Systematic review and meta-analysis

Dose dependent efficacy and safety of vamorolone in duchenne muscular dystrophy: a systematic review and meta analysis of randomized controlled trials

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ABSTRACT

Background: Duchenne muscular dystrophy (DMD) is a severe inherited neuromuscular disorder causing progressive muscle weakness in boys. Corticosteroids are standard therapy but have significant long-term adverse effects. Vamorolone, a dissociative steroid, may preserve efficacy while reducing toxicity. This systematic review and meta-analysis evaluated whether higher doses improve motor outcomes while maintaining safety in boys with DMD.

Methods: A systematic search of PubMed, Web of Science, Embase, Scopus, and the Cochrane Library was conducted to identify randomized controlled trials comparing vamorolone at 2 mg/kg/day versus 6 mg/kg/day in boys with DMD. Primary motor outcomes included time to stand from supine (TTSTAND), six-minute walk distance (6-MWD), time to run or walk 10 meters (TTRW), and time to climb four stairs (TTCLIMB). Changes in BMI z score were assessed as a safety indicator. Data were analyzed using Review Manager (RevMan) 5.4 following PRISMA guidelines.

Results: Three randomized controlled trials involving 118 boys met the inclusion criteria. The 6 mg/kg/day dose demonstrated significantly greater improvement in motor outcomes compared with the 2 mg/kg/day dose, including TTSTAND (MD = 0.04, 95% CI [0.02-0.07], $p < 0.0001$), 6-MWD (MD = 26.27, 95% CI [1.55-50.99], $p = 0.04$), TTRW (MD = 0.13, 95% CI [0.07-0.19], $p < 0.0001$), and TTCLIMB (MD = 0.04, 95% CI [0.01-0.07], $p = 0.006$). BMI z score changes were comparable between groups.

Conclusion: Vamorolone 6 mg/kg/day improves motor function more than 2 mg/kg/day without increased safety concerns. Larger long-term trials are required to confirm these findings.

Keywords: Duchenne muscular dystrophy, vamorolone, dosing, Duchenne.

Introduction

Duchenne muscular dystrophy (DMD) is an X-linked recessive neuromuscular disorder resulting from mutations in the DMD gene, leading to the absence of dystrophin, a protein normally expressed in cardiac and skeletal muscles, the brain, and the retina [1]. A meta-analysis estimated the worldwide prevalence of DMD to be 4.8 cases per 100,000 people [2]. Dystrophin is a crucial component of the dystrophin-glycoprotein complex,

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which is essential for maintaining muscle integrity. In DMD, the absence of dystrophin and the dystrophin-glycoprotein complex leads to membrane fragility and increased permeability, dysregulation of calcium homeostasis, and oxidative injury. Consequently, muscle necrosis occurs, followed by regenerative exhaustion of muscle fibers and their replacement with adipose and connective tissue [3]. Boys with DMD typically present between 3 and 5 years of age with proximal lower limbs and truncal weakness, which is later followed by involvement of the upper limbs and distal muscles. Other manifestations may include dilated cardiomyopathy, chronic respiratory insufficiency, subnormal intelligence quotient, scoliosis, attention deficit hyperactivity disorder, and autism spectrum disorder [4]. Progressive deterioration of muscle strength usually occurs after 6 years of age, and without treatment, most patients become wheelchair-bound by 11–12 years of age [5]. Despite therapeutic advances, no definitive cure for DMD has been established. However, glucocorticoids are strongly recommended for patients whose motor development has stopped or begun to decline, and, according to the most recent guidelines, treatment should be continued lifelong [6,7]. The chronic use of glucocorticoids is associated with several adverse effects, including an increased risk of growth suppression and delayed puberty, weight gain, hyperglycemia, adrenal suppression, recurrent infections, and osteoporosis with fractures. Consequently, prolonged glucocorticoid therapy is generally avoided [8]. Vamorolone is a novel modified steroid with a structure similar to that of glucocorticoids but characterized by a D-9,11 double bond within the steroid ring. Like glucocorticoids, vamorolone binds to glucocorticoid receptors and suppresses transcriptional signaling of the NF-κB pathway. However, vamorolone appears to largely avoid the broad transcriptional activity associated with the numerous adverse effects of conventional glucocorticoids [9]. Evidence from early pilot studies suggests that vamorolone retains the therapeutic efficacy of traditional glucocorticoids while significantly reducing the adverse effects associated with long-term corticosteroid therapy [10,11]. This systematic review and meta-analysis aim to evaluate the efficacy and safety of varying doses of vamorolone in improving gross motor function among boys with DMD.

Methods

This systematic review and meta-analysis were conducted in accordance to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (PRISMA) 2020 guidelines [12]. Also, this review has been registered in international prospective register of systematic reviews (PROSPERO) with the registration number of CRD420251164159.

Data sources and search

Multiple databases, including MEDLINE, Web of Science, Cochrane Library, Scopus, and Embase, were systematically searched from their inception until October 12, 2025. Keywords and Medical Subject Headings (MeSH terms) included vamorolone, Agamree, VBP15, Duchenne muscular dystrophy, Duchenne, and DMD, combined using Boolean operators ("OR" and "AND").

Inclusion and exclusion criteria

Relevant Randomized Controlled Trials (RCTs) evaluating different doses of vamorolone and their effects on multiple motor outcomes of interest in patients with DMD were included in this review. Non-randomized studies, studies with alternative designs, animal studies, studies including patients with Becker muscular dystrophy, and non-English publications were excluded.

Data extraction

After systematically searching the databases for relevant records, duplicates were removed, and the remaining records were distributed in sets to two independent reviewers for screening. The screening process was conducted in two stages: initial screening by title and abstract, followed by full-text assessment to identify eligible RCTs of interest. For both vamorolone treatment arms (6 mg/kg/day and 2 mg/kg/day) in the included studies, multiple variables were extracted, including the duration of vamorolone therapy, time points of outcome measurement, number of participants, as well as their age, weight, height, and baseline measurements of all motor outcomes of interest.

Study outcomes

Motor outcomes assessed include the Time to Stand from Supine Test (TTSTAND), which measures how fast a patient can transition from a supine lying position to a standing one, measured as rises per second (1/s); the Six-Minute Walking Distance (6-MWD), which measures the distance a patient can walk within the stated time, measured in meters (m); the Time to Run or Walk 10 Meters (TTRW), which evaluates the speed at which a patient can run or walk, depending on ability, for a 10-meter distance, measured in meters per second (m/s); and finally, the Time to Climb (TTCLIMB), which assesses how quickly a patient can ascend four stairs without assistance, measured as tasks per second (1/s). The Body Mass Index (BMI) was also evaluated to assess changes in muscle mass over time and the possible effects of vamorolone as a dissociative corticosteroid.

Quality assessment

The Risk of Bias tool (RoB 2) by Cochrane was utilized by two independent authors to assess the quality of the included RCTs and to evaluate multiple types of bias across five domains. Each study was rated as having a low risk, some concerns, or a high risk of bias, with an overall risk judgment used to evaluate the methodological frameworks the studies adhered to.

Statistical analysis

RevMan [version 5.4; Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014], was utilized to conduct the statistical analysis [13]. A random-effects model with the inverse variance

statistical method was applied, with a p-value of less than 0.05 considered statistically significant. Since all outcomes were quantitative and reported using similar units of measurement, the mean difference (MD) was used to report the overall effect, along with a 95% confidence interval (CI) and the I^2 statistic to account for heterogeneity among studies. A subgroup analysis was conducted for different time points at which the outcomes were assessed: 24-weeks and 48-weeks. The change from baseline in all outcomes was used when reporting the meta-analysis, as all included studies presented their results in this manner.

Results

Study selection

The search strategy with the MeSH terms used are summarized in Supplementary Table 1. The systematic and comprehensive search across five databases yielded 394 records. Following the deduplication process, 208 duplicates were removed, leaving 186 articles for title, abstract, and full-text screening. Of these, 183 articles were excluded for not meeting the inclusion criteria. Ultimately, three RCTs were included in this systematic review and meta-analysis [11,14,15]. The detailed PRISMA flow diagram can be found in Figure 1. Leinonen et al. represents an extension study that followed the same patient cohort included in Guglieri et al. [11,14].

Study characteristics

Details of the study characteristics, including demographics and baseline measurements of the participants, are presented in Table 1. The total number of participants was 118 male patients, with a mean age of 5.35 years. The mean weight of the patients was 19 kg, while the height percentile was at the 31st percentile for the 6 mg group and at the 23rd percentile for the 2 mg group. Details of the intervention, including time points of outcome assessment and units of measurement used for reporting the outcomes, are provided in Table 2.

Risk of bias assessment

The summary and graphical representation of the risk of bias assessment, conducted using the RoB2 tool, are presented in Figures 2 and 3. All three RCTs were evaluated as having a low risk of bias across all five domains, resulting in an overall low risk of bias rating due to the rigorous methodologies implemented.

TTSTAND

All three studies have assessed the effect of vamorolone on TTSTAND reported as (rises/s) [11,14,15]. The overall pooled effect demonstrated a significant difference favoring the 6 mg group (MD = 0.04, 95% CI [0.02, 0.07], $p < 0.0001$, $I^2 = 49\%$). In the subgroup analysis, no significant difference was observed between the two dosages at the 24-week mark (MD = 0.01, 95% CI [–0.03, 0.05], $p = 0.64$). However, a significant difference favoring the 6 mg group was observed at the 48-week mark (MD = 0.05, 95% CI [0.05, 0.06], $p < 0.00001$, $I^2 = 0\%$), Figure 4.

6-MWD

All three studies have evaluated 6-MWD reported as (m) [11,14,15]. The overall pooled effect demonstrated a significant difference favoring the 6 mg dose over the 2 mg dose in improving the 6-MWD outcome (MD = 26.27, 95% CI [1.55, 50.99], $p = 0.04$, $I^2 = 66\%$). Similar to TTSTAND, there was no significant difference between the doses at the 24-week subgroup (MD = −2.20, 95% CI [−33.44, 29.04], $p = 0.89$), whereas the 6 mg group was significantly favored at the 48-week mark (MD = 38.42, 95% CI [28.28, 48.55], $p < 0.00001$, $I^2 = 0\%$), Figure 5. Due to the moderate heterogeneity observed, a sensitivity

Table 1. *Study characteristics of the included studies.*

	Guglieri et al.	Leinonen et al.	Dang et al.
Number of patients	Vamorolone 6mg: 28 Vamorolone 2mg: 30	Vamorolone 6mg: 28 Vamorolone 2mg: 28	Vamorolone 6mg: 30 Vamorolone 2mg: 30
Age in years, Mean (SD)	Vamorolone 6mg: 5.4 (0.9) Vamorolone 2mg: 5.3 (0.9)	Vamorolone 6mg: 5.4 (0.9) Vamorolone 2mg: 5.3 (0.9)	NR
Weight (Kg)	Vamorolone 6mg: 19 Vamorolone 2mg: 19	Vamorolone 6mg: 43.7 (Percentile) Vamorolone 2mg: 43.1 (Percentile)	NR
Height (percentile)	Vamorolone 6mg: 23 Vamorolone 2mg: 30	Vamorolone 6mg: 23.2 Vamorolone 2mg: 32	NR
TTSTAND (Rises/s)	Vamorolone 6mg: 0.19 Vamorolone 2mg: 0.18	Vamorolone 6mg: 6.0 (sec) Vamorolone 2mg: 6.0 (sec)	Vamorolone 6mg: 0.19 Vamorolone 2mg: 0.19
6-MWD (Meters)	Vamorolone 6mg: 313 Vamorolone 2mg: 316	Vamorolone 6mg: 313 Vamorolone 2mg: 317	Vamorolone 6mg: 312 Vamorolone 2mg: 317
TTCLIMB (Tasks/s)	Vamorolone 6mg: 0.21 Vamorolone 2mg: 0.20	NR	Vamorolone 6mg: 0.21 Vamorolone 2mg: 0.20
TTRW (m/s)	Vamorolone 6mg: 1.6 Vamorolone 2mg: 1.6	NR	Vamorolone 6mg: 1.6 Vamorolone 2mg: 1.6
BMI (Kg/m^2)	Vamorolone 6mg: 16.6 Vamorolone 2mg: 16.2	Vamorolone 6mg: 69.8 (Percentile) Vamorolone 2mg: 63.5 (Percentile)	NR

Abbreviations: DMD: Duchenne Muscular Dystrophy; 6-MWD: Six-Minute Walk Distance; TTSTAND: Timed Test to Stand; TTCLIMB: Timed Test to Climb; TTRW: Timed Test to Run/Walk; BMI: Body Mass Index; NR: Not Reported; SD: Standard Deviation.

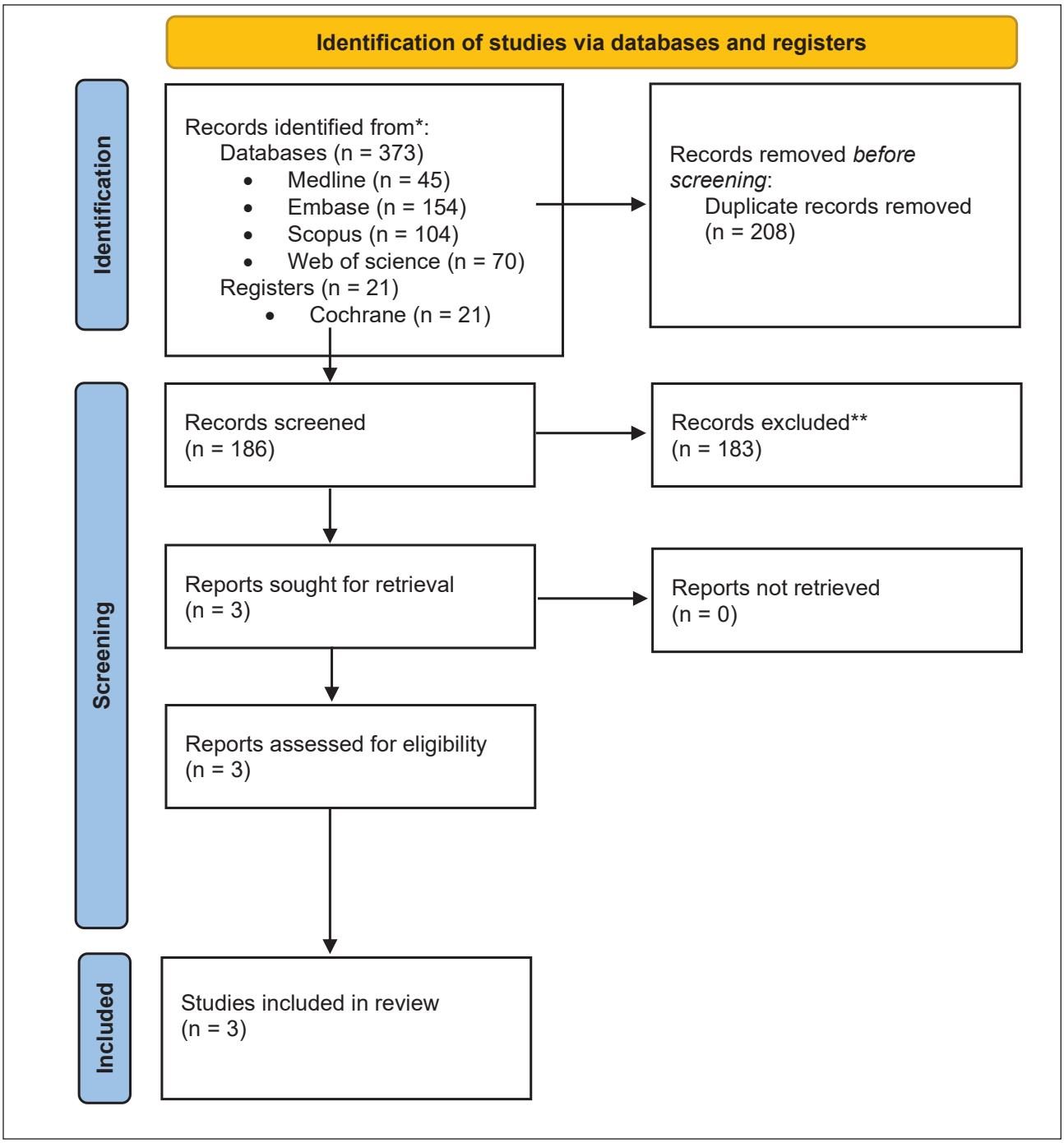

Figure 1. *PRISMA flow diagram.*

analysis was conducted excluding Guglieri et al., the only study contributing to the 24-week subgroup [11]. This resulted in a substantial reduction in heterogeneity in the overall effect (MD = 38.42, 95% CI [28.28, 48.55], $p < 0.00001$, $I^2 = 0\%$), Supplementary Figure 1.

TTRW

All three RCTs have assessed the impact of vamorolone on the TTRW outcome reported as (m/s) [11,14,15]. The overall pooled effect demonstrated a significant difference favoring the 6 mg dose (MD = 0.13, 95% CI [0.07, 0.19], $p < 0.0001$, $I^2 = 0\%$). The subgroup analysis revealed no significant difference at the 24-week mark (MD = 0.12, 95% CI [−0.02, 0.26], $p = 0.10$), whereas a significant difference was observed at the 48-week mark (MD = 0.13, 95% CI [0.07, 0.20], $p < 0.0001$, $I^2 = 0\%$), Figure 6.

TTCLIMB

All three studies have evaluated the TTCLIMB motor outcome reported as (tasks/s) [11,14,15]. The overall pooled effect demonstrated a significant difference favoring the 6 mg arm (MD = 0.04, 95% CI [0.01, 0.07], $p = 0.006$, $I^2 = 0\%$). The subgroup analysis revealed no significant difference at the 24-week mark (MD = 0.01, 95% CI [−0.05, 0.07], $p = 0.73$), whereas a significant

Table 2. *Intervention details of the included studies.*

Study		Guglieri	Leinonen	Dang
Duration of intervention		24 weeks	48 weeks	48 weeks
Time point of outcome measurement (Weeks)		12 weeks, 24 weeks	24 weeks, 48 weeks	12 weeks, 24 weeks, 40 weeks, 48 weeks (TTSTAND was additionally performed at 6 weeks and 34 weeks)
Outcome measurment	Primary effect (motor endpoints)	TTSTAND (Rise/s), 6MWD (M), TTCLIMB (tasks/s), TTRW (m/s), NSAA	TTSTAND (Rise/s), 6MWD (M), TTCLIMB (tasks/s), TTRW (m/s), NSAA	TTSTAND (Rise/s), 6MWD (M), TTCLIMB (tasks/s), TTRW (m/s), NSAA
	Secondary effect	Handheld myometry, Treatment satisfaction questionare, PODCI, psychosocial adjustment and role skills scale III, BMI (z score)	BMI (z score)	Handheld myometry, Treatment satisfaction questionare, PODCI, psychosocial adjustment and role skills scale III, BMI (z score)

TTSTAND: Timed Test to Stand; 6-MWD: Six-Minute Walk Distance; TTCLIMB: Timed Test to Climb; TTRW: Timed Test to Run/Walk; NSAA: North Star Ambulatory Assessment; PODCI: Pediatric Outcomes Data Collection Instrument; BMI: Body Mass Index.

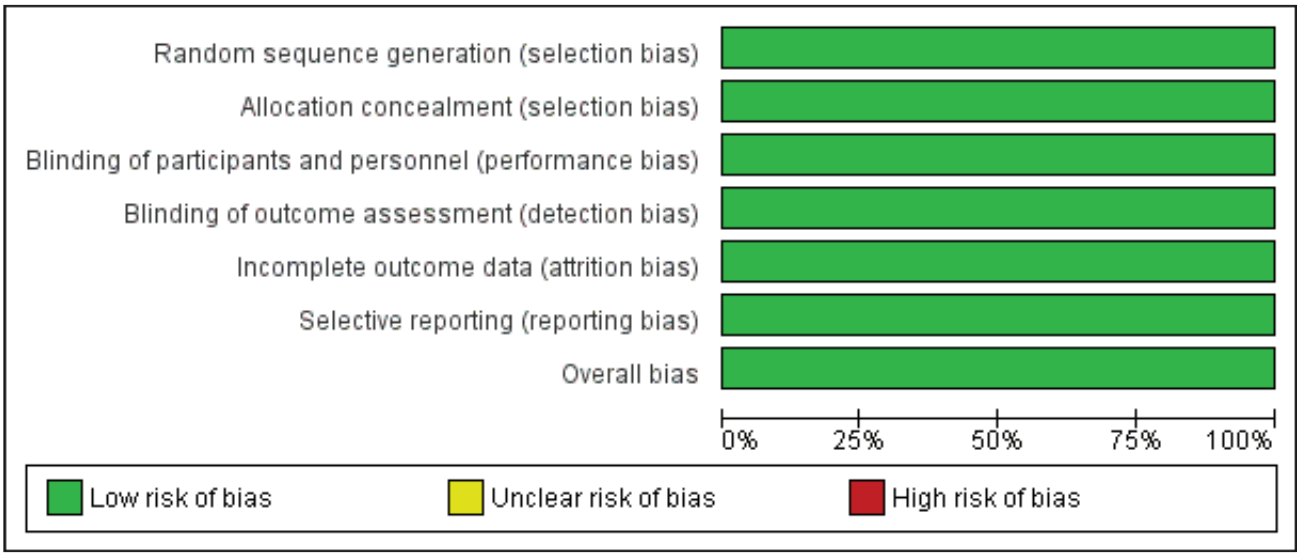

Figure 2. *Risk of bias graph.*

difference was observed at the 48-week mark (MD = 0.05, 95% CI [0.02, 0.09], $p = 0.003$, $I^2 = 0\%$), Figure 7.

BMI Z score

All three RCTs have evaluated the impact of vamorolone on BMI change [11,14,15]. The overall pooled effect revealed no significant difference between the dosages in impacting the BMI z-score (MD = 0.13, 95% CI [−0.06, 0.33], $p = 0.18$, $I^2 = 51\%$). This non-significant difference was similarly observed in the subgroup analyses at both the 24-week mark (MD = 0.12, 95% CI [−0.17, 0.41], $p = 0.42$) and the 48-week mark (MD = 0.16, 95% CI [−0.17, 0.49], $p = 0.33$, $I^2 = 75\%$), Figure 8. The sensitivity analysis, conducted after excluding Dang et al., maintained the non-significant effect while demonstrating a substantial reduction in heterogeneity in the overall analysis (MD = 0.04, 95% CI [−0.09, 0.17], $p = 0.54$, $I^2 = 0\%$), Supplementary Figure 2 [15].

Discussion

This systematic review and meta-analysis demonstrated that the 6 mg/kg dose of vamorolone significantly improved motor outcomes, including TTSTAND, 6-MWD, TTRW, and TTCLIMB, compared with the 2 mg/kg dose in boys with DMD. However, there was no significant difference between the doses in changes to the BMI z score.

Our findings are consistent with the conclusions of the systematic review and meta-analysis by Wang et al. Notably, our methodology differed from that of Wang et al., as they included nonrandomized studies in their review and evaluated outcome measures in the meta-analysis as endpoint readings, whereas our approach implemented subgroup analyses to improve the accuracy of the conclusions of this analysis and to detect the point at which a specific dose of vamorolone exerted a significant impact [16].

Vamorolone was FDA-approved in 2023 for the treatment of DMD in patients aged two years or older [17]. It is designed to reduce the incidence of glucocorticoid therapy–related adverse effects. It exerts its anti-inflammatory and immunosuppressive effects by acting as a dissociative glucocorticoid ligand. It inhibits the NF-kB pathway while lacking the chemical structure that binds to the glucocorticoid receptor elements, which is

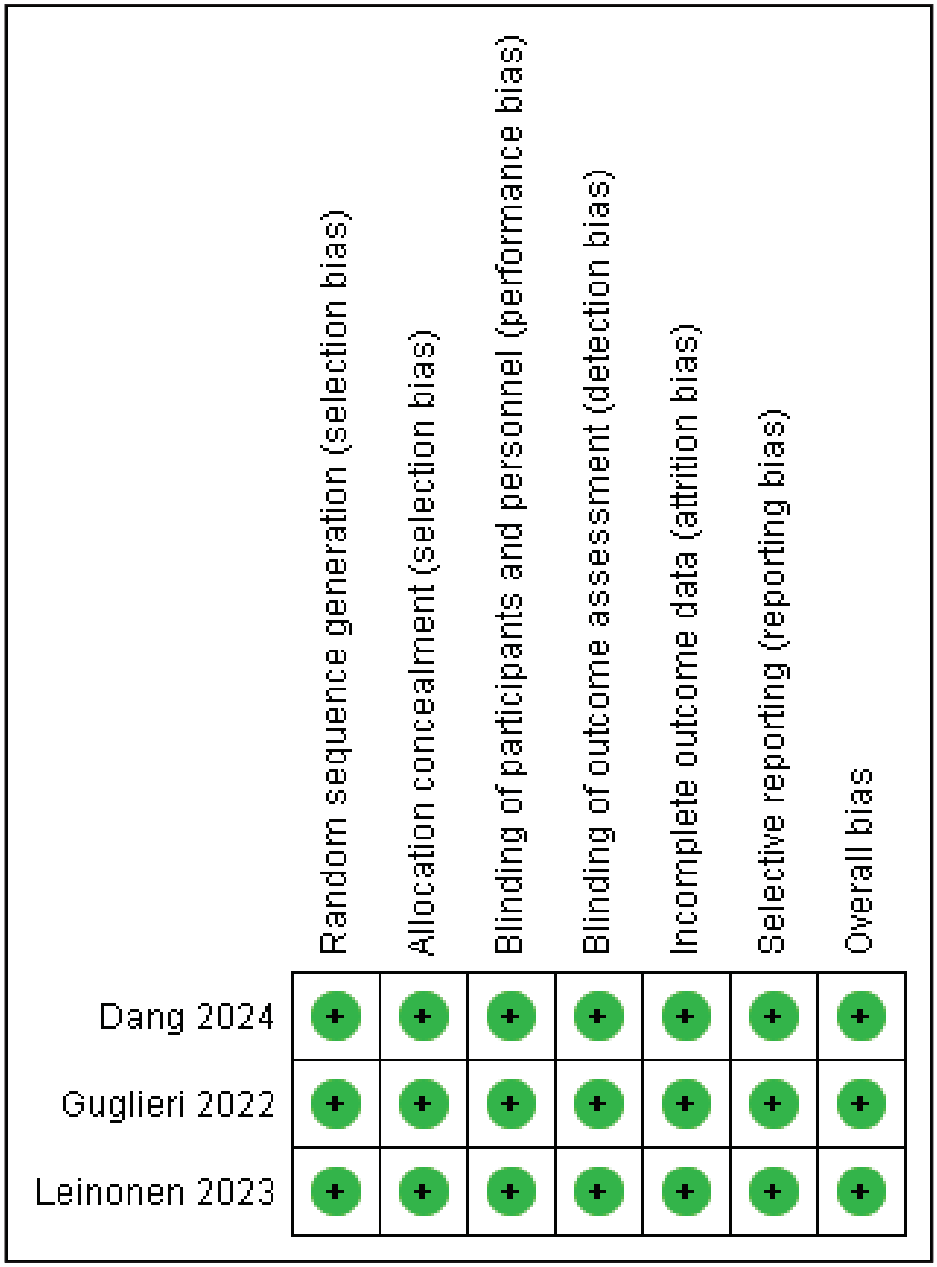

Figure 3. *Risk of bias summary.*

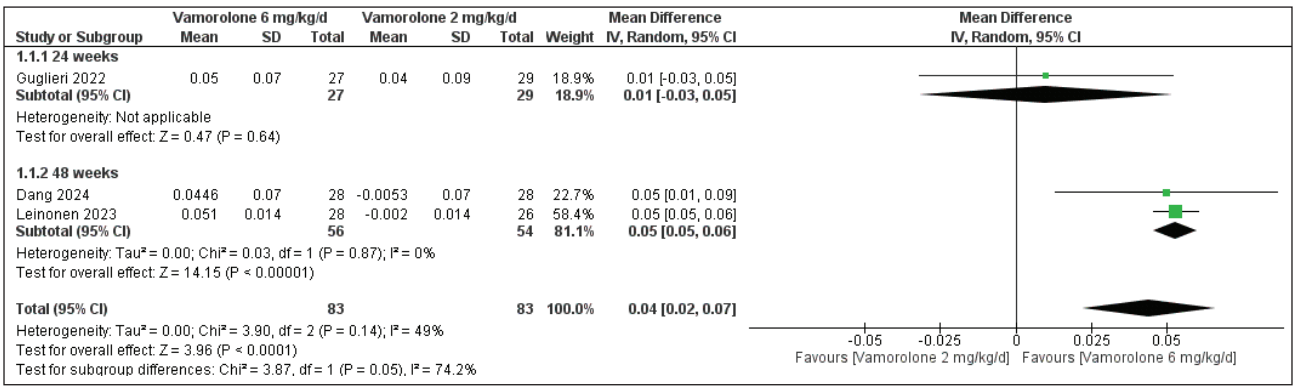

Figure 4. *Forest plot for TTSTAND.*

the 11 betahydroxyl/carbonyl group, that is hypothesized to exert some of the adverse effects of prednisone. While glucocorticoids serve as mineralocorticoid receptor agonists, vamorolone serves as a potent antagonist.

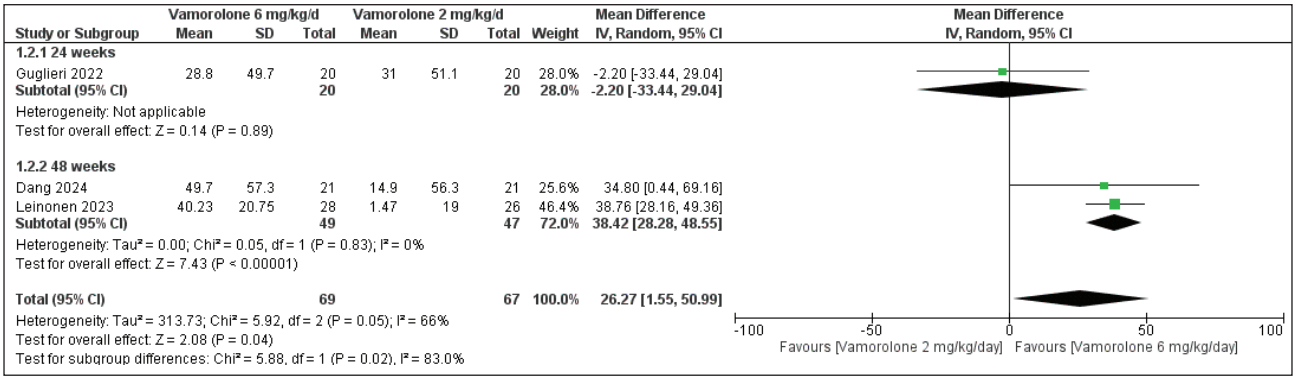

Figure 5. *Forest plot for 6-MWD.*

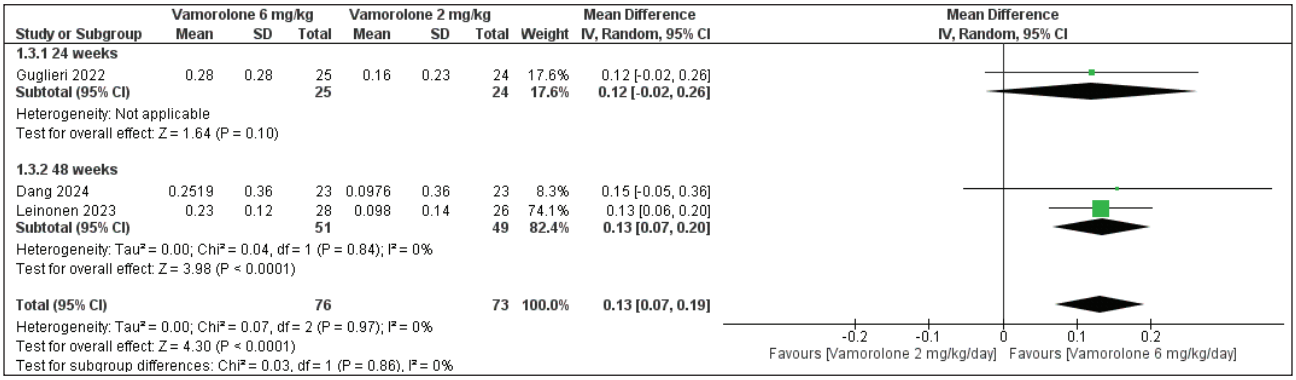

Figure 6. *Forest plot for TTRW.*

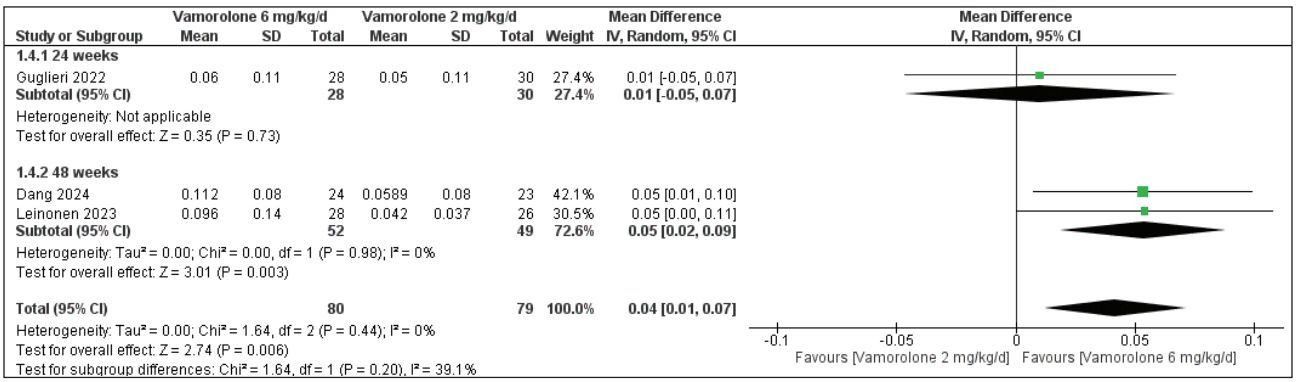

Figure 7. *Forest plot for TTCLIMB.*

This difference could minimize the negative effects of activating the mineralocorticoid receptors, such as hypertension, weight gain, and electrolyte abnormalities [18,19].

The 6 mg/kg dose of vamorolone demonstrated a dose-responsive effect by significantly improving all assessed motor outcomes in patients with DMD, particularly at 48-weeks. Although there was a trend favoring the 6 mg/kg group at 24-weeks, this difference did not reach statistical significance. However, the positive impact became significant at 48-weeks, suggesting that a clinically meaningful effect of vamorolone requires long-term administration. In an open-label, nonrandomized extension study by Smith et al., individuals treated with vamorolone showed improvements in all motor outcomes across an 18-month treatment period [20]. Hoffman et al. further argued that the motor improvement associated with vamorolone is clinically meaningful, as patients transitioned from milestone group 2, characterized by functional deterioration and possible loss of standing ability, to milestone group 1, characterized by potential stability or improvement [21]. The body of evidence supports the incorporation of vamorolone into the treatment regimen for DMD, with the potential to delay loss of ambulation, slow disease progression, enhance motor function, and improve overall survival.

Dose escalation of vamorolone over 48-weeks did not appear to significantly impact BMI in patients with DMD. In the study by Smith et al., patients treated with vamorolone experienced fewer corticosteroid-associated

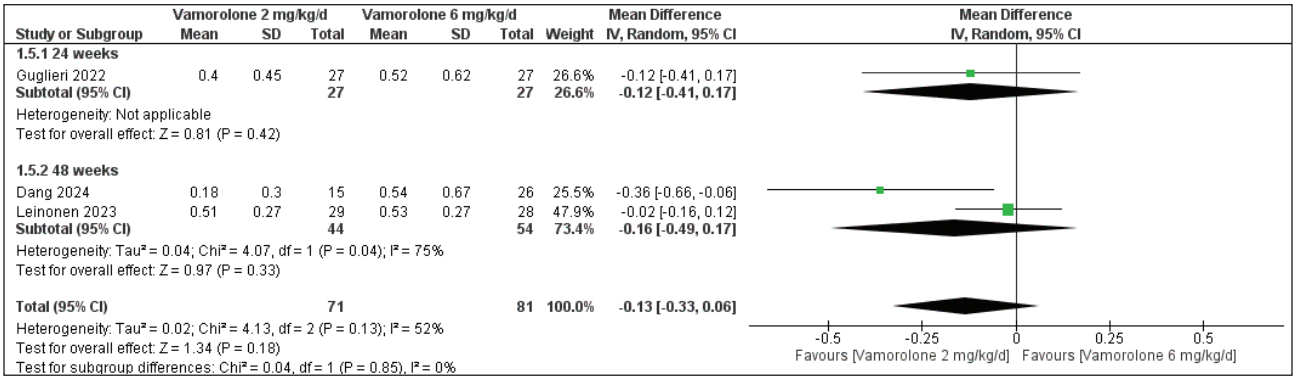

Figure 8. *Forest plot for BMI z score.*

adverse effects, including mood disturbances, cushingoid appearance, hirsutism, and weight gain. They also reported significant growth stunting in the corticosteroid-treated group, whereas no such effect was observed in patients receiving vamorolone [20]. Conklin et al. further reported that vamorolone demonstrated an acceptable tolerability and safety profile at the maximum dose of 6 mg/kg, although increased insulin levels were observed, suggesting a potential risk of insulin resistance [22]. In a meta-analysis by Ibrahim et al., they reported that treatment with vamorolone does not appear to increase the risk of growth stunting, although weight gain remains evident. However, they considered the medication to lack serious adverse effects, noting that the risk of weight gain may be mitigated through dose reduction [23]. Conversely, Hoffman et al. reported increased BMI z score, adrenal suppression, and insulin resistance [21]. Collectively, these findings suggest that vamorolone maintains the therapeutic efficacy of corticosteroids while minimizing adverse effects, and that safety outcomes appear to be dose dependent, which is particularly important for patients requiring long-term treatment.

This study has several notable strengths. First, inclusion was restricted to RCTs, which strengthens the level of evidence and the validity of the pooled estimates. Second, this review addresses a gap in the literature by evaluating different doses of vamorolone and assessing whether outcomes vary according to the administered dose, rather than focusing solely on comparisons between the medication and placebo, which has been previously studied. Third, subgroup analyses based on treatment duration allowed evaluation of the effects of different doses at multiple time points, thereby revealing the temporal pattern of treatment response. Finally, both efficacy and safety outcomes were assessed simultaneously, enabling a balanced clinical interpretation of the therapeutic value of the medication.

Our study has several limitations. First, the small sample sizes of the included RCTs may limit the generalizability of the conclusions drawn. Second, there is a scarcity of randomized controlled trials evaluating vamorolone in general, and over extended treatment durations in particular, which hinders a comprehensive understanding of its long-term efficacy and safety in the DMD population. Third, no data regarding changes in height percentiles between the two dosing regimens were reported, and therefore, this parameter could not be evaluated in the meta-analysis.

Future randomized controlled trials with larger sample sizes and longer follow-up durations are recommended to further evaluate the clinical role and dose-dependent effects of vamorolone in patients with DMD.

Conclusion

This systematic review and meta-analysis demonstrated that the 6 mg/kg dose of vamorolone significantly improved motor outcomes, including standing, walking, running, and climbing, compared with the 2 mg/kg dose in patients with Duchenne muscular dystrophy, while maintaining a tolerable and acceptable safety profile. Future randomized controlled trials with larger sample sizes and longer follow-up durations are needed to confirm these findings and further characterize the long-term efficacy and safety of vamorolone.

List of abbreviations

DMD	Duchenne Muscular Dystrophy
TTSTAND	Timed Test to Stand
6-MWD	Six-Minute Walk Distance
TTRW	Timed Test to Run/Walk
TTCLIMB	Timed Test to Climb
BMI	Body Mass Index
RCT	Randomized Controlled Trial
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROSPERO	International Prospective Register of Systematic Reviews
RoB 2	Risk of Bias 2 tool
RevMan	Review Manager
MD	Mean Difference
CI	Confidence Interval
NSAA	North Star Ambulatory Assessment
PODCI	Pediatric Outcomes Data Collection Instrument
SD	Standard Deviation
NR	Not Reported
NF-κB	Nuclear Factor Kappa B

Acknowledgment

None.

Ethical Approval

Not applicable

Consent to Publication

Not applicable, as no individual data requiring consent for publication were included.

Data Availability Statement

All data supporting the findings of this study are included in the main manuscript and the accompanying supplementary materials.

Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this article.

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Supplementary content (If any) is available online.

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