REVIEW

Advances in management of sarcoidosis-associated fatigue: A narrative review

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ABSTRACT

Background and aim: Sarcoidosis-associated fatigue (SAF) occurs in approximately 30% to 90% of patients. While previous reviews examined select medications, these omitted nonpharmacological and emerging treatments that could significantly improve fatigue for individuals with sarcoidosis. Limited guidance exists for excluding alternative causes of fatigue and selecting between treatment options for these patients. This narrative review synthesized pharmacological and nonpharmacological interventions for SAF and interpreted evidence strength to guide clinical decision-making.
Methods: PubMed was queried in December 2025 for clinical trials, reviews, and meta-analyses published within the last 10 years. This yielded 41 results which were supplemented by manual review of bibliographies, clinical guidelines, and a search of the Cochrane Library. Evidence was interpreted and analyzed for quality using a modified GRADE-informed approach.
Results: Treatment of active disease with prednisone or methotrexate improves systemic inflammation but may paradoxically worsen fatigue with chronic use. Stimulants (e.g., dexmethylphenidate, armodafinil) display low-quality evidence for improving SAF and side effects may be prohibitive for some patients. TNF-α inhibitors (e.g., infliximab) have very low-quality evidence with few studies and negative findings. Pulmonary rehabilitation and exercise training show low-to-moderate quality evidence with few adverse effects but lack specific implementation protocols.
Conclusions: Diagnosis of SAF requires exclusion of alternative causes which may be challenging. Active disease should be treated appropriately while monitoring for adverse effects. Despite low-to-moderate quality evidence for most interventions, nonpharmacological approaches (e.g., pulmonary rehabilitation, exercise) are recommended as first-line therapy given favorable risk-benefit profiles. Larger, well-designed RCTs are needed given the substantial disease burden.

Key words: pulmonary sarcoidosis, sarcoidosis associated fatigue, treatment of sarcoidosis, exercise training, pulmonary rehabilitation

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Introduction

Sarcoidosis is a multisystem inflammatory condition characterized by granuloma formation, most commonly in the lung (1). Typical clinical presentations include cardiopulmonary symptoms such as dyspnea, chest pain, or a dry cough occurring in roughly 50% of symptomatic patients (2). Other affected organs may include the skin, eyes, heart, and the central nervous system. Constitutional symptoms like fatigue, fevers, or night sweats are common (1,2). Sarcoidosis-associated fatigue (SAF) is reported in approximately 30% to 90% of patients; this variation reflects differences in assessment methods and disease populations (3,4). No formal definition of SAF exists, but some advocate the Centers for Disease Control and Prevention definition of chronic fatigue syndrome, which is "a debilitating and complex disorder characterized by intense fatigue that is not improved by bed rest and that may be worsened by physical activity or mental exertion" (5). It is not always directly proportional to disease activity or objective measures such as pulmonary function testing or the 6-minute walk test (3). Patients often describe the fatigue as "frustrating, exhausting, [or] frightening," and as occurring with temporal phenotypes such as persistent, intermittent, early-morning, or afternoon-onset fatigue that may have implications for treatment (6,7). Evidence suggests a multifactorial etiology involving both inflammatory and noninflammatory mechanisms. Early observational studies demonstrated that those with SAF display statistically significant elevations in C-reactive protein and higher resting energy expenditures compared to non-fatigued controls (8). Tumor necrosis factor-α (TNF-α), an inflammatory cytokine linked to changes in the central nervous system, may influence fatigue, cognitive failure, and other common comorbidities such as sleep disorders (9). While associations between circulating biomarkers are inconsistent, these negative findings might reflect the variations in individual phenotype, disease activity, and use of non-uniform fatigue instruments rather than absence of inflammatory mechanisms (10–12). Recent studies show increased circulating mitochondrial DNA is associated with fatigue, which could be a future biomarker for guiding treatment (13). Significant overlap between comorbid conditions such as mood disorders, sleep-disordered breathing, restless legs syndrome, and physical deconditioning complicates diagnosis, treatment, and research of SAF (5,14,15). Depressive symptoms are recognized predictors of fatigue in sarcoidosis, with evidence suggesting a bidirectional relationship (16,17). Sleep disturbance occurs frequently and correlates well with fatigue, cognitive symptoms, and depression (18). Evidence from large cohort studies suggests widespread multisystem involvement, particularly of the nerves (i.e., small-fiber neuropathy), is a mediator of SAF associated with fatigue severity (16,17). In recognition of extensive symptom burden, there has been increased focus on patient-reported outcomes like fatigue in the sarcoidosis literature. Two review articles—one published in 2017 and the other in 2020—have attempted to provide an overview of SAF treatment. Atkins and Wilson conducted a manual database search in 2015 to identify publications describing SAF management and found 18 studies meeting their inclusion criteria with the final analysis including eight trials (19). The authors concluded the "evidence base for treating fatigue in sarcoidosis remains weak." Vis and colleagues reviewed pharmacological interventions through 2018, though this review omitted nonpharmacological interventions that are now recommended as first-line interventions for SAF (20,21). A recent position paper from the World Association of Sarcoidosis and Other Granulomatous Disorders argues for careful consideration before initiating glucocorticoids and frequent attempts to transition patients to steroid-sparing agents with fewer adverse effects (22). The exclusion of nonpharmacological interventions from some reviews is notable, as these approaches offer the advantage of minimal adverse effects compared to medications like glucocorticoids which may worsen fatigue. More broadly, guidance for clinicians managing SAF is incomplete (20,23). Society guidelines either do not thoroughly address the management of fatigue or highlight the limited evidence available to make recommendations (20,24). Further, SAF may be diagnosed and managed by general practitioners with less experience managing this condition while patients await evaluation by pulmonary medicine clinicians (25). Given the increasing incidence of sarcoidosis and the substantial burden of

SAF, this review synthesizes evidence for recent pharmacological and nonpharmacological interventions to provide clinicians with a practical management framework (26).

Methods

This targeted narrative review focused on recent SAF evidence. A search of PubMed and the Cochrane Library was performed to support thorough coverage of key interventions and recent trials, but the review did not follow a registered protocol or use full systematic-review methodology. PubMed was searched using the term: sarcoidosis [title] AND fatigue [title/abstract] AND (treatment [title/abstract] OR management [title/abstract] OR therapy [title/abstract] OR intervention [title/abstract]). The search was performed in December 2025 and included articles published within the last 10 years (2015-2025) to capture recent advances in pharmacological and nonpharmacological management. Clinical trials, meta-analyses, narrative reviews, and systematic reviews were eligible for inclusion. Articles were required to involve human subjects and be in English. The Cochrane Library was searched using the term "sarcoidosis" for articles within the last 10 years. All 41 PubMed results and 4 Cochrane Reviews were manually screened for eligibility by a single reviewer using broad inclusion criteria for a narrative review. Studies were included if they evaluated pharmacological or nonpharmacological interventions for SAF in adult patients and provided measurable fatigue outcomes. Clinical practice guidelines from major societies were also included. Of these, 25 studies met inclusion criteria, including 12 randomized controlled trials (RCTs) and 4 systematic reviews or meta-analyses. Review of the search results revealed that many foundational studies from before 2015, which still inform SAF pathophysiology, diagnosis, and management, were absent from the initial search. To ensure sufficient coverage while retaining the targeted narrative review format, pre-2015 literature was identified through bibliography review of key studies and guidelines. This approach located several additional articles including studies on fatigue phenotyping, instrument validation, descriptions of fatigue, and seminal randomized controlled trials on stimulants and TNF-α inhibitors, which were included in the review. Case reports, study protocols, or articles without focus on treatment interventions for SAF were excluded. Articles were reviewed for fatigue metrics such as the Fatigue Assessment Scale (FAS) or the Checklist Individual Strength (CIS-20). The FAS was the most frequently used instrument and includes a score range of 10 to 50 with higher scores indicating more significant fatigue (27). A narrative review approach was selected to allow for synthesis across the study designs due to inclusion of observational studies without fatigue as the primary endpoint and previously published systematic reviews. Given the heterogeneity of study designs and outcomes, a qualitative, modified, GRADE-informed approach was used to assess evidence strength based on study design, sample size, consistency of findings, and number of supporting trials (28). Evidence strength for each intervention was rated as high, moderate, low, or very low. Higher quality evidence required multiple RCTs with reliable positive findings, while lower quality data was limited to single small trials, observational studies, or mixed evidence for benefit.

Results

Pharmacological interventions

Stimulants

Methylphenidate (MPH) and armodafinil are stimulants commonly used to treat SAF. MPH increases dopamine in the basal ganglia, while armodafinil promotes wakefulness as an indirect dopamine receptor agonist (29–31). Early evidence for potential benefit included a double-blind, crossover RCT of dexmethylphenidate (d-MPH) in 10 sarcoidosis patients on systemic therapy that found statistically significant improvements in fatigue and median forced vital capacity (32). Similarly, four weeks of armodafinil treatment in an older double-blind crossover RCT significantly reduced fatigue measured with the FAS by a median of −4.5 ($p < .05$) compared to placebo (33). This improvement was independent of changes in sleep onset latency. However, MPH was

reassessed in a double-blind placebo-controlled RCT in patients with significant fatigue (FAS score ≥22), and those who received MPH had similar fatigue to the placebo group at the end of the intervention (29). Notably, this study was exploratory and not powered for clinical effect. No studies within the search window were located for modafinil or armodafinil. Small sample sizes and randomization difficulties are limitations of stimulant research (19,32,33). Adverse effects include cardiovascular conditions (e.g., arrhythmias, tachycardia, hypertension), hypersensitivity reactions (e.g., Stevens-Johnson syndrome, drug reaction with eosinophilia and systemic symptoms), anorexia, and risk of mania or psychosis (31,34). Although considerably more participants in trials of MPH developed adverse effects compared to placebo, they were generally mild and therapy was well tolerated (29). Clinicians should limit use in malnourished patients since some participants lost approximately 3 kg of weight (29). This side effect may be beneficial in patients with overweight or obesity since weight reduction may improve dyspnea and well-being (35). Patients should be monitored for hypertension, especially those with sleep-disordered breathing (36). Despite reassuring short-term (<1 year) data, research on long-term safety is needed, as both agents carry risks of dependence and abuse (20,31,34). Overall evidence quality is considered low based on limited RCTs with small sample sizes and conflicting results. Older trials show a reduction in FAS score from −4.5 to −6.6 points, while recent exploratory data on MPH found no benefit (29,32,33). The magnitude of effect in the positive studies is clinically relevant with improved fatigue often evident within 1 month without additional improvement thereafter and a potentially stronger benefit with d-MPH (33,37). Given low-quality evidence but quick onset of action, stimulants may be considered in patients requiring rapid fatigue reduction when fatigue is unrelated to active disease and can be quickly titrated (32). Patients with early-morning fatigue may be better candidates for stimulant therapy than those with the afternoon phenotype due to the duration of action and risk of insomnia (31). A guideline-endorsed 8-week trial in those with SAF unrelated to disease activity after consideration of exercise or rehabilitation programs is reasonable using d-MPH 2.5 mg to 5 mg twice daily (or extended-release d-MPH 10 mg once daily in the morning), or armodafinil 150 mg to 250 mg daily (20,31,34).

Glucocorticoids

Glucocorticoids reduce inflammation by inhibiting nuclear factor-κB, downregulating pro-inflammatory cytokines such as TNF-α, and shifting helper-T cells away from inflammatory subtypes (38–40). An open-label prospective study of 21 patients with symptomatic sarcoidosis found prednisone reduced fatigue at months one and three (41). While the reduction in FAS from baseline to month one exceeded the minimal clinically important difference (MCID), no statistically significant difference was found between month one and month three (37). Another study of 51 newly diagnosed treatment-naïve sarcoidosis patients demonstrated that while prednisolone showed statistically significant FAS reductions, especially in those with severe symptoms, others developed new or worsened fatigue, suggesting glucocorticoids may offer no additional benefit once active disease is controlled and have potential to increase fatigue (42). Two studies investigated alternatives with potentially fewer adverse effects. A recent double-blind RCT of 16 participants found 1 mg dexamethasone (equivalent to 6.67 mg of prednisone) may improve quality of life and fatigue among patients without an indication for active disease treatment (43). A second trial of 18 individuals found that repository corticotropin (i.e., ACTH) displayed statistically significant fatigue reduction with potentially fewer adverse effects than oral steroids (44). Adverse effects include adrenal insufficiency, gastrointestinal bleeding, reduced immunity, neuropsychiatric effects, and others (22,38). Weight gain is common and can lead to self-discontinuation (43,45). Patients on long-term therapy (≥3 months) require monitoring of weight, blood pressure, glucose, lipids, and osteoporosis risk (45). Prophylaxis against infections such as Pneumocystis jirovecii pneumonia is often advised when receiving ≥20 mg of prednisone daily for more than one month (46). Evidence for efficacy in SAF is considered moderate with multiple small RCTs and prospective studies showing generally positive findings. The magnitude of benefit frequently exceeds the

MCID with reduction in FAS and CIS scores of approximately −2.6 to −7.2 (FAS) and −18 to −27 (CIS) across different studies (41–44,47,48). Reduction in fatigue appears to be delayed, consistent with the intracellular mechanisms of action, with several months before significant benefits are observed. Recent guidance emphasizes that even low doses are associated with harm; most patients with SAF should not be treated with glucocorticoids due to adverse effects, with the potential for worsened fatigue often occurring as they are tapered (20,22). Patients should be transitioned to steroid-sparing agents within several weeks (22). Glucocorticoids should be reserved for brief courses (e.g., <4 weeks) and for treatment of active disease but may be used for patients with severe fatigue (FAS ≥35) also at low risk of adverse events (42,49). Low-dose dexamethasone may be an attractive option for patients transitioning off steroids due to its longer half-life and absent mineralocorticoid effects, though repository corticotropin should be limited given the high cost of therapy, route of administration, and limited benefit over traditional glucocorticoids (43,44,50).

TNF-α Inhibitors

Tumor necrosis factor-α (TNF-α) is a macrophage-produced inflammatory cytokine crucial to developing and maintaining granulomas (5). It is believed to mediate many sarcoidosis symptoms, including fatigue, and has been a therapeutic target for decades (1,51,52). Foundational studies of anti-TNF-α therapy showed a potential for improved fatigue and reduced everyday cognitive failure (53). Some pre-2015 non-randomized controlled trials found potential for improved fatigue; however, no recent data supporting TNF-α inhibition in SAF were published (54,55). Two observational studies assessed adalimumab in sarcoidosis. One found no significant effect on physical or mental quality of life questionnaire scores, while the other study found evidence for a modest statistically significant reduction in fatigue (51,56). Notably, the latter initiated adalimumab therapy while simultaneously tapering the participants' adjunctive therapy with prednisone and methotrexate, potentially confounding the results. There is very low-quality evidence supporting use of TNF-α inhibitors in SAF limited to small observational studies with conflicting results and no recent RCTs. The magnitude of reduction in FAS score is likely from −2.6 to −4.9 with any potential benefits likely to occur within 6 months (51,53,56). Key considerations include increased risk of infection, mandatory screening for tuberculosis, and high cost, though infliximab biosimilars are now available (57,58). Use of anti-TNF-α therapy is not likely to achieve clinical fatigue reduction without the presence of active disease, and monotherapy for fatigue should generally be avoided (20,21,59). These agents should be reserved for patients with active disease-related fatigue requiring steroid-sparing therapy (60).

Methotrexate and azathioprine

Methotrexate (MTX), a reversible inhibitor of dihydrofolate reductase, leads to impaired purine and pyrimidine nucleotide synthesis (61). MTX has experienced increasing interest as a potential first-line therapy for active sarcoidosis (22). The open-label, multicenter PREDMETH trial included 138 patients and compared MTX against prednisone demonstrating a −1.6 reduction in FAS score with MTX (62). *Post hoc* analysis revealed the prednisone group had a more rapid and greater reduction in FAS score by week four, but the difference compared to MTX was non-significant. MTX presents a paradox in use for SAF due to a potential for improved or worsened fatigue. The RCT found a potential for reduced fatigue though reporting of adverse effects noted more fatigue reported in the MTX group (26%) compared to the steroid group (10%). Theories regarding how MTX might induce fatigue are varied, but disruptions in cellular energy metabolism via the homocysteine-methionine-polyamine pathway, which may be modulated by folic acid supplementation, have been described (63). Azathioprine (AZA) has a similar mechanism and can be as effective as MTX in sarcoidosis; however, no studies investigating its use in SAF were available (20,64). Side effects are generally mild at lower doses and include malaise, rash, abnormal liver function tests, and a minor predisposition to infections (61). Mucosal ulcers and gastrointestinal effects can be reduced with concurrent use of folic acid (61,63). Subcutaneous formulations are preferred due to greater efficacy and lower risk of

gastrointestinal side effects (30). While liver injury is often discussed, it is rarer than previously thought and is less common than liver abnormalities caused by glucocorticoids (30). MTX shows moderate quality evidence for use in SAF based on a single, well-designed RCT, with magnitude of FAS reduction of −1.6 that did not exceed the MCID (62). There is likely a slower onset of potential benefit for fatigue than with glucocorticoids. A concern with use for SAF is that fatigue might worsen in certain individuals with present evidence showing 26% of MTX-treated patients displayed fatigue compared to 10% of those on prednisone. Potential for inducing fatigue is likely more significant than classical adverse effects such as hepatotoxicity, which is less common than previously thought (62,65). MTX should be considered for treatment of active disease and for SAF in patients currently receiving glucocorticoid therapy where it may reduce steroid side effects and improve glucocorticoid-mediated fatigue (22). In isolated SAF without active disease, it should be initiated with caution due to potentially worsened fatigue. AZA may be considered when MTX is not tolerated, or in pregnant individuals (MTX is teratogenic). Monitoring of a complete blood count and liver function tests is advised when starting therapy, though annual laboratory testing shows similar safety to more intensive monitoring (e.g., every three months) (65).

Emerging pharmacological approaches

Efzofitimod (ATYR1923) is an investigational fusion protein that selectively inhibits neuropilin-2 (NRP2), a receptor primarily found on monocytes, macrophages, and dendritic cells (66). NRP2 is upregulated in inflammatory states and is believed to play a role in granuloma formation, supporting its possible use in sarcoidosis (66,67). A double-blind phase 1b/2a RCT showed that efzofitimod improved quality of life and reduced FAS scores at 24 weeks (adjusted mean −7.77, p = .010), which exceeded the MCID (67). Despite promising initial results, a multicenter phase III trial of 268 participants, which has not yet undergone formal peer review, failed to reach the primary endpoint for glucocorticoid reduction (68). The path forward for the drug is unclear until publication of final data, though future studies might further investigate its use for improving quality of life and fatigue due to preliminary signals reported in topline data (69). Quality of evidence is very low for SAF, and it remains investigational. Hydroxychloroquine (HCQ) is an immunomodulator with mild side effects compared to other agents (70). A pre-2015 prospective longitudinal follow-up study noted patients being treated with HCQ had lower FAS scores than patients treated with alternative agents despite no differences between the groups in stage or disease activity (71). The magnitude of FAS reduction was −3.5 (p = .003), though evidence quality is very low. HCQ is safe in pregnancy, does not appear to cause significant fatigue, and could be considered as a steroid-sparing agent for SAF with shared decision making (70,72). Transdermal nicotine patches were evaluated in a small pilot RCT, though with very low-quality evidence, and the reduction in FAS score was not statistically significant (73). Clinician and patient acceptance of this intervention is likely poor and transdermal nicotine is not recommended. Table 1 provides a summary of trials evaluating pharmacological interventions published from 2020-2025.

Nonpharmacological interventions

Pulmonary rehabilitation

Pulmonary rehabilitation (PR) is frequently recommended as an effective treatment for sarcoidosis-associated fatigue (20). A Cochrane systematic review located four studies that included sarcoidosis patients and found a general trend for improved dyspnea and fatigue that may be generalized to SAF (74). A 2023 meta-analysis of four sarcoidosis studies revealed a trend toward fatigue reduction, but no overall difference between the intervention and control groups, with low strength of evidence (75). However, a pre-post study of 41 patients enrolled in a four-week inpatient rehabilitation program not included in the prior meta-analysis noted a statistically significant decrease (FAS score −1.7 ± 3.9; p = .009) in fatigue (76). Outside of sarcoidosis, other studies support that shorter exercise programs may have benefit in chronic illness (77). Strength of evidence is low to moderate with mixed positive and negative findings with magnitude of FAS decrease of approximately −1.7 to −6.7 points

Table 1. Recent Evidence (2020-2025) for Pharmacological Interventions for Sarcoidosis-Associated Fatigue

Intervention	Study	Design	Key Findings	Implications
Methylphenidate	Atkins 2021 (29)	Exploratory RCT (n = 23)	No significant difference vs. placebo; tolerability concerns	Larger trials needed; caution in those with CV disease; weight loss less problematic in co-morbid obesity; controlled substance
Dexamethasone	Vis 2020 (43)	RCT (n = 16)	1 mg daily improved FAS over 12 months	Good response at 3 months; low-dose option; weight gain for some
Methotrexate	Kahlmann 2025 (62)	RCT (n = 138)	Non-inferior to prednisone for FAS reduction by week 24; slower onset	First RCT evidence; steroid-sparing option but fatigue as possible side effect (26%)
Efzofitimod	Culver 2023 (67) Non-peer reviewed data 2025 (69)	Phase 2 RCT (n = 37) Phase 3 RCT (n = 268)	Phase 2: improved QoL and reduced FAS at 24 weeks vs. placebo Phase 3: non-peer reviewed; failed primary endpoint	Investigational; Phase 3 RCT not yet published, efficacy for fatigue is unproven
Transdermal nicotine	Crouser 2021 (73)	Pilot RCT (n = 16)	FAS improved, but not significant	Preliminary evidence not encouraging

Abbreviations: RCT: randomized controlled trial; CV: cardiovascular; FAS: Fatigue Assessment Scale; MCID: minimal clinically important difference; QoL: quality of life

with wide variability reflecting heterogeneity in patient populations and program designs (75,76,78). PR is generally safe with other benefits beyond fatigue (e.g., reduced dyspnea, improved cardiovascular fitness), supporting its recommendation for most patients with SAF (74,79). Patients with fatigue mediated by deconditioning or dyspnea are excellent candidates for referral. It is possible that pharmacological therapy for SAF may improve engagement in PR due to enhanced exercise capacity. Those who participate in rehabilitation may then be able to engage more fully in physical activity in the future, leading to continued reduction in long-term fatigue (80). Shared decision making should be utilized extensively when prescribing PR to ensure patient adherence.

Exercise, resistance, and inspiratory muscle training

Like PR, structured exercise programs are often recommended to patients. An RCT of 18 participants found that a 12-week structured exercise course dramatically improved quality of life and fatigue (change in FAS –7.0 points; $p = .001$) (81). Exercise programs demonstrate benefit across a wide range of patients, such as those above the age of 50 or with obesity, with a recent study of 26 individuals showing that one-legged or two-legged cycling both improved fatigue with no difference between the two groups (82). A crossover study of 41 participants found no significant difference in fatigue between vigorous and moderate-intensity resistance training at 24 hours following a single session, suggesting neither intensity offers acute advantage over the other (23). Although data are limited, inspiratory muscle training may improve severe fatigue with one RCT showing a strong and statistically significant mean reduction in Fatigue Severity Scale score of –8.0 ($p = .01$) (83). Studies of exercise training in sarcoidosis support meaningful reductions in fatigue with overall moderate quality evidence. Exercise training should be recommended to all patients with SAF, particularly deconditioned individuals, with data showing clinically relevant and statistically significant reductions in fatigue instrument scores from –2.7 to –8.0 points across various modalities (81–84). Moreover, exercise training programs and PR are safe for patients with sarcoidosis with few absolute contraindications (23,79). Prescribing physical activity

for SAF can be more complex than initiating pharmacological therapy since recommendations for specific implementation protocols are elusive, though many studies found benefit with one-hour sessions two to three times per week similar to general population recommendations (79,85). A single session of resistance exercise (e.g., 2 sets with a 25-repetition maximum), or more vigorous intensity if preferred, both appear reasonable to recommend and high-intensity exercise need not be avoided (77,82). Inspiratory muscle training may specifically be considered in those with muscular weakness or small-fiber neuropathy, severe fatigue, or early disease stage, though this is preliminary (83). Patients should be counseled that consistent, frequent bouts of activity throughout the week appear more important than the type or duration of activity, as benefits from a single bout may rapidly diminish (23,86,87). Nonpharmacological interventions, specifically PR, exercise training, and inspiratory muscle strength training, are guideline recommended for 6–12 weeks, which remains reasonable despite some negative data (20).

Other nonpharmacological interventions

Wearable activity trackers increase physical activity time and improve cardiometabolic health in chronic diseases (88). A cohort study of 54 sarcoidosis patients revealed statistically significant FAS reduction, with nearly half (42%) reporting increased self-management insight (89). Mobile health (mHealth) interventions such as the Sarcoidosis Patient Resource and Companion (SPARC) App, which promotes breathing awareness, meditation, and self-efficacy, displayed improved fatigue and stress levels at month six in a pilot RCT of 50 fatigued patients, although adherence was lower than expected (90). Mindfulness-based cognitive therapy was evaluated in a prospective, multicenter, open-label RCT (TIRED) of 99 participants and found significantly reduced fatigue (FAS −4.53; $p < .0001$) after the 12-week online intervention with statistically significant improvements in anxiety and depression (91). Evidence quality for emerging nonpharmacological interventions in reducing fatigue ranges from very low (activity trackers) to low (SPARC) to moderate (mindfulness-based cognitive therapy). However, the magnitude of potential benefit is encouraging with clinically relevant reductions in FAS scores in both TIRED and SPARC trials (FAS −4.53 to −5.9 points, respectively). Table 2 provides a summary of common nonpharmacological interventions. These approaches, particularly mHealth, may better engage patients with SAF in therapy, reduce healthcare disparities for sarcoidosis patients, and improve perceived fatigue with lower costs and risks than alternative therapies (92). Mindfulness-based cognitive therapy should be recommended to those with psychological comorbidities given moderate quality evidence for potential improvement in mood (91). While mHealth interventions like SPARC and wearable activity trackers have strong potential for patient engagement and self-management, more rigorous data are needed to ensure patient tolerability and adherence to therapy before formally recommending these programs.

Approach to management

Once sarcoidosis-associated fatigue is suspected, a search for other causes should be conducted using the history, physical exam, and laboratory studies. Since fatigue is a common outpatient complaint with a broad differential, it is reasonable to keep the search for other causes focused in this population given the high prevalence of SAF while maintaining clinical suspicion for alternative causes. The clinician should evaluate for pain, sleep disturbance, neurocognitive symptoms, mood, and exacerbation of symptoms during exertion (93). Healthcare professionals should assess for associated conditions such as hypercalcemia (from increased 1-α hydroxylase within macrophages), hematologic disorders (e.g., malignancy, anemia), autoimmune diseases (e.g., Lupus, Sjögren's, vasculitis), hypothyroidism, medication side effects (e.g., prednisone), and neurologic or mood disorders (94,95). Reasonable testing includes thyroid-stimulating hormone, free thyroxine, complete blood count, and a comprehensive metabolic panel with additional testing (e.g., iron studies, vitamin B12, homocysteine, methylmalonic acid, neuroimaging, autoantibodies) based on clinical suspicion (93,94). Sleep-disordered breathing, particularly obstructive sleep apnea, is highly

Table 2. Major Nonpharmacological Interventions in Sarcoidosis-Associated Fatigue

Intervention	Key Evidence	Evidence Quality	Effect on Fatigue	Implementation
Pulmonary Rehabilitation	Alsina-Restoy 2023 meta-analysis (4 studies) (75); Grongstad 2020 pre-post (n = 41) (76)	Low - Moderate	Trend toward benefit non-significant; reduced dyspnea; other 4-week study significant	8-12 weeks, 2-3x/week; possibly more benefit as inpatient; modifications for sarcoidosis patients may be required
Exercise Training	Naz 2018 RCT (n = 18) (81); Tahmaz 2025 RCT (n = 26) (82); Strookappe 2016 (multiple studies) (79)	Moderate	Statistically significant reductions and can prevent further worsening	Supervised 8–12-week exercise programs, 2-3x/week; either vigorous or moderate intensity acceptable
Resistance Training	Grongstad 2020 cross-over (n = 41) (23)	Very low	No significant difference at 24 hours with either vigorous or moderate intensity; both equally tolerated	High-intensity (3–5 rep max) as single sessions
Inspiratory Muscle Training	Karadalli 2016 RCT (n = 30) (83)	Low	Significant reduction in severe fatigue; no benefit for quality of life	Pressure threshold-loading device training, 30 min daily for 6 weeks
Mindfulness-Based Cognitive Therapy	Kahlmann 2023 RCT (n = 99) (91)	Moderate	Significant reduction in fatigue, anxiety, depression	12-week program; mindfulness ~30 min x 6-7 day/week; education and diary

Abbreviations: RCT: randomized controlled trial; FAS: Fatigue Assessment Scale

prevalent in sarcoidosis and should be excluded before diagnosing SAF. The STOP-BANG (Snoring, Tired, Observed, Pressure, Body mass index, Age, Neck size, Gender) questionnaire may be used for screening (93). If pharmacological therapy is elected, armodafinil has evidence for use in these patients (33). Glucocorticoids and other substances (e.g., sedating medications, alcohol) may worsen sleep disturbance (15). Question-based screening tools such as the Fatigue Assessment Scale (FAS) should be used at diagnosis and at least annually to screen for SAF, or sooner after an intervention to monitor efficacy. Prior research shows FAS score ≥22 is suggestive of mild-moderate fatigue, and a score ≥35 is severe fatigue (27,37,96). It is reasonable to repeat the FAS after beginning an intervention to track progress, with a mean difference of four points denoting a clinically significant change in fatigue (37,96). A patient's fatigue phenotype (e.g., early-morning, persistent) should be assessed during the clinical evaluation (7). Patients with different SAF phenotypes are likely to respond differently to both medication and nonpharmacological therapies. Some data suggest the early-morning fatigue phenotype may signal an underlying mood disorder or circadian dysregulation that could respond better to stimulant therapy dosed between 6 AM and 7 AM and might be less responsive to anti-inflammatory therapy (97). The Patient Health Questionnaire-9 may be used to screen for depressive symptoms (93). Patients with persistent, chronic fatigue should be closely evaluated for active disease and recommended exercise, physical activity, and mindfulness-based interventions. Lifestyle factors and iatrogenic causes of fatigue should be assessed. Medication reconciliation and a social history should especially be performed for apparent treatment-resistant or unexplained fatigue (93). Tobacco use should be assessed at every visit, and patients should be offered psychological and social support resources with pharmacological therapy (85). Tobacco has been shown to induce fatigue and result in reduced effectiveness of anti-TNF-α therapy, which may cause premature drug discontinuation (98,99). Monitoring the patient for worsening fatigue and medication adverse effects is critical. Medications frequently used for sarcoidosis

(e.g., prednisone, methotrexate) or other conditions (e.g., antidepressants, antihistamines, gabapentinoids, or opioids) may induce fatigue during use or during withdrawal of therapy, and differences in drug metabolism in sarcoidosis may contribute (93,100). After diagnosis and exclusion of alternative etiologies, a stepwise approach to management (Figure 1) is advised. Active disease should be treated with glucocorticoids or methotrexate (20,62). Treatment of active disease appears to improve fatigue within 1 month, though high-dose therapy beyond this may risk worsening symptoms. Glucocorticoids should be aggressively restricted to the lowest dose and duration possible (22). Low doses, such as prednisone 20 mg daily (or lower), are noninferior to higher doses for improving quality of life and do so with significantly fewer side effects, though even small doses of glucocorticoids should be avoided, if possible, with rapid tapering in most patients (22,47). Nonpharmacological approaches should be considered early given low risks and moderate quality evidence. However, current physical activity, exercise training, and pulmonary rehabilitation approaches are likely not optimized for patients with SAF and borrow from the chronic obstructive pulmonary disease literature (101). Healthcare professionals involved in therapy can adapt general principles such as close monitoring of patients with severe dyspnea, consideration of interval training, education regarding the benefits of rehabilitation programs, and maintaining availability of supplemental oxygen if needed. Patients with SAF may benefit from more aggressive self-pacing and coaching during a program (101). Fatigue should be assessed using the FAS (or similar instrument) before beginning a program and approximately 6–12 weeks after to document response and guide escalation if no improvement is seen. Modification of therapy will likely be required to accommodate those with SAF, especially to aid with symptoms of muscle weakness, joint pain, stiffness, or neuropathy (79). For those with persistent or severe symptoms (e.g., FAS ≥35, or as determined by clinical evaluation), a combination approach with exercise training and/or pulmonary rehabilitation coupled with

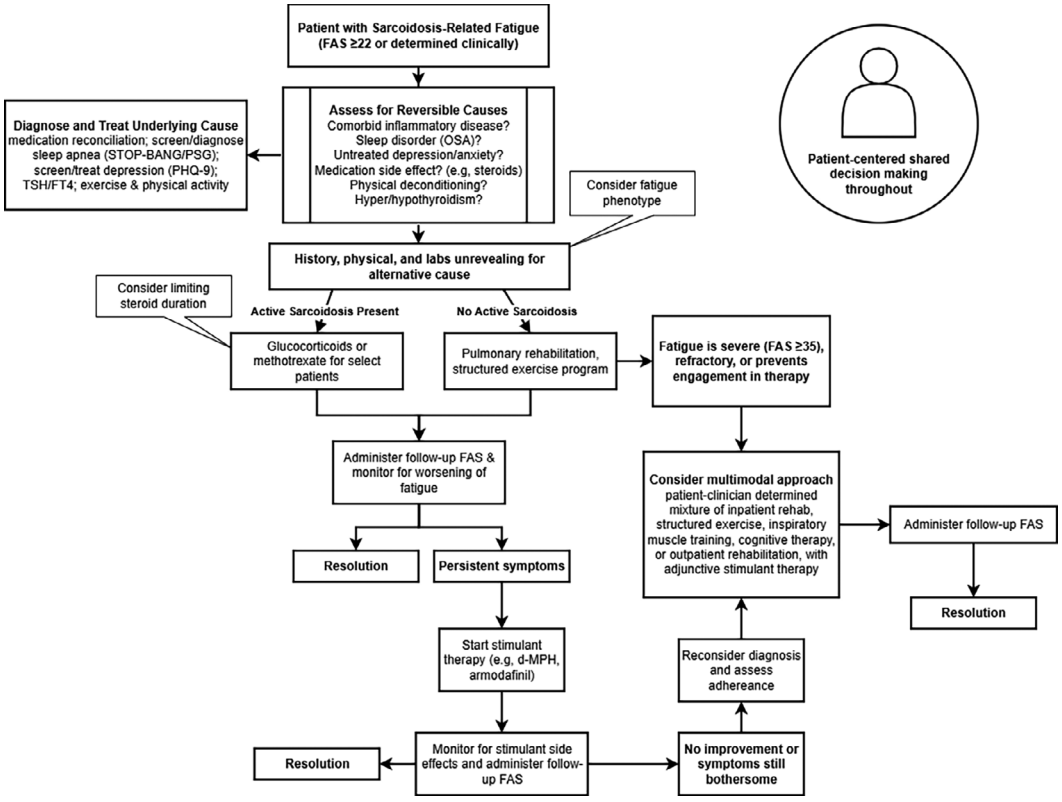

Figure 1. Suggested Approach for Sarcoidosis-Associated Fatigue Treatment.

stimulant therapy may be beneficial in select patients given low overall harm and potential to improve engagement in therapy. Continuation or worsening of fatigue despite interventions should prompt a "diagnostic time-out" and reassessment of alternative causes.

Initial evaluation of SAF focuses on patient assessment and exclusion of alternative causes, such as iatrogenic factors. Treatment selection should be individualized based on fatigue phenotype, disease activity, and patient preferences. *Abbreviations:* FAS: Fatigue Assessment Scale; OSA: obstructive sleep apnea; PSG: polysomnography; TSH/FT4: Thyroid Stimulating Hormone and Free Thyroxine; d-MPH: Dexmethylphenidate; STOP-BANG: STOP-BANG Questionnaire; PHQ-9: Patient Health Questionnaire-9.

Discussion

Fatigue affects up to 90% of sarcoidosis patients and may not mirror systemic disease activity (4). Despite research into new therapies for active disease, less attention has been devoted to treating sarcoidosis-associated fatigue (SAF). This article updates older reviews with additional focus on emerging therapeutics, nonpharmacological treatment, and treatment selection. Several years after prior reviews on this topic, there remains limited conclusive evidence for most treatments prescribed for SAF. In 2017, Atkins and Wilson published a review synthesizing the available evidence on SAF, including two randomized controlled trials on stimulant therapy and two non-randomized studies assessing TNF-α inhibitors (19). Since the 2020 update by Vis and colleagues, one new study was neutral on the use of d-MPH, and none have assessed use of modafinil, armodafinil, or TNF-α inhibitors. Current theories support a multifactorial pathophysiology involving inflammatory and noninflammatory causes including the innate and adaptive immune response, sleep-disordered breathing, mood disorders, drug side effects, and medical comorbidities. Although inconsistently elevated, the absence of inflammatory or disease activity biomarkers (e.g., C-reactive protein, angiotensin-converting enzyme, soluble interleukin-2 receptor) does not refute an inflammatory etiology for SAF due to the multiple mechanisms involved (102,103). While targeting TNF-α-mediated neuroinflammation provides a foundation for possible benefit, studies thus far demonstrate very low-quality evidence for SAF. Emerging biomarkers such as mitochondrial DNA support a more complex role of the immune system in SAF than previously understood and may guide future treatment (13). Among pharmacological options, stimulants have the most consistent RCT evidence for disease-unrelated fatigue, while TNF-α inhibitors show evidence primarily for disease-specific fatigue. Armodafinil also has multiple studies over a one-year period supporting a good safety profile, assuming monitoring for cardiovascular effects, undesired weight loss, and insomnia (36,104). Studies of newer stimulants (e.g., lisdexamfetamine) are needed since they may be more effective with similar, or improved, tolerability compared to current agents (105). While safety data supporting long-term stimulant use in the sarcoidosis population is sparse, long-term studies in other populations suggest good safety profiles assuming monitoring for cardiovascular side effects (106). Recent studies emphasize limiting the risk of adverse effects of treatment (22). Patients and healthcare professionals should frequently reconsider use of glucocorticoids for SAF due to the potential for worsened fatigue and adverse effects. Complete steroid withdrawal with transition to alternative medications, or inclusion of a second steroid-sparing agent to facilitate dose reduction, is highly encouraged. Nonpharmacological approaches, especially pulmonary rehabilitation, have demonstrated safety but still lack robust data for fatigue reduction, which may be explained by study duration, heterogeneity in behavioral interventions, and reduced ability for participants to engage in therapy if meaningfully fatigued. Given the limited risks and potential for benefit, pulmonary rehabilitation, exercise training, and mindfulness-based interventions should be considered for every patient with SAF. Patients with comorbid insomnia should promptly be considered for exercise interventions (107). As a targeted narrative review, this study has several limitations. The focused search strategy, utilizing PubMed and the Cochrane Library, was limited in scope and may have missed relevant studies in other databases. More broadly, conclusions are constrained by the relatively small number and size of interventional RCTs for SAF. Although important,

many studies focused on treatment of active disease or quality of life measures, and did not thoroughly report fatigue, making it difficult to draw firm conclusions. Sarcoidosis and associated patient-reported outcomes remain understudied and publication bias favoring positive studies cannot be excluded. Evidence strength was interpreted using a GRADE-like approach to enhance evidence-based clinical application, and this should not be equated to formal guideline-based recommendations. Despite limited RCT evidence, clinicians should consider how fatigue phenotypes and biological mechanisms may impact treatment. Treatment with stimulants might be more beneficial in patients with early-morning or intermittent fatigue with lower potential for adverse effects like insomnia in those populations, while immunomodulatory agents may be preferred in patients with co-existing insomnia. Pharmacogenomic testing will likely have a greater role in the future as clinicians reduce use of glucocorticoids and transition to steroid-sparing alternatives (100). Study of the biological mechanisms mediating SAF is critical in establishing the basic science background for drug development and objective diagnostic criteria. Research on the optimal mode, duration, and intensity of physical activity is needed to effectively guide exercise prescription. Head-to-head stimulant trials (e.g., MPH vs. armodafinil vs. newer agents) would provide valuable prescriber data. Longer follow-up durations with higher sample sizes are crucial given the brief nature of pharmacological studies for SAF. Efzofitimod or HCQ may have promise for SAF according to preliminary findings but require publication of rigorous trials to fully assess any potential indications. Trials comparing experimental agents to more established medications such as MPH and armodafinil will be required to justify the probable higher cost of new therapeutics. Given the multidimensional and often chronic challenges faced by patients with sarcoidosis, particularly SAF, an integrated, multidisciplinary approach delivering personalized, patient-centered care is essential, as standardized management strategies are insufficient to address these complex needs.

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