

Efficacy and Safety of Stiripentol on Dravet Syndrome: A Mini- Meta-Analysis of Randomized, Double-Blind, Placebo-Controlled Trials

Yujie Ma

Qilu Hospital (Qingdao), Cheeloo College of Medicine, Shandong University

Peiyuan Liao

1py020240@qlyyqd.com

Qilu Hospital (Qingdao), Cheeloo College of Medicine, Shandong University

Research Article

Keywords:

Posted Date: October 19th, 2026

DOI: <https://doi.org/10.21203/rs.3.rs-10869245/v1>

License: © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Additional Declarations: No competing interests reported.

Abstract

Objective

To evaluate the efficacy and safety of stiripentol (STP) as adjunctive therapy for clonic and generalized tonic-clonic seizures in patients with Dravet syndrome (DS).

Methods

We systematically searched PubMed, Embase, CNKI, Wanfang, CBM, VIP, and CMBM databases for randomized controlled trials (RCTs) assessing STP as an add-on treatment for clonic and generalized tonic-clonic seizures in DS, from database inception through January 20, 2025. Two reviewers independently performed literature search, screening, data extraction according to a prespecified protocol, and risk-of-bias assessment. Meta-analyses of efficacy and safety outcomes, together with publication bias assessment, were conducted using RevMan version 5.4.1. Sensitivity and subgroup analyses were performed where appropriate.

Results

Two RCTs, reported in three publications, met the inclusion criteria, comprising 33 patients in the STP group and 31 in the placebo (PLB) group. Meta-analyses were performed for 50%, 75%, and 100% seizure-reduction responder rates, percentage change in seizure frequency, serious adverse events (SAEs), and treatment-discontinuation rates. Pooled results demonstrated that STP was significantly superior to PLB across all efficacy endpoints. STP also markedly reduced the percentage change in seizure frequency compared with PLB. No significant between-group differences were observed in the incidence of SAEs or discontinuation rates.

Conclusions

Adjunctive STP effectively reduces the frequency of clonic and generalized tonic-clonic seizures in patients with DS and exhibits a favorable safety profile and treatment tolerability.

Introduction

DS, formerly known as severe myoclonic epilepsy of infancy, is a devastating developmental and epileptic encephalopathy with onset in the first year of life. The disorder is characterized by pharmacoresistance, multiple seizure types, persistent lifelong seizures, and a broad spectrum of comorbidities—including intellectual disability, behavioral disturbances, sleep disorders, and gait abnormalities. These neurological and neurodevelopmental impairments impose a substantial burden on affected children and their families and markedly compromise quality of life.^[1–3]

STP is a structurally unique antiseizure medication that inhibits multiple cytochrome P450 enzymes^[4]. Its precise anticonvulsant mechanism remains incompletely elucidated; it primarily enhances GABAergic neurotransmission by modulating the activity of GABA_A receptors. When combined with clobazam, STP increases serum concentrations of clobazam and its active metabolite, thereby amplifying the antiepileptic effect of clobazam. Treatment with valproate alone or valproate plus clobazam fails to achieve adequate seizure control in the majority of patients with DS. Approximately 15%–20% of children with DS die before adulthood as a consequence of status epilepticus and sudden unexpected death in epilepsy (SUDEP). The principal therapeutic objective is therefore to reduce seizure frequency through optimized add-on therapy^[2]. Clinical observational studies, small-sample randomized double-blind placebo-controlled parallel-group trials, and network meta-analyses^[1, 2, 4, 5] have demonstrated that adjunctive STP effectively controls clonic and tonic-clonic seizures in children with DS whose seizures remain inadequately controlled by clobazam and valproate. STP received regulatory approval for the treatment of DS in Europe (2007), Japan and Canada (2012), and the United States (2018)^[3]. Nevertheless, because high-quality, large-scale randomized, double-blind, placebo-controlled trials remain scarce and existing studies have enrolled relatively small cohorts, the efficacy and safety profile of STP in patients with DS warrants further clarification. The present meta-analysis was therefore undertaken to systematically evaluate and directly compare the efficacy and safety of adjunctive STP therapy in the treatment of DS.

Materials and Methods

This systematic review and meta-analysis was prospectively registered on the PROSPERO platform (registration number: CRD42025640232; [https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=640232](https://www.crd.york.ac.uk/prospero/display_record?RecordID=640232)). The review was performed following the recommendations of AMSTAR 2^[6], the PRISMA 2020 statement^[7], and the Cochrane Collaboration handbook^[8]. Since all data were extracted from already-published studies (secondary research), ethical approval and written patient informed consent were not required.

Search Strategy, Screening, and Data Extraction

PubMed and Embase were searched using the following strategy: (((randomized) AND (double-blinded)) AND (controlled)) AND ((Stiripentol) OR (Diacomit))) AND ((Dravet syndrome) OR (severe myoclonic epilepsy of infancy)). CNKI, Wanfang, VIP, CBM, and CMBM were comprehensively searched using the keywords stiripentol AND Dravet syndrome. The search covered all years from database inception to January 20, 2025. All identified records were imported into EndNote for deduplication. Two reviewers independently screened titles, abstracts, and full texts in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement^[7]. Ineligible studies were excluded. Quality assessment, risk-of-bias (ROB) evaluation, and data extraction were performed independently by the two reviewers and cross-verified. Any disagreements were resolved through discussion between the reviewers.

Inclusion and Exclusion Criteria

Inclusion criteria

1. Clinical studies involving patients diagnosed with DS whose seizures were inadequately controlled by valproate alone or in combination with clobazam.
2. Study design: randomized, double-blind, parallel-group, placebo-controlled trials.
3. Intervention: add-on STP versus add-on placebo.
4. Language: English or Chinese.
5. Availability of at least one of the following parameters at baseline and during the double-blind phase: 50% responder rate, 75% responder rate, seizure-free rate, change in seizure frequency, the number of patients with serious adverse events (SAEs), or the number of patients with discontinuations.

Exclusion criteria

1. Non-randomized parallel-group trials, single-arm trials, observational studies, case reports, or cohort studies.
2. Publications in languages other than English or Chinese.

Outcome Measures and Definitions

Efficacy outcomes

1. 50% responder rate: the proportion of patients achieving $\geq 50\%$ reduction in monthly convulsive seizure frequency (MCSF) from baseline (clinically meaningful response).
2. 75% responder rate: the proportion of patients achieving $\geq 75\%$ reduction in MCSF from baseline.
3. 100% responder rate: the proportion of patients achieving 100% reduction in MCSF (seizure-free) from baseline.
4. Percentage change in MCSF: Percentage change in MCSF of included patients from baseline to endpoint.

Safety outcomes

1. Rate of SAEs: the proportion of patients experiencing SAEs relative to the intention-to-treat population.
2. Rate of discontinuations: the proportion of patients withdrawing from the study relative to the intention-to-treat population.

Risk of Bias Assessment

Two authors independently assessed the ROB of included studies using the Cochrane ROB 1.0 tool^[9] and cross-verified their judgments. Discrepancies were resolved through consultation. A summary ROB figure was generated using RevMan 5.4.1 software. Funnel plots were planned for publication bias assessment if five or more studies had been included.

Sensitivity Analysis and Subgroup Analysis

To evaluate the robustness of the pooled estimates, sensitivity analysis was performed by sequentially omitting one study at a time to explore potential sources of heterogeneity whenever moderate heterogeneity was observed ($50\% < I^2 < 75\%$). Subgroup analysis was also conducted to investigate heterogeneity where appropriate.

Statistical Methods

Patients lost to follow-up or withdrawn from treatment were handled according to the intention-to-treat principle. Statistical analyses were performed using RevMan version 5.4.1. The Mantel–Haenszel (M–H) method was used for dichotomous variables, and the inverse-variance method for continuous variables.

If the number of outcome events was zero in one or more included RCTs, the risk ratio (RR) could not reliably estimate intervention effects, and the risk difference (RD) was used instead. Heterogeneity was quantified using the I^2 statistic:

- $I^2 < 50\%$ indicates low heterogeneity among included trials; a fixed-effect model was applied to calculate RR or RD with 95% confidence interval (CI).
- $50\% < I^2 < 75\%$ indicates moderate heterogeneity among included trials; a random-effects model was applied to calculate RR or RD with 95% CI.
- $I^2 > 75\%$ indicates high heterogeneity among included trials; under such circumstances, pooled meta-analysis was abandoned and narrative synthesis was performed.

Evidence Quality and Recommendations

- The quality of evidence was evaluated in accordance with relevant guidelines^[10]. Clinical practice recommendations were then formulated based on the GRADE guidelines^[11].

Results

This meta-analysis was prospectively registered in the PROSPERO platform (registration number: CRD42025640232).

Literature Search Results

A systematic literature search was conducted in the targeted databases using a predefined search strategy. A total of 58 publications were identified and imported into EndNote. After deduplication, the remaining records were screened on reviewing titles, abstracts, and full texts by two review authors. Discrepant decisions were resolved through discussion. Ultimately, two randomized controlled trials (RCTs), reported in three publications, met the eligibility criteria and were included in the meta-analysis (Fig. 1).

Basic Characteristics and Quality Assessment of Included Studies

Two RCTs (three publications)^[3–5] were enrolled in this study, comprising 33 patients in the STP group and 31 patients in the PLB group. Key baseline and double-blind phase parameters of the included studies are summarized in Table 1.

Two authors independently assessed the ROB of the two included RCTs using the Cochrane ROB 1.0 tool^[9]. Both RCTs were rated as having a high risk of bias, and the overall ROB was graded as high ROB. A ROB figure was generated using RevMan 5.4.1 software (Fig. 2). Publication bias was not assessed because only two studies were included.

Table 1
Main Characteristics of Included Studies

Items	STICLO-FranceSTP (n = 22)	PLB (n = 20)	STICLO-ItalySTP (n = 11)	PLB (n = 11)
Baseline characteristics				
Randomized patients	22	20	11	11
Patients evaluated at baseline	21	20	11	11
Median age (y), IQR	9.4 (3–16.7)	9.3 (3.2–20.7)	NA	NA
Sex: male/female	6/15	11/9	NA	NA
Mean weight (kg), IQR	32 (14–60)	31 (15–70)	NA	NA
Double-blind phase				
MCSF 50% responders, n	15	1	8	1
MCSF 75% responders, n	12	0	6	1
MCSF 100% responders, n	9	0	3	0
Percentage change in seizure frequency Mean $\pm$ SD	–62.0 $\pm$ 51.2	12.1 $\pm$ 44.4	–74 $\pm$ 26.7	–13 $\pm$ 62.0
SAEs, n	5	1	2	3
Discontinuations, n	1	4	1	2
Abbreviations: STP, stiripentol; PLB, placebo; IQR, interquartile range; MCSF, monthly convulsive seizure frequency; SAEs, serious adverse events; SE, status epilepticus; AE, adverse event; IE, inefficiency.				

Forest Plot Analyses of Efficacy Outcomes

Response Rates

- 50% response rate: Two studies were included. The number of responders was greater than one in both the STP and PLB groups; therefore, RR with 95% CI was used.

- 75% response rate: Two studies were included; the PLB group had zero responders in one study. Seizure-free rate: Two studies were included; the PLB group had zero responders in both studies. Consequently, RD and 95% CI were used for the 75% response rate and seizure-free rate.

Heterogeneity was low ($I^2 = 0\%$) across all three outcomes (i.e. 50% responder rate, 75% responder rate, seizure-freedom rate); a fixed-effect model was applied.

- 50% response rate: STP group (n = 33, 22 responders) versus PLB group (n = 31, 2 responders); RR = 10.40, 95% CI [2.64, 40.87]. STP was significantly superior to PLB(Fig. 3.1).
- 75% response rate: STP group (n = 33, 18 responders) versus PLB group (n = 31, 1 responder); RD = 0.51, 95% CI [0.33, 0.70]. STP was significantly superior to PLB(Fig. 3.2).
- Seizure-free rate: STP group (n = 33, 12 responders) versus PLB group (n = 31, 0 responders); RD = 0.36, 95% CI [0.18, 0.54]. STP was significantly superior to PLB(Fig. 3.3).

Percentage Change in Seizure Frequency

Two studies were included (STP n = 33, PLB n = 31). Heterogeneity was low ($I^2 = 0\%$); a fixed-effect model was used. Mean difference (MD) = - 69.59, 95% CI [- 93.00, - 46.17], Z = 4.82 (P < 0.00001). STP significantly reduced seizure frequency compared with PLB(Fig. 3.4).

Safety Assessment

Incidence of Serious Adverse Events

Two studies were included (STP n = 33, PLB n = 31). Moderate heterogeneity ($I^2 = 55\%$) was observed; a random-effects model was applied. RR = 1.56, 95% CI [0.23, 10.55], Z = 0.45 (P = 0.65). No significant difference was found between the STP and PLB groups(Fig. 3.5).

Discontinuation Rate

Two studies were included (STP n = 33, PLB n = 31). Heterogeneity was low ($I^2 = 0\%$); a fixed-effect model was used. RR = 0.24, 95% CI [0.06, 1.03], Z = 1.92 (P = 0.05). No significant difference in discontinuation rate was observed between groups, indicating favorable tolerability(Fig. 3.6).

Sensitivity Analysis

Sensitivity analysis was performed for treatment-related SAEs owing to moderate heterogeneity ($I^2 = 55\%$). Sequential omission of either study did not alter the overall results((Fig. 4.1 ,Fig. 4.2). Potential sources of heterogeneity may include small sample size, differences in sex and age distribution, and variability in baseline concomitant medications. Subgroup analysis was not performed because only two trials were included.

Evidence Quality and Recommendations

The quality of evidence was evaluated as the overall high ROB based on the Cochrane ROB 1.0 tool; and the pooled efficacy and safety derived from RCTs; by balancing risks and benefits, Clinical practice recommendations were formulated as a strong recommendation for DS based on the GRADE guideline, efficacy and safety outcomes.

Discussion

This meta-analysis, synthesizing evidence from randomized, double-blind, placebo-controlled parallel-group trials, provides robust support for the efficacy and safety of STP in the management of clonic and tonic-clonic seizures among patients with DS. As reported by Guerrini and colleagues^[3], STP exerts a rapid onset of antiseizure action from day 4 of treatment and maintains sustained efficacy throughout the observation period.

Our pooled analyses demonstrated that STP was significantly more effective than PLB on achieving $\geq 50\%$ and $\geq 75\%$ responder rates, as well as seizure freedom. In addition, STP substantially reduced seizure frequency, indicating effective control of clonic and generalized tonic-clonic seizures in children with DS. These findings are consistent with prior reports^[3–5]. A previous meta-analysis of randomized double-blind trials¹ showed that STP had a higher seizure-free rate than pharmaceutical cannabidiol, fenfluramine hydrochloride, and soticlestat, as well as a higher treatment response rate than pharmaceutical cannabidiol.

Regarding safety, common adverse events associated with STP involved multiple organ systems^[5]: Nervous system: somnolence, hyperirritability, aggression, insomnia, mental retardation, ataxia, tremor, hypotonia, dysarthria; Gastrointestinal system: decreased appetite, weight loss, weight gain, abdominal pain, nausea, vomiting; Hematological system: neutropenia, eosinophilia, and thrombocytopenia.

Although the overall incidence of adverse events was higher in the STP group^[3], the frequency of serious adverse events was comparable between the STP and PLB groups, supporting the favorable safety profile of STP in patients with DS. Moreover, treatment discontinuation rates were similar between groups and were consistent with previous reports^[1], indicating good efficacy, safety, and tolerability. The principal reasons for treatment discontinuation included lack of efficacy, treatment-related adverse events, and epilepsy-related death.

As an adjunct to valproate and/or clobazam, STP effectively controls clonic and generalized tonic-clonic seizures in patients with DS at standard doses and is associated with low rates of serious adverse events and treatment discontinuation. These findings support the use of STP as a promising adjunctive therapy for DS. Nevertheless, further large-scale, high-quality randomized, double-blind, placebo-controlled trials are warranted to strengthen the current evidence base.

Strengths

This meta-analysis synthesized data from the limited randomized controlled trials available, effectively expanding the pooled sample size and enhancing the level of evidence for clinical application.

Limitations

Although STP has been approved for the treatment of DS in many countries, high-quality large-scale randomized controlled trials remain limited because of the rarity of the disease. Consequently, most available evidence is derived from small randomized trials and retrospective studies, which may constrain the strength and generalizability of the current evidence regarding efficacy and safety. Further large-scale, randomized, double-blind, placebo-controlled trials are warranted to provide more robust evidence to guide clinical practice.

Declarations

Author Contributions

Peiyuan Liao and Yujie Ma participated in study design, literature retrieval, screening and selection of studies, data extraction and analysis, and manuscript drafting. Peiyuan Liao was responsible for resolving discrepancies, manuscript revision, and data rechecking. Yujie Ma undertook manuscript review and journal submission.

Declaration of Competing Interest

All authors declare that they have no conflicts of interest.

Funding

No financial support was received for this study. All authors had full access to the research data and bear final responsibility for the decision to submit the manuscript for publication.

Ethics approval and consent to participate

Not applicable

Clinical trial number

not applicable

Consent to Publish declaration

not applicable

Data availability

This meta-analysis was prospectively registered in the PROSPERO platform (registration code: CRD42025640232). The full review protocol can be accessed at https://www.crd.york.ac.uk/prospERO/display_record.php?RecordID=640232. No amendments were made to the registered PROSPERO protocol. All data used in this meta-analysis are derived from previously published articles. Data-extraction templates, extracted study-level datasets and RevMan analysis files are not publicly available.

References

1. Lattanzi S, Trinka E, Russo E, et al. Pharmacotherapy for Dravet Syndrome: A Systematic Review and Network Meta-Analysis of Randomized Controlled Trials. *Drugs* Oct. 2023;83(15):1409–24.
2. Guerrini R, Chiron C, Vandame D, Linley W, Toward T. Comparative efficacy and safety of stiripentol, cannabidiol and fenfluramine as first-line add-on therapies for seizures in Dravet syndrome: A network meta-analysis. *Epilepsia Open* Apr. 2024;9(2):689–703.
3. Guerrini R, Chancharme L, Serraz B, Chiron C. Additional Results from Two Randomized, Placebo-Controlled Trials of Stiripentol in Dravet Syndrome Highlight a Rapid Antiseizure Efficacy with Longer Seizure-Free Periods. *Neurol Ther* Jun. 2024;13(3):869–84.
4. Guerrini RTS, Athis P, Rey E, Vincent J, Pons G, Bemardina BD, Ferrari AR, Veggiotti P, Veneselli E, Pascottol A. Vigevano. Stiripentol in severe myoclonic epilepsy in infancy(SMEI): a placebo-controlled Italian trial. *Epilepsia*. 2002;43(Suppl 8):155.
5. Chiron C, Marchand MC, Tran A, et al. Stiripentol in severe myoclonic epilepsy in infancy: a randomised placebo-controlled syndrome-dedicated trial. STICLO study group. *Lancet* Nov. 2000;11(9242):1638–42.
6. Shea BJ, Reeves BC, Wells G, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *BMJ* Sep. 2017;21:358:j4008.
7. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021;372:n71. 10.1136/bmj.n71.
8. Cumpston M, Li T, Page MJ, et al. Updated guidance for trusted systematic reviews: a new edition of the Cochrane Handbook for Systematic Reviews of Interventions. *Cochrane Database Syst Rev* Oct. 2019;3(10):ED000142.
9. Sterne JAC, Savovic J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ* Aug. 2019;28:366:l4898.
10. Brozek JL, Akl EA, Alonso-Coello P, et al. Grading quality of evidence and strength of recommendations in clinical practice guidelines. Part 1 of 3. An overview of the GRADE approach and grading quality of evidence about interventions. *Allergy* May. 2009;64(5):669–77.
11. Brozek JL, Akl EA, Compalati E, et al. Grading quality of evidence and strength of recommendations in clinical practice guidelines part 3 of 3. The GRADE approach to developing recommendations. *Allergy* May. 2011;66(5):588–95.

Figures

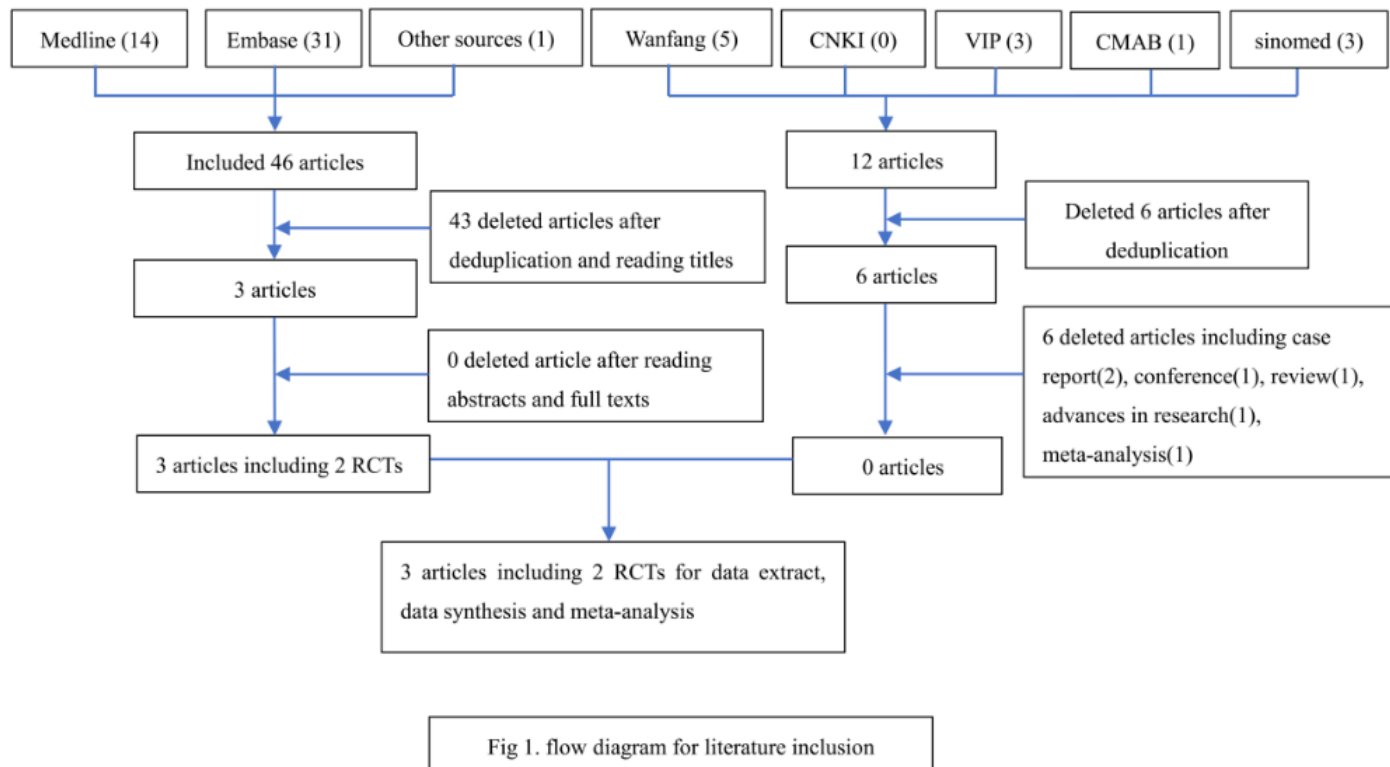


Figure 1

Legend not included with this version

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Chiron 2000	+	+	+	?	-	-	?
Guerrini 2002	?	?	?	?	-	-	?

Figure 2

Risk of bias assessment

Fig 3.1 50% response rate (STP vs. PLB)

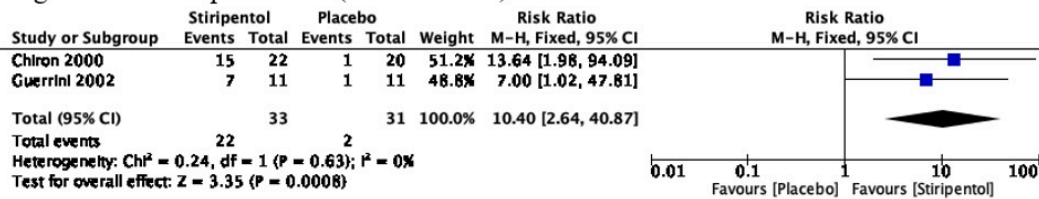


Fig 3.2 75% response rate (STP vs. PLB)

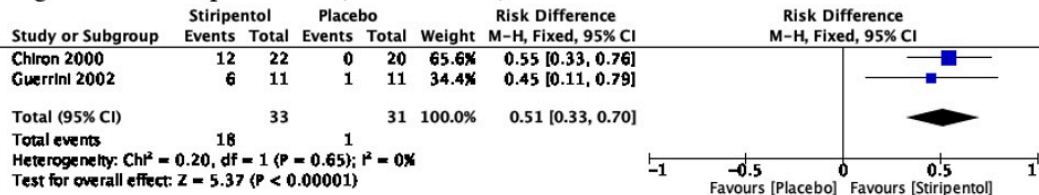


Fig 3.3 Seizure-free patients (STP vs. PLB)

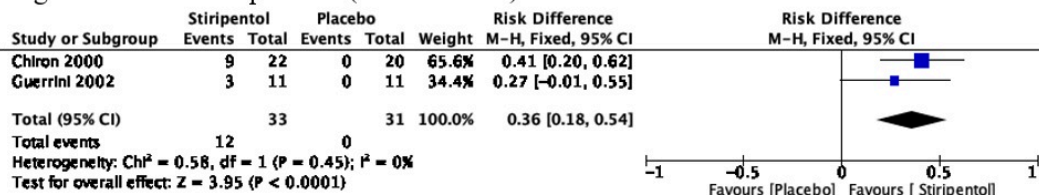


Fig 3.4 Percentage change in seizure frequency (STP vs. PLB)

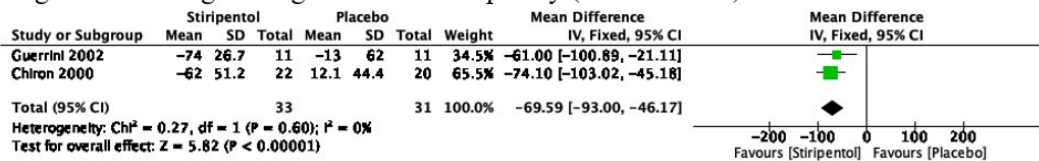


Fig 3.5 Treatment-related serious adverse events (STP vs. PLB)

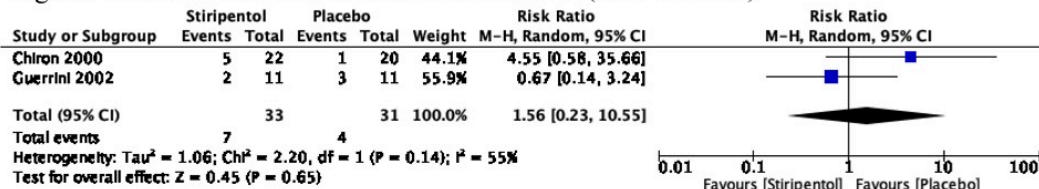


Fig 3.6 Discontinuations (STP vs. PLB)

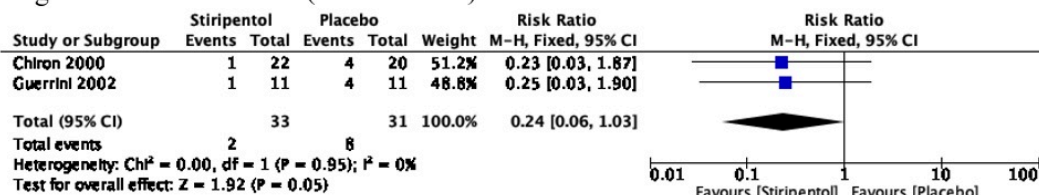


Figure 3

Forest plots of efficacy and safety outcomes

Fig 4.1 Excluding Chiron 2000

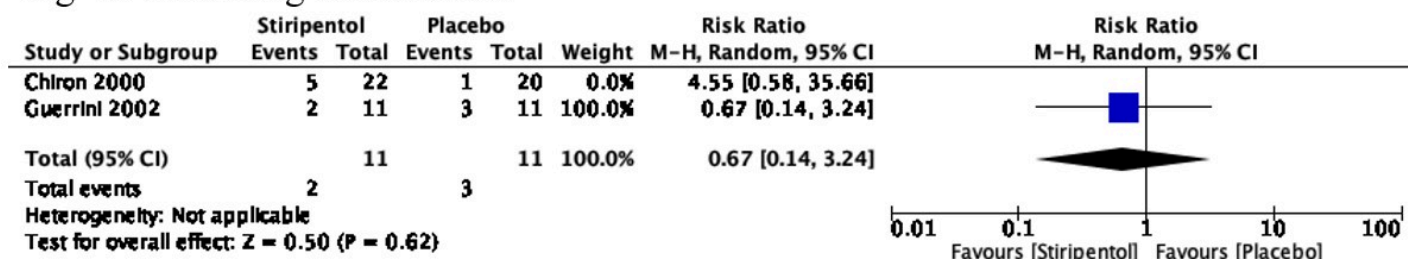


Fig 4.2 Excluding Guerrini 2002

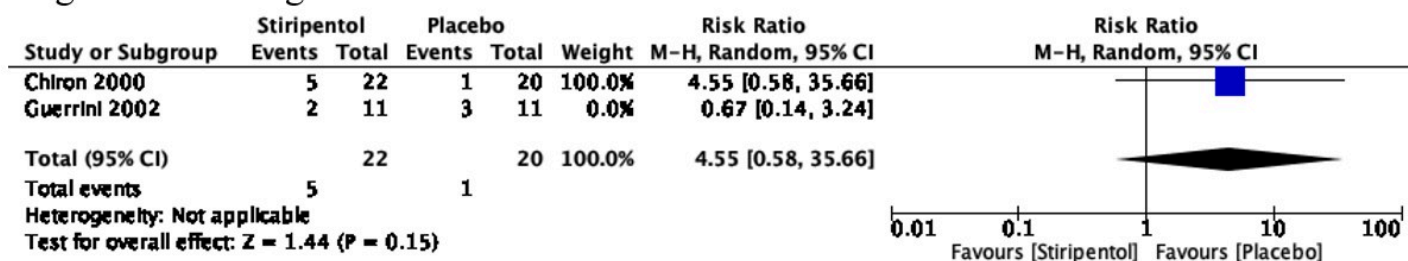


Figure 4

Sensitivity analysis (treatment-related SAEs)