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Review Article

Effect of Complementary Pharmacological Therapy on Fatigue in Patients with Multiple Sclerosis: A Systematic Review and Meta-Analysis

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Abstract

Background: Fatigue is among the most common and disabling symptoms of multiple sclerosis (MS), significantly impairing quality of life, daily functioning, and work capacity. Given the variety of pharmacological approaches and the lack of consensus on their effectiveness, this study systematically evaluated the evidence on complementary pharmacological therapies for MS-related fatigue.

Methods: A systematic search of PubMed, Scopus, and Web of Science (through May 2026) identified randomized controlled trials (RCTs) evaluating complementary pharmacological interventions for MS-related fatigue. Two reviewers independently performed study selection, data extraction, and risk-of-bias assessment using the Cochrane RoB 2 tool. Heterogeneity was assessed via chi-square and I^2 statistics, and publication bias via Begg's and Egger's tests. Pooled effects were reported as standardized mean differences (SMD) with 95% confidence intervals using a random-effects model.

Results: Thirteen RCTs met inclusion criteria for the systematic review, with eight trials (439 participants) contributing to the quantitative synthesis. Complementary interventions significantly reduced fatigue compared with controls (SMD = -1.44, 95% CI: -2.30 to -0.58, $p = 0.001$), although heterogeneity was very high ($I^2 = 93.7\%$). After excluding one outlying study, sensitivity analysis remained statistically significant while substantially lowering heterogeneity (SMD = -0.61, 95% CI: -0.91 to -0.31, $p < 0.001$; $I^2 = 49.9\%$). No clear publication bias was detected (Begg's $p = 0.293$; Egger's $p = 0.477$; trim-and-fill method). Risk-of-bias analysis showed low risk for randomization and blinding across studies, though incomplete outcome data and unclear allocation concealment were common limitations.

Conclusion: Complementary pharmacological therapy may reduce fatigue in some patients with MS, but current evidence remains insufficient to support a definitive, generalizable recommendation. Larger, methodologically standardized trials with consistent outcome reporting are needed to establish the conclusive effectiveness of these therapies.

Keywords: Complementary Therapies; Fatigue; Meta-Analysis; Multiple Sclerosis; Randomized Controlled Trial; Systematic Review

Introduction

Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system characterized by demyelination and gliosis in the brain and spinal cord, and it is a leading cause of non-traumatic neurological disability in young adults [1]. Among the many symptoms of MS, fatigue is one of the most prevalent, disabling, and clinically challenging, affecting more than 80% of patients [2]. MS-related fatigue extends beyond ordinary tiredness: it is a multidimensional phenomenon that simultaneously affects physical, cognitive, and psychological function and substantially reduces quality of life and daily performance [3].

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Despite considerable progress in disease-modifying therapies (DMTs), the management of fatigue remains a major unmet therapeutic need. Because conventional treatments often provide limited relief or cause adverse effects, many patients turn to complementary and alternative therapies [4]. However, the scientific evidence supporting the effectiveness of these interventions — including vitamin D and other anti-inflammatory compounds — is often inconsistent and scattered across the literature [5].

A major challenge in interpreting prior studies is the heterogeneity of fatigue-assessment instruments. Standardized tools such as the Fatigue Severity Scale (FSS) [5], the Multidimensional Fatigue Inventory (MFI) [6], the Fatigue Impact Scale (FIS), [7] and visual analogue scales (VAS) [8] quantify this subjective experience in different ways, complicating direct comparison across studies.

Given the high prevalence of fatigue in MS, its substantial economic and social burden, and the need for evidence-based treatment strategies, a systematic review and meta-analysis synthesizing the available data is warranted. The present study aimed to rigorously evaluate the effect of complementary pharmacological therapy on fatigue in patients with MS, in order to resolve existing uncertainties and provide robust evidence to inform clinical decision-making.

Materials and Methods

Study design

This study was conducted as a systematic review and meta-analysis in accordance with PRISMA guidance, during 2025–2026.

Eligibility criteria

Eligibility was defined using the PICOS framework: Population — patients diagnosed with MS reporting fatigue, regardless of race or age; Intervention — complementary pharmacological therapy; Comparator — placebo, standard care, or no intervention; Outcome — change or improvement in fatigue severity, measured with validated instruments (FSS, MFI, FIS, VAS); Study design — randomized controlled trials (RCTs). All eligible studies were included irrespective of language, publication date, or publication status.

Search strategy

The PubMed, Scopus, and Web of Science databases were searched from inception through May 4, 2026, using the following strategy: ("Multiple Sclerosis" OR MS OR "demyelinating disease" OR "relapsing remitting multiple sclerosis" OR "secondary progressive multiple sclerosis" OR "primary progressive multiple sclerosis") AND ("Complementary Therapies" OR "Complementary medicine" OR "complementary therap*") AND (Fatigue OR "fatigue syndrome" OR "physical fatigue" OR "mental fatigue" OR FSS OR MFI OR FIS OR "Modified Fatigue Impact Scale" OR "Fatigue Severity Scale"), filtered to clinical trials and randomized controlled trials. Google Scholar was additionally searched, and the reference lists of eligible articles were hand-searched to identify further studies. Corresponding authors of selected articles were contacted to obtain unpublished data where needed.

Study selection and data extraction

Records were imported into EndNote and duplicates were removed. Two reviewers independently screened titles and abstracts and then assessed full texts against the eligibility criteria; disagreements were resolved by discussion (inter-rater agreement, Kappa = 78%). For excluded full-text articles, the author, publication year, and reason for exclusion were recorded. A structured, piloted electronic data-extraction form (Stata 17) was used to record: first author, publication year, country, language, mean age and sex distribution per arm, type and dose of complementary intervention, duration and frequency of the intervention, fatigue-assessment instrument, study design, mean and standard deviation of fatigue scores before and after intervention, total and per-arm sample size, and risk-of-bias judgments.

Risk of bias assessment

Because all included studies were randomized controlled trials, methodological quality and risk of bias were assessed using the Cochrane Risk of Bias 2 (RoB 2) tool [9, 10] across the following domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other sources

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of bias. Each domain was rated as low risk, unclear risk, or high risk.

Statistical analysis

Heterogeneity among studies was assessed with the chi-square (Q) test and quantified with the I^2 statistic (<50% low, 50–74% moderate, ≥75% high heterogeneity). Publication bias was evaluated with Begg's rank-correlation test and Egger's linear regression test, complemented by visual inspection of the funnel plot and the trim-and-fill method. Where heterogeneity between studies was moderate to high ($I^2 \geq 50\%$), sensitivity analysis was performed using the sequential leave-one-out approach implemented in the Stata MetaPlot module. Because fatigue was measured with different instruments across studies, the standardized mean difference (SMD) with 95% confidence interval was used as the pooled effect estimate, combined using a random-effects model. A p-value < 0.05 was considered statistically significant. All analyses were conducted in Stata version 17 (StataCorp, College Station, TX, USA) and Review Manager (RevMan).

Ethical considerations

As a secondary analysis of previously published data, this study required no direct patient contact. Data from all included articles were collected carefully and referenced appropriately. The study was approved under ethics code IR.UMSHA.REC.1403.844.

Results

Study selection

The search identified 1,745 records: 162 from PubMed, 988 from Scopus, and 595 from Web of Science; no additional records were identified through Google Scholar. After removing 460 duplicates, 1,285 records were screened by title and abstract, of which 1,249 were excluded as irrelevant. Of the remaining 36 full-text articles assessed for eligibility, 23 were excluded (review articles, non-RCT design, or interventions not addressing fatigue), leaving 13 studies that met the inclusion criteria for the systematic review. Of these, eight studies (439 participants) reported data in a format suitable for quantitative pooling and were included in the meta-analysis [11-18]. The study selection process is summarized in Figure 1.

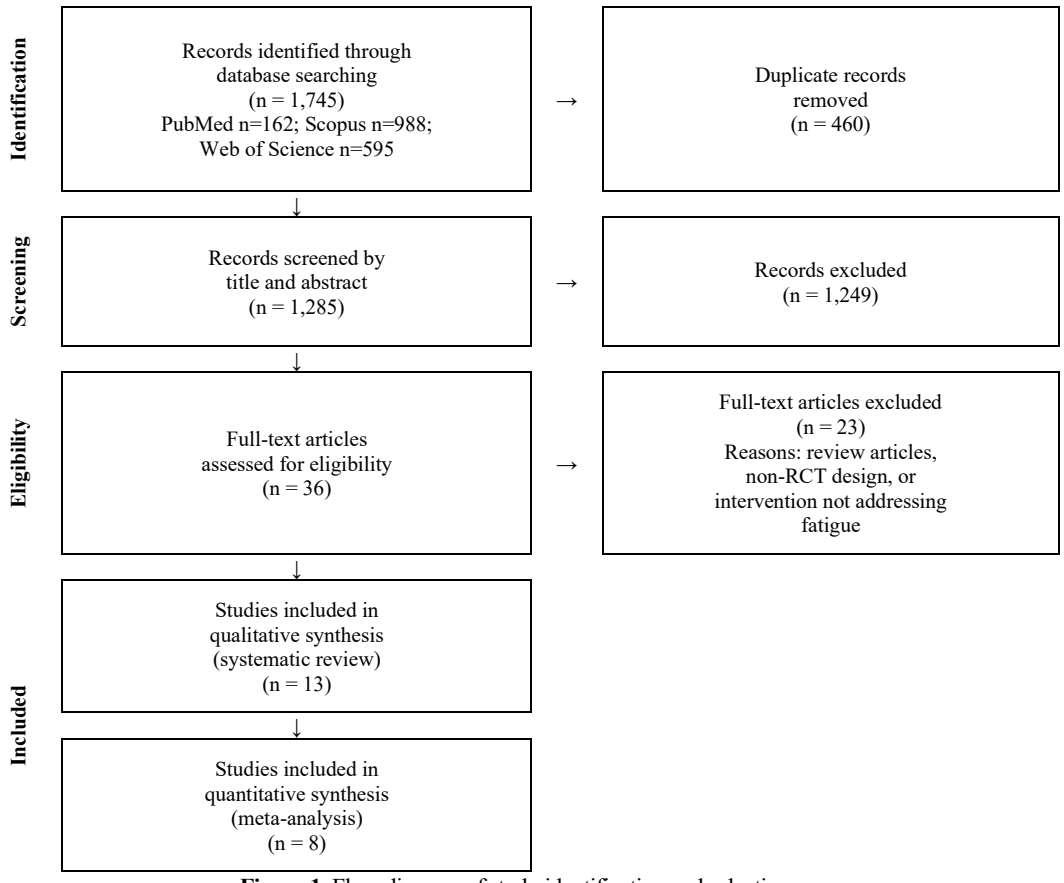


Figure 1. Flow diagram of study identification and selection

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Characteristics of included studies

Table 1 summarizes the characteristics of the 13 included studies, conducted in Iran, Turkey, Israel, the United Kingdom, and Italy, with sample sizes ranging from 40 to 424 participants. Interventions were heterogeneous and included multivitamin-mineral supplementation, vitamin A, coenzyme Q10, omega-3 fatty acids, alfacalcidol, cannabis extract, cocoa-based products, traditional herbal formulations, and lavender aromatherapy. Fatigue was most commonly assessed with the FSS, followed by the MFIS and FIS.

Table 1. Characteristics of studies included in the systematic review

Author	Year	Country	N	Design	Intervention	Dose	Duration	Fatigue tool
Namjooyan et al.	2019	Iran	60	Double-blind RCT	Traditional herbal formulation (cinnamon, ajwain, Iranian borago)	15 cc/day	3 months	FSS
Kavuran and Yurttaş	2024	Turkey	63	RCT	Lavender essential oil aromatherapy	3 drops on cotton pad	30 days	FSS
Adibi et al.	2024	Iran	60	Double-blind RCT	Cocoa powder	25 g/day	8 weeks	FSS
Adalat et al.	2018	Iran	46	Double-blind RCT	Traditional herbal extract (*Crocus sativus*, *Hypericum perforatum*, *Cinnamon verum*, Vitis vinifera)	10 mL	1 month	FSS
Bitarafan et al.	2020	Iran	41	Triple-blind RCT	Multivitamin-mineral (MVM)	2 capsules/day	3 months	FSS
Babaki et al.	2023	Iran	56	Double-blind RCT	"Jollab Monzej" (traditional Persian compound)	10–15 mL (weight-based)	1 month	FSS
Sanoobar et al.	2015	Iran	45	Double-blind RCT	Coenzyme Q10	500 mg/day	3 months	FSS
Golabi et al.	2025	Iran	68	Double-blind RCT	Omega-3 fatty acids	1000 mg/day	3 months	MFIS
Achiron et al.	2014	Israel	158	Double-blind RCT	Alfacalcidol	1 µg/day	6 months	FIS (primary), MFIS
Bitarafan et al.	2016	Iran	101	Double-blind RCT	Vitamin A	25 000 IU/d (6 mo), then 10 000 IU/d (6 mo)	12 months	MFIS
Coe et al.	2019	UK	40	Double-blind RCT	High-flavonoid cocoa beverage	—	—	—
Ferorelli et al.	2021	Italy	50	RCT	Citozym® and Ergozym®	—	70 days	—
Zajicek et al.	2003	UK	424	Multicenter RCT	Cannabis extract	—	15 weeks	—

Meta-analysis of fatigue outcomes

Pooling of the eight eligible studies under a random-effects model showed that complementary interventions produced a statistically significant reduction in fatigue compared with the control groups (SMD = -1.44, 95% CI: -2.30 to -0.58, p=0.001; Figure 2). However, heterogeneity across studies was very high (I^2 = 93.7%). Inspection of study-level contributions identified Namjooyan et al. [13] as an influential outlier substantially driving the observed heterogeneity (Figure 3). A sensitivity analysis excluding this study reduced the number of pooled trials to seven; the pooled effect remained statistically significant (SMD = -0.61, 95% CI: -0.91 to -0.31, p = 0.001), and heterogeneity fell to a moderate level (I^2 = 49.9%). These findings indicate that, despite the disproportionate influence of one outlying study on between-study heterogeneity, the overall meta-analytic conclusion — a beneficial effect of complementary pharmacotherapy on fatigue — remained stable.

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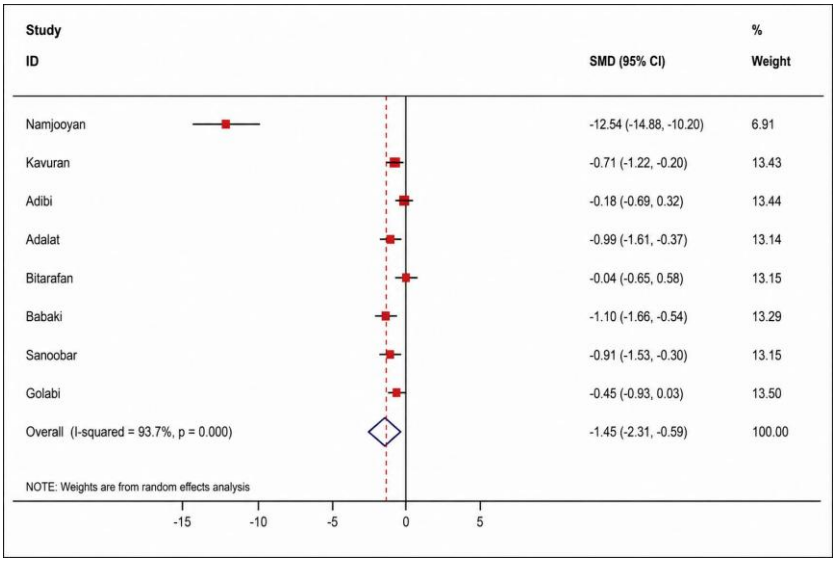


Figure 2. Forest plot of the pooled effect of complementary pharmacological therapy on fatigue in patients with MS

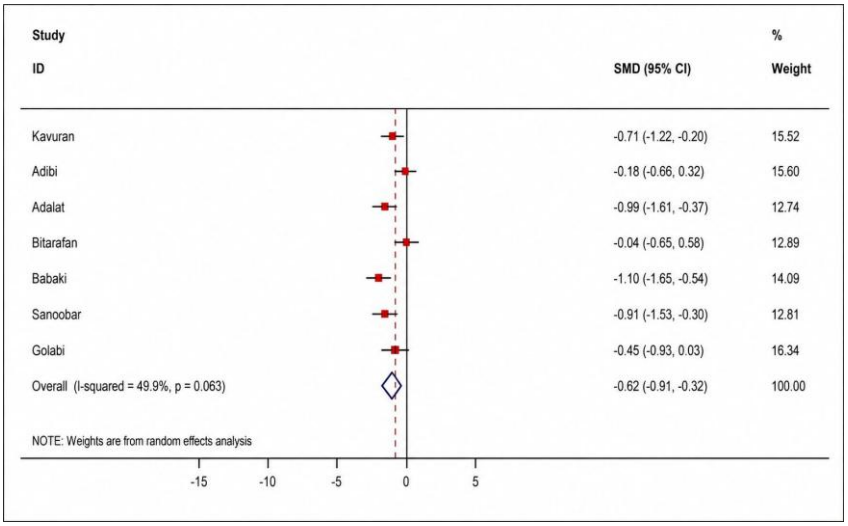


Figure 3. Sensitivity (leave-one-out) forest plot after exclusion of the outlying study

Publication bias

Visual inspection of the funnel plot showed that most studies fell within the hypothetical 95% confidence limits around the pooled effect, with a modest asymmetric clustering of studies toward more negative effect sizes on the left side of the plot (Figure 4); given the small number of included studies (fewer than 10), this pattern should be interpreted cautiously. Begg's test found no significant correlation between effect size and study variance (z = -1.05, p = 0.293), and Egger's regression test likewise showed no statistical evidence of small-study effects (intercept = -4.31, t=-0.77, p = 0.477). The trim-and-fill method did not identify or impute any missing studies, and pooled estimates were therefore unchanged after adjustment (fixed-effect model: -0.603, 95% CI: -0.811 to -0.395; random-effects model: -0.615, 95% CI: -0.911 to -0.319). The heterogeneity test in this restricted analysis was borderline (Q = 11.97, df = 6, p = 0.063; τ^2 = 0.079), consistent with moderate, non-significant heterogeneity. Overall, no clear evidence of publication bias was found, though the limited number of studies constrains the power of these tests.

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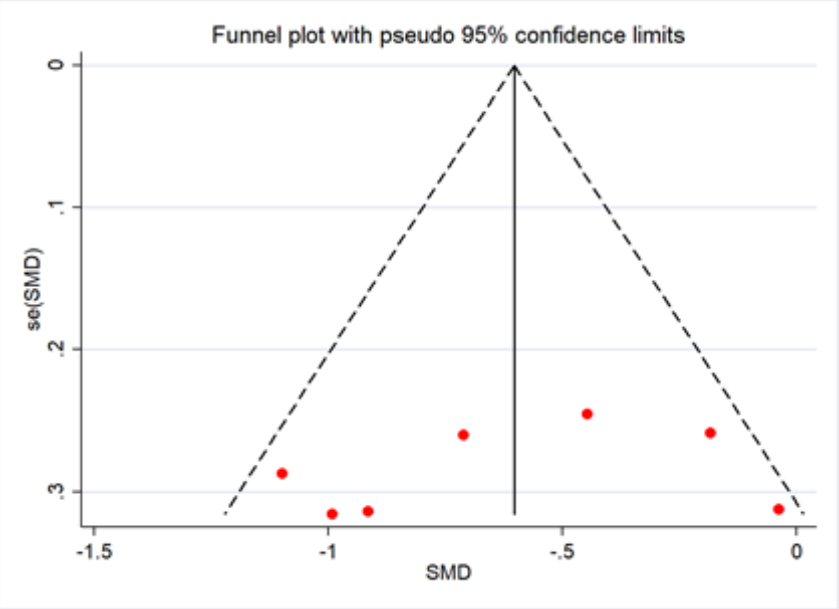


Figure 4. Funnel plot for assessment of publication bias

Methodological quality (risk of bias)

Risk-of-bias assessment of the eight pooled studies using the Cochrane RoB two tool showed generally favorable methodological quality, with some domain-specific heterogeneity. All eight studies (100%) were judged at low risk for random sequence generation, blinding of participants and personnel, and blinding of outcome assessment, reflecting robust intervention design. In contrast, allocation concealment was rated as low risk in only two studies (Babaki 202316 and Namjooyan 201913), with the remainder rated unclear or, in one case (Kavuran 202411), high risk. The most substantial quality concern was incomplete outcome data, where three studies (Adalat 2018,18 Babaki 2023,16 and Golabi 202514) were rated at high risk owing to attrition or incomplete reporting. For selective reporting and other potential sources of bias, more than 60% of studies were classified as unclear because of insufficient protocol registration or statistical transparency. Overall, while blinding-related methodological rigor was high, the results should be interpreted with attention to potential biases from incomplete outcome data and reporting (Figure 5 and Figure 6).

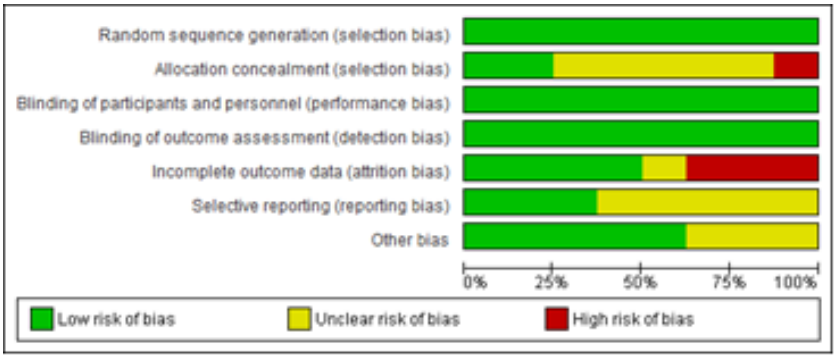


Figure 5. Risk-of-bias graph: review authors' judgments about each risk-of-bias item, presented as percentages across included studies

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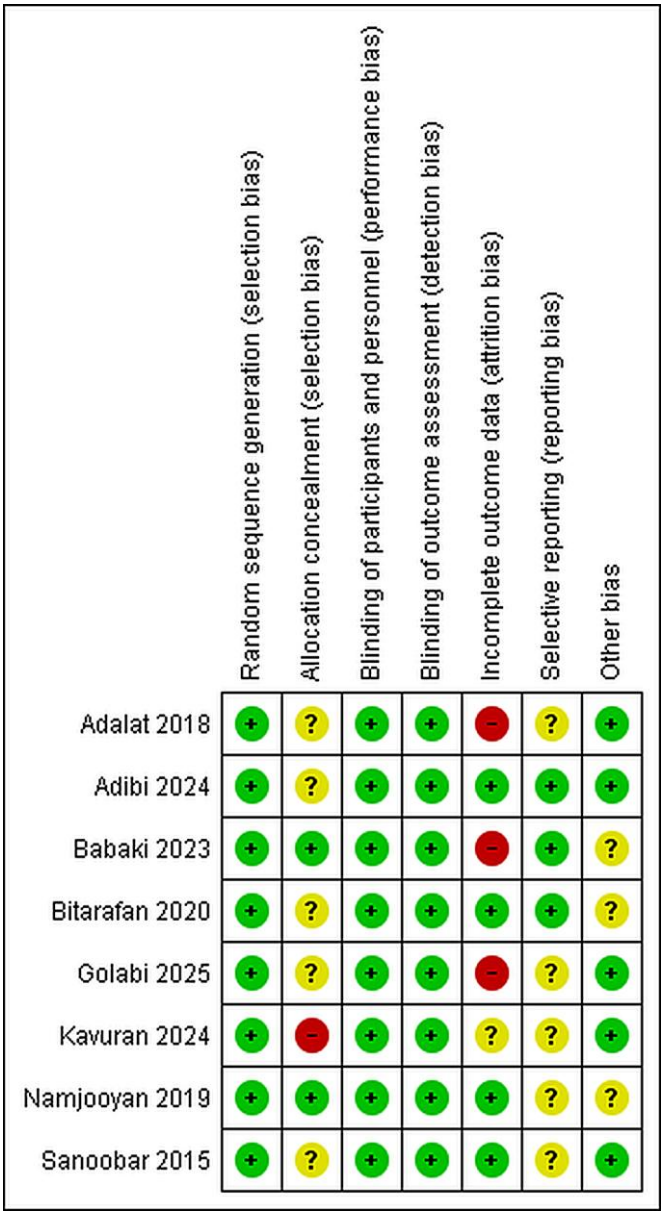


Figure 6. Risk-of-bias summary: review authors' judgments about each risk-of-bias item for each included study

Discussion

Fatigue is one of the most common and disabling symptoms among patients with MS, with a substantial impact on quality of life, daily functioning, and employment capacity. Systematic reviews have reported a prevalence ranging from 36.5% to 78%, and a recent meta-analysis estimated a global pooled prevalence of approximately 59.1% (2, 19). Fatigue has also been shown to be associated with reduced quality of life and impaired work capacity [19, 20], underscoring the clinical importance of identifying effective treatments.

The findings of this systematic review suggest that complementary pharmacological therapy may reduce fatigue in some patients with MS, although the current evidence remains insufficient for a definitive conclusion. In a review of published evidence on pharmacological and non-pharmacological treatments for MS-related fatigue, no single pharmacological intervention demonstrated consistently strong evidence of effectiveness [21]. This observation aligns with the present findings, which show that despite the evaluation of several agents, the reported effects varied considerably across studies.

Among the agents studied, amantadine has the longest track record. In a randomized, blinded trial by Tur et al., amantadine produced a significantly greater improvement in fatigue than placebo, while modafinil showed only a trend toward improvement

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and acetyl-L-carnitine showed limited, borderline findings [20]. However, subsequent studies have not consistently confirmed this effect, so amantadine cannot currently be recommended as a definitive, standard treatment for all patients [21].

Modafinil is another agent of interest for MS-related fatigue. In a recent systematic review and meta-analysis of controlled trials, modafinil reduced fatigue as measured by the MFIS compared with placebo, but was also associated with a higher rate of adverse events [22]. This suggests that although modafinil may benefit some patients, its risks and benefits should be weighed on an individual basis, with particular caution in patients more susceptible to side effects.

Evidence for acetyl-L-carnitine and related carnitine compounds remains limited and inconsistent. In the comparative trial noted above, this intervention's effect reached only the level of a trend and lacked adequate statistical or clinical power [23]. The role of these compounds in managing MS-related fatigue therefore remains unclear and warrants further investigation with more rigorous study designs.

An important consideration in interpreting these results is the methodological quality of the included studies. Risk-of-bias assessment with the Cochrane RoB 2 tool addressed domains including random sequence generation, allocation concealment, blinding, incomplete outcome data, and selective reporting [9, 10]. Similarly, reviews of modafinil have applied PRISMA and GRADE frameworks to assess reporting quality and the strength of evidence [22]. This underscores that valid conclusions about the effectiveness of complementary pharmacotherapy depend not only on the presence of a statistical effect, but also on methodological rigor and the overall certainty of the evidence.

Differences in dose, duration of intervention, disease severity, and fatigue-assessment instruments were among the main sources of heterogeneity across studies [21, 22]. This heterogeneity likely explains much of the observed variability in results and the difficulty of pooling evidence. Future studies should therefore be designed with larger sample sizes, standardized protocols, and consistent outcome measures to enable more precise treatment recommendations.

Limitations

A key limitation of this review was restricted access to the full text of some potentially eligible articles, owing to the unavailability of electronic versions or paywalled access to relevant publications; this issue could not be resolved through the university library service or by contacting study authors. In addition, the small number of pooled trials limited the statistical power of heterogeneity and publication bias analyses, and the substantial clinical heterogeneity in interventions, doses, and outcome instruments limits the precision and generalizability of the pooled estimate.

Overall, the findings of this review indicate that complementary pharmacological therapy may be beneficial for some patients with MS-related fatigue, but the current evidence is not yet sufficient to support a definitive, universal recommendation. Among the agents studied, amantadine and modafinil have the strongest evidentiary support, though both are still limited by inconsistencies in quality and reproducibility [22, 23]. Treatment decisions should therefore be individualized, taking into account fatigue severity, prior treatment response, and the likelihood of adverse effects.

Conclusion

This systematic review confirms that fatigue is a common, chronic, and disabling problem in patients with MS. Complementary pharmacological therapy may be effective for some patients, but the available evidence is not yet sufficiently robust or consistent. Among the agents examined, amantadine and modafinil have received the most research support, although findings regarding their effectiveness remain conflicting. Larger, more standardized clinical trials with lower risk of bias are needed before definitive treatment recommendations can be made.

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