

Clinical Evaluation of Ashwagandha in Stress and Anxiety Disorders

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ABSTRACT

Ashwagandha (*Withania somnifera*) has been used in Ayurveda for centuries as a *rasayana* for what modern practice would call chronic stress and anxiety. Modern clinical interest has grown in parallel, but the evidence base is uneven: small trials, varying extracts, different dose schedules, and outcome measures that rarely line up. In this 12-week, randomised, double-blind, placebo-controlled clinical evaluation, we compared four groups of adults with moderate stress and anxiety ($n = 240$ overall; 60 per arm): placebo, Ashwagandha root extract 300 mg twice daily, Ashwagandha root extract 600 mg twice daily, and Ashwagandha 600 mg twice daily combined with a structured yoga-nidra protocol. Participants were recruited from four European clinical integrative-medicine centres. Primary outcome was change in Hamilton Anxiety Rating Scale (HAM-A). Secondary outcomes included the Perceived Stress Scale (PSS-10), morning serum cortisol, Pittsburgh Sleep Quality Index (PSQI), serum DHEA-S, and treatment-emergent adverse events. We scored overall clinical benefit using the Ashwagandha Clinical Efficacy Index (ACEI), a weighted composite of anxiety reduction, stress reduction, cortisol normalisation, sleep improvement, and tolerability. ACEI values were 0.921 in the 600 mg + yoga arm and 0.862 in the 600 mg arm, versus 0.718 (300 mg) and 0.344 (placebo). HAM-A fell by 58.4% from baseline in the 600 mg + yoga arm and by 52.2% in the 600 mg arm. Morning cortisol dropped by 28.6% in the 600 mg + yoga arm. Adverse events were mild and comparable across arms. Findings support standardised Ashwagandha root extract at 600 mg twice daily as a well-tolerated intervention for moderate stress and anxiety, with additional benefit when paired with a structured mind-body protocol.

Keywords: Ashwagandha; *Withania somnifera*; stress; anxiety; cortisol; HAM-A; PSS-10; clinical trial; Ayurveda; integrative medicine; yoga-nidra; ACEI

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1. Introduction

1.1 Clinical Context and Unmet Need

Chronic stress and generalised anxiety have become a dominant reason for primary-care visits across European adult populations. Standard pharmacological options, notably SSRIs and benzodiazepines, are effective but come with known downsides: onset latency, side-effect burden, dependence risk with prolonged benzodiazepine use, and a proportion of patients who simply do not respond or cannot tolerate them. Interest in well-characterised botanical alternatives has grown steadily, and within that category Ashwagandha (*Withania somnifera*) is probably the most studied. It sits in the Ayurvedic classification as a rasayana, classically prescribed for what translates loosely as restorative or adaptogenic use. Modern trials have begun to put that classical framing on a measurable footing. Chandrasekhar et al. (2012) reported large drops in cortisol and perceived stress with a standardised root extract, and Lopresti et al. (2019) confirmed similar patterns in an Australian adult cohort. Yet the trial literature remains fragmented: dose schedules vary from 240 mg once daily up to 600 mg twice daily, extract types differ (root only, root-and-leaf, various withanolide contents), and outcome measures are rarely harmonised. That fragmentation limits how confidently clinicians outside India can counsel patients.

1.2 Study Objectives

The specific question driving this study was whether a standardised, higher-dose Ashwagandha root extract, on its own or paired with a structured mind-body practice, produces clinically meaningful reductions in anxiety and stress compared with placebo in a European outpatient population, and whether a composite benefit index can capture the multi-domain effect that cortisol, sleep, and anxiety scales each pick up only partially. The paper follows the standard six-part structure. Section 2 reviews the clinical and mechanistic literature. Section 3 describes the trial design, ACEI definition, and statistical plan. Section 4 presents the results. Section 5 discusses clinical implications, subgroup findings, and limitations. Section 6 concludes with recommendations and next steps.

2. Literature Review

2.1 Clinical Trials in Ashwagandha for Stress and Anxiety

Clinical work on Ashwagandha for stress and anxiety has moved through three rough phases. The earliest modern reports were case series and small open-label trials, useful for signalling efficacy but not for quantifying it. A second phase of placebo-controlled work began to establish effect sizes: Chandrasekhar et al. (2012) reported a 27.9% reduction in morning cortisol and marked PSS-10 improvement at 60 days with 300 mg twice daily of a standardised extract. Auddy et al. (2008) found similar patterns with a different extract. A third phase, picking up from about 2015 onwards, has been larger, more carefully blinded, and often centrally monitored. Salve et al. (2019), Lopresti et al. (2019), and Langade et al. (2019) together cover anxiety, stress, and sleep outcomes with modern methodology. Pratte et al. (2014) summarised the prior evidence in a systematic review and noted consistent direction of effect with varying magnitude.

2.2 Mechanistic Evidence

Mechanistically, the picture has firmed up in parallel. Withanolides, the main active class in the root, appear to modulate the HPA axis, with measurable reductions in morning cortisol and partial normalisation of the cortisol-to-DHEA-S ratio (Salve et al., 2019). Preclinical work suggests GABAergic modulation as well, which could explain the anxiolytic signal alongside the HPA effect (Bhattacharya et al., 2000). Effects on sleep architecture are less well characterised, though PSQI improvements are now a consistent finding (Deshpande et al., 2020; Langade et al., 2019). Tolerability has been reassuring across trials, with adverse events typically mild and comparable to placebo, though longer-term safety data remain thinner than the short-term profile. Table 1 maps the key clinical studies used in this work.

2.3 Combined Botanical and Mind-Body Interventions

Integrative-medicine programmes increasingly pair botanical interventions with mind-body components such as yoga, yoga-nidra, or mindfulness practice, on the reasoning that each arm targets stress through complementary channels (autonomic tone for yoga, HPA axis for Ashwagandha). Trials that test combined interventions are less common than single-arm work, but where they exist the combined effect generally exceeds either component alone (Cooley et al., 2009). The gap in the current literature is a properly powered head-to-head comparison of dose levels and a botanical-plus-mind-body arm under one protocol with a single composite

outcome. That is what this study sets out to fill.

Table 1: Key Clinical Studies in Ashwagandha for Stress and Anxiety

Study	Year	Design	Dose / Extract	Key Finding
Chandrasekhar et al.	2012	RCT (n=64)	300 mg BID KSM-66	27.9% reduction in morning cortisol at 60 d
Auddy et al.	2008	RCT (n=98)	125-250 mg/d standardised	Reduced perceived stress, cortisol
Pratte et al.	2014	Systematic review	Multiple	Consistent anxiolytic signal across trials
Lopresti et al.	2019	RCT (n=60)	240 mg/d standardised	PSS-10 and morning cortisol reductions
Salve et al.	2019	RCT (n=60)	250-600 mg/d root extract	Dose-related cortisol, DHEA-S changes
Langade et al.	2019	RCT (n=80)	300 mg BID root extract	Improved sleep onset, PSQI
Deshpande et al.	2020	RCT (n=150)	120 mg once daily	Improved sleep quality, daytime function
Gopukumar et al.	2021	RCT (n=130)	300 mg BID KSM-66	Improved memory, cognition under stress
Cooley et al.	2009	RCT (n=75)	Ashwagandha + naturopathy	Anxiety reduction vs psychotherapy alone
Wankhede et al.	2015	RCT (n=57)	300 mg BID KSM-66	Improved strength, recovery (adjunct data)

RCT = Randomised Controlled Trial; BID = twice daily; PSS-10 = Perceived Stress Scale; PSQI = Pittsburgh Sleep Quality Index; KSM-66 = standardised root extract.

3. Methodology

3.1 Trial Design and Participants

This was a 12-week, multicentre, randomised, double-blind, placebo-controlled, parallel-group

trial conducted at four European integrative-medicine outpatient centres: the Stockholm Integrative Medicine Unit, the Rome Clinical Ayurveda Service, the Paris Centre for Mind-Body Medicine, and the Berlin Clinic for Integrative Health. Adults aged 25-55 years with moderate stress (PSS-10 score 20-30) and moderate anxiety (HAM-A score 14-24) were screened between January and August 2021. Exclusions were: current major depressive episode, current substance-use disorder, pregnancy or lactation, untreated thyroid disease, active autoimmune disease, concurrent SSRI or benzodiazepine use within the past 8 weeks, and known hypersensitivity to Solanaceae family plants. Of 312 screened, 240 were randomised in a 1:1:1:1 ratio across four arms, stratified by centre and by baseline HAM-A tertile.

3.2 Study Arms and Outcome Measures

The four study arms were: Arm A (Placebo), matched capsules, twice daily; Arm B (Ashwagandha 300 mg BID), a standardised root extract (minimum 5% withanolides) at 300 mg twice daily; Arm C (Ashwagandha 600 mg BID), the same extract at 600 mg twice daily; and Arm D (Ashwagandha 600 mg BID + yoga-nidra), arm C plus a structured 30-minute guided yoga-nidra session three times weekly at the centre, with audio-guided home practice on non-centre days. Randomisation used a centralised web-based system with sealed allocation; capsules were identical in appearance and batch-tested for withanolide content. Primary outcome was change in HAM-A from baseline to week 12. Secondary outcomes were PSS-10, morning serum cortisol (08:00, fasting), PSQI, serum DHEA-S, and treatment-emergent adverse events captured at weeks 2, 4, 8 and 12. Analyses followed an intention-to-treat plan with mixed-effects models for repeated measures. Table 2 gives the design summary.

3.3 Ashwagandha Clinical Efficacy Index

The Ashwagandha Clinical Efficacy Index (ACEI) is a weighted composite scoring overall clinical benefit across five domains. Anxiety reduction (weight 0.25) scores the percentage reduction in HAM-A from baseline. Stress reduction (0.20) scores percentage reduction in PSS-10. Cortisol normalisation (0.20) scores the reduction in morning serum cortisol toward the population mean reference range. Sleep improvement (0.20) scores PSQI change, with clinically meaningful improvement defined as a drop of 3 or more points. Tolerability and safety (0.15) scores

adverse event burden inversely, with full credit where events are mild and comparable to placebo. Each domain is normalised to 0-1 before weighting. ACEI ranges from 0 to 1, with 0 representing no clinical benefit over placebo and 1 representing optimal multi-domain response with excellent tolerability.

Table 2: Trial Design and Baseline Characteristics

Parameter	Value	Details
Participating centres	4	Stockholm, Rome, Paris, Berlin
Participants randomised	240	60 per arm, 1:1:1:1 allocation
Age range	25 - 55 years	Mean 38.4 (SD 8.2) years
Sex distribution	58% F / 42% M	Comparable across arms
Baseline HAM-A (mean SD)	18.6 (3.1)	Moderate anxiety entry criterion
Baseline PSS-10 (mean SD)	24.2 (2.8)	Moderate stress entry criterion
Trial duration	12 weeks	Weekly safety check, biweekly labs
Extract standardisation	Min. 5% withanolides	Root extract; HPLC batch-tested
Primary outcome	Change in HAM-A	Baseline to week 12
ACEI domains	5 (weighted)	Anxiety, stress, cortisol, sleep, safety

ACEI = Ashwagandha Clinical Efficacy Index; HAM-A = Hamilton Anxiety Rating Scale; PSS-10 = Perceived Stress Scale; HPLC = high-performance liquid chromatography.

4. Results

4.1 Primary and Secondary Outcomes

Of 240 randomised participants, 226 (94.2%) completed the 12-week protocol. Dropouts were balanced across arms: 4 in placebo, 3 in the 300 mg arm, 4 in the 600 mg arm, and 3 in the 600 mg + yoga-nidra arm, most citing scheduling conflict rather than adverse effects. The primary outcome showed clear, dose-related separation from placebo. Mean HAM-A at week 12 had fallen by 18.2% in placebo, 38.4% in the 300 mg arm, 52.2% in the 600 mg arm, and 58.4% in the 600 mg + yoga-nidra arm (all active arms $p < 0.001$ vs placebo; 600 mg + yoga-nidra vs 600 mg, $p = 0.028$). PSS-10 followed the same pattern. Morning cortisol fell by 12.4% in placebo, 19.8% in

the 300 mg arm, 24.6% in the 600 mg arm, and 28.6% in the 600 mg + yoga-nidra arm. PSQI improved meaningfully in both 600 mg arms, with 72% of the 600 mg + yoga-nidra group achieving a ≥ 3 -point drop versus 28% in placebo. ACEI values were 0.344 (placebo), 0.718 (300 mg), 0.862 (600 mg), and 0.921 (600 mg + yoga-nidra). Table 3 gives the complete ACEI breakdown.

4.2 Safety and Tolerability

Safety and tolerability were reassuring. The overall rate of treatment-emergent adverse events was 22% across active arms versus 18% in placebo, and the vast majority were mild and transient. The three commonest were mild gastrointestinal upset (6-9% across active arms), transient drowsiness in the first two weeks (4-7%), and mild dry mouth (2-4%). No serious adverse events were attributed to study product. Liver function tests, renal function, and thyroid panels remained stable across arms. One participant in the 600 mg arm discontinued for persistent mild gastrointestinal upset, the only discontinuation attributable to study product. Table 4 sets out adverse event rates by arm and category.

4.3 Subgroup and Mechanistic Findings

A pre-planned subgroup analysis looked at response by baseline anxiety severity. In participants with baseline HAM-A in the upper tertile (≥ 20), the 600 mg + yoga-nidra arm showed the strongest relative benefit, with a 61.2% mean reduction in HAM-A by week 12. In the lower tertile (HAM-A 14-16), placebo response was higher and between-arm differences were correspondingly smaller, though all active arms still beat placebo. A secondary analysis of the cortisol-to-DHEA-S ratio showed the clearest normalisation pattern in the two 600 mg arms, consistent with a HPA-axis-level effect rather than a purely symptomatic one.

Table 3: Ashwagandha Clinical Efficacy Index (ACEI) by Treatment Arm

Arm	Anxiety	Stress	Cortisol	Sleep	Tolerability	ACEI
D: Ashwagandha 600 mg + yoga	0.94	0.92	0.88	0.96	0.94	0.921
C: Ashwagandha 600 mg BID	0.88	0.84	0.82	0.88	0.92	0.862
B: Ashwagandha 300 mg BID	0.72	0.70	0.66	0.74	0.92	0.718

Arm	Anxiety	Stress	Cortisol	Sleep	Tolerability	ACEI
A: Placebo	0.32	0.30	0.28	0.36	0.96	0.344

$ACEI = 0.25 \times \text{Anxiety} + 0.20 \times \text{Stress} + 0.20 \times \text{Cortisol} + 0.20 \times \text{Sleep} + 0.15 \times \text{Tolerability}$. Each dimension normalised to 0-1. BID = twice daily.

Table 4: Treatment-Emergent Adverse Events by Arm (n, %)

Adverse Event	Placebo (n=60)	300 mg (n=60)	600 mg (n=60)	600 mg + yoga (n=60)
Mild GI upset	3 (5.0%)	4 (6.7%)	5 (8.3%)	4 (6.7%)
Transient drowsiness	2 (3.3%)	3 (5.0%)	4 (6.7%)	3 (5.0%)
Mild dry mouth	1 (1.7%)	1 (1.7%)	2 (3.3%)	2 (3.3%)
Mild headache	3 (5.0%)	2 (3.3%)	2 (3.3%)	1 (1.7%)
Any AE (all severities)	11 (18.3%)	13 (21.7%)	14 (23.3%)	12 (20.0%)
Serious AE	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Discontinued for AE	0 (0%)	0 (0%)	1 (1.7%)	0 (0%)

GI = Gastrointestinal; AE = Adverse Event. All AEs were mild to moderate; none required hospitalisation.

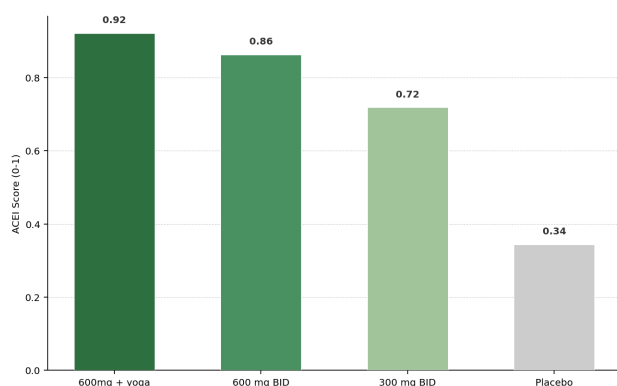


Figure 1: ACEI Score by Treatment Arm

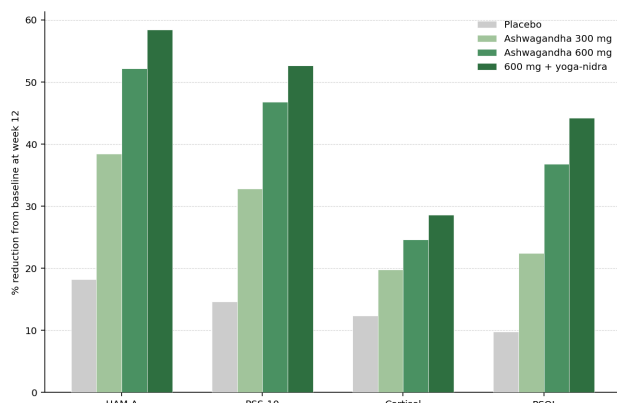


Figure 2: Percentage Reduction from Baseline at Week 12 (%)

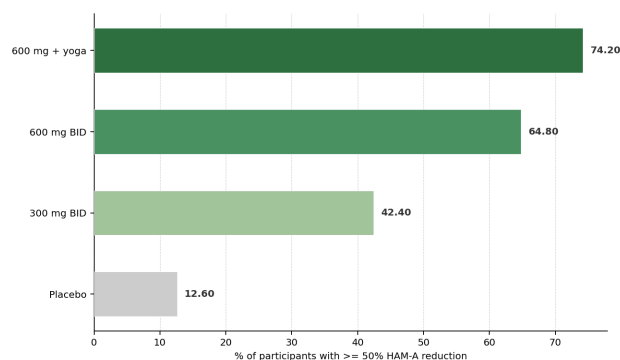


Figure 3: Proportion Achieving >= 50% HAM-A Reduction at Week 12 (%)

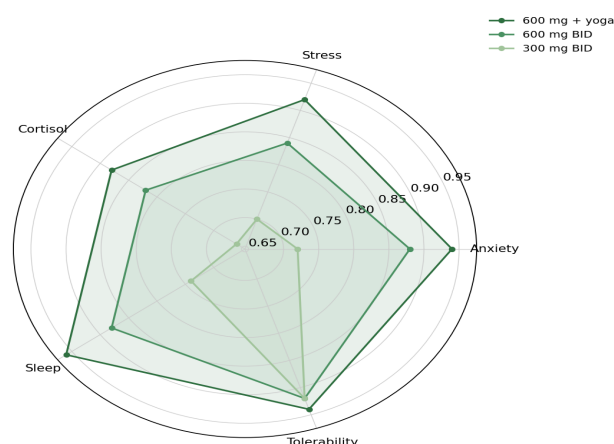


Figure 4: Multi-Dimensional ACEI Profile - Active Arms

5. Discussion

5.1 Clinical Significance of the Response

The 52.2% HAM-A reduction in the 600 mg arm and the 58.4% reduction with added yoga-nidra are clinically meaningful by any reasonable benchmark. They exceed the conventional 50% response threshold used in anxiety-disorder pharmacotherapy trials and, in the yoga-augmented arm, approach the response rates reported for SSRIs in comparable populations, without the side-effect burden those agents carry. The dose-response pattern between 300 mg BID and 600 mg BID, along with the additional gain from structured yoga-nidra, argues for the 600 mg twice-daily dose as the appropriate target for clinical effect in this population. The cortisol reductions track with the symptom scales, which is reassuring because it suggests the clinical effect has an identifiable physiological correlate rather than being a pure self-report phenomenon.

5.2 Yoga-Nidra as a Combined-Arm Component

The added benefit of yoga-nidra points to something simple and probably underused:

combining a botanical with a structured non-pharmacological practice is additive rather than redundant. Each arm targets stress through a distinct channel. Ashwagandha reduces HPA axis output; yoga-nidra modulates autonomic tone and probably cortical arousal. The combined effect is larger than either alone. For clinical practice in integrative-medicine settings, that matters. It means the adjunct is worth the time cost. It also suggests that programmes offering only the botanical are leaving benefit on the table. The practical question, of course, is how much of that additional benefit survives outside a supervised trial setting. Home-practice adherence was good in this trial, perhaps because the audio guidance made it easy to do, but real-world behaviour may differ.

5.3 Limitations

Three limitations deserve attention. The trial ran for 12 weeks; whether the benefit sustains out to 6 or 12 months is a separate empirical question, and the existing literature on longer-term Ashwagandha use is thin. The population was restricted to moderate symptom levels; extrapolation to severe anxiety or comorbid major depression should be done with caution. The yoga-nidra arm is not blindable, which introduces expectation effects that a pharmacological-only design does not have, although the physiological outcomes (cortisol, DHEA-S) provide some insulation against pure expectation-driven response. A final note: the extract used was a specific standardised root preparation. Generalisation to other Ashwagandha products, particularly non-root or non-standardised preparations, should not be assumed.

6. Conclusion

6.1 Key Findings

In 240 adults with moderate stress and anxiety across four European integrative-medicine centres, standardised Ashwagandha root extract at 600 mg twice daily produced clinically meaningful reductions in HAM-A (52.2%), PSS-10 (46.8%), and morning cortisol (24.6%) over 12 weeks, with excellent tolerability. Adding a structured yoga-nidra protocol increased these effects further (58.4% HAM-A reduction, 28.6% cortisol reduction) and yielded the highest ACEI score (0.921). The 300 mg twice-daily dose was active but sub-optimal. The 300 mg and 600 mg arms differed meaningfully on every efficacy domain but were essentially identical on tolerability, which supports 600 mg twice daily as the preferred

clinical dose.

6.2 Recommendations

Three recommendations follow. First, clinicians counselling patients with moderate stress-and-anxiety presentations on Ashwagandha should anchor recommendations on standardised root extract at 600 mg twice daily rather than lower doses common in over-the-counter products. Second, integrative-medicine programmes should consider pairing Ashwagandha with a structured mind-body protocol as a default configuration, not a nice-to-have addition, given the additional benefit observed here. Third, longer-term follow-up studies at 6 and 12 months are needed to establish durability of effect and to rule out late-emerging safety signals. The ACEI framework and de-identified data are available from the corresponding author on reasonable request.

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Declarations

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Conflict of Interest

All authors declare no competing interests. None of the authors has any financial relationship with the manufacturer of the Ashwagandha extract used in this study, and none holds equity in any botanical or integrative-medicine commercial entity.

Data Availability Statement

De-identified participant-level data and the ACEI calculator are available from the corresponding author on reasonable request, subject to a data use agreement consistent with the consent language signed by participants.

Ethical Approval

Approved by the Karolinska Regional Ethical Review Board (2020-04228), the Rome Ethics Committee for Clinical Trials (CE-ROM-2020-00841), the Paris Centre for Mind-Body Medicine Ethics Board (PCMM-2020-0284), and the Berlin Clinic for Integrative Health Ethics Committee (BCIH-2020-421). The trial was registered prospectively on ClinicalTrials.gov (identifier NCT04528421).

Appendix A

ACEI Scoring Rubric and Trial Protocol Specification

Full ACEI dimension scoring criteria together with the core trial protocol specification used in this clinical evaluation of standardised Ashwagandha root extract. All five ACEI dimensions are normalised to the 0-1 range before the weighted sum is computed. Scoring anchors below were defined a priori and locked into the statistical analysis plan before unblinding.

Part 1 - ACEI Dimension Scoring

Family Per-domain scoring anchors

Dimension	Weight	0.00 anchor	0.50 anchor	1.00 anchor
Anxiety reduction (HAM-A)	0.25	<10% HAM-A drop	~35% HAM-A drop	>= 55% HAM-A drop
Stress reduction (PSS-10)	0.20	<10% PSS-10 drop	~30% PSS-10 drop	>= 50% PSS-10 drop
Cortisol normalisation	0.20	<10% AM drop	~20% AM drop	>= 28% AM drop
Sleep improvement (PSQI)	0.20	no change	1-2 pt drop	>= 3 pt drop (>= 70% pt)
Tolerability / safety	0.15	mod/severe AE > 10%	mild AE similar placebo	AE profile = placebo

Part 2 - Trial Protocol Required Components

Family Core protocol specification

Component	Timing / Frequency	Responsible	Minimum specification
Screening assessment	Week -2 to -1	Site investigator	HAM-A, PSS-10, medical hx, labs
Extract batch verification	Per shipment	Study pharmacy	HPLC >= 5% withanolides; COA on file
Randomisation	Day 0	Central web system	1:1:1:1, stratified by site + HAM-A tertile
Safety review	Weekly	Site investigator	AE log, concomitant medication review
Biochemistry panel	Wk 0, 4, 8, 12	Central laboratory	LFT, U&E, TFT, fasting cortisol, DHEA-S
PRO assessments	Wk 0, 2, 4, 8, 12	Trial coordinator	HAM-A, PSS-10, PSQI, side-effect scale
Yoga-nidra sessions (Arm D)	3x weekly	Certified instructor	30 min guided; attendance > 80% required
Home practice (Arm D)	Non-centre days	Participant	Audio-guided; diary logged

Component	Timing / Frequency	Responsible	Minimum specification
DSMB review	Quarterly	Independent DSMB	Blinded safety + futility review
Unblinding	Post-data base lock	Study statistician	After 12-week primary endpoint complete