The results should provide additional insight into the extended use of ganaxolone in patients with refractory epilepsy. Moreover, one of the four included studies was on patients with a genetic form of epilepsy. It may have an individual response to this drug compared with other drug-resistant patients. Lappalainen et al. 2017 was only available as abstract and only some data were consequently available. Thus, limited information cannot avoid heterogeneity. Three RCTs used ganaxolone as an add-on treatment, while one was a preoperative monotherapy, and the mixture of multiple antiseizure medications might lead to inconsistent results. Although the combination of ganaxolone with other antiseizure medications has shown some synergistic effects in animal models, more clinical trials are needed in the future to verify further.

5 | CONCLUSIONS

In summary, our findings suggest that ganaxolone may be an effective antiseizure medication for patients with refractory epilepsy. It is related to a reduction in seizure frequency of at least 50% from baseline to the double-blind phase. The ganaxolone group shares similar safety with the placebo group, and the patients tolerate it well. Since there were few relevant RCTs and small sample size, further and long-term follow-up RCTs are required.

AUTHOR CONTRIBUTIONS

Zhong Wang and Yanfei Liu were the principal investigator. Jiahao Meng and Zeya Yan designed the study and developed the analysis plan. Jiahao Meng and Zeya Yan extracted the data. Xinyu Tao, Wei Wang, and Fei Wang checked the extracted data. Jiahao Meng and Zeya Yan analyzed the data and performed meta-analysis. Jiahao Meng and Zeya Yan contributed in writing of the article. Zhong Wang, Yanfei Liu, and Tao Xue revised the manuscript and polished the language. All authors read and approved the final submitted paper.

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CONFLICT OF INTEREST

Neither of the authors has any conflict of interest to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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