

GEMS of the Week

SPOTLIGHT

Don't Sleep on Ashwagandha

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Effect of Ashwagandha (*Withania somnifera*) Extract on Sleep: A Systematic Review and Meta-Analysis

Cheah KL, Norhayati MN, Husniati Yaacob L, Abdul Rahman R. Effect of Ashwagandha (*Withania somnifera*) Extract on Sleep: A Systematic Review and Meta-analysis. *PLoS One*. 2021;16(9):e0257843. Published 2021 Sep 24. doi:10.1371/journal.pone.0257843

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KEY TAKEAWAY: Ashwagandha improves sleep quantity and quality compared to placebo in adults ≥ 18 years old with or without insomnia.

STUDY DESIGN: Systematic review and meta-analysis of five randomized controlled trials (RCTs) (N=1,764)

LEVEL OF EVIDENCE: STEP 2 (downgraded due to significant heterogeneity for outcome measures)

BRIEF BACKGROUND INFORMATION: Poor sleep and insomnia are frequent concerns brought by patients due to the significant impact of sleep on functionality, wellness, and quality of life. Because of the side effects of many pharmaceuticals that treat insomnia, there is increased public interest in the use of herbals and supplements. This review aimed to determine the effect of Ashwagandha on sleep.

PATIENTS: Adults ≥ 18 years old with or without insomnia

INTERVENTION: Ashwagandha extract in any form, any dose, or any duration

CONTROL: Placebo

PRIMARY OUTCOME: Sleep quantity and quality

Secondary Outcome: Mental alertness on rising, anxiety, quality of life

METHODS (BRIEF DESCRIPTION):

- The systematic review included human RCTs with participants who were ≥ 18 years old with or without insomnia (as diagnosed by standard criteria, such as the DSM), using Ashwagandha extract in any form, any dose, or any duration as the intervention, and evaluated at least one outcome on sleep.
- The following databases were searched: CENTRAL, MEDLINE, SCOPUS, Google Scholars, World Health Organization Trials Portal, ClinicalTrials.gov., and Clinical Trial Registry of India (CTRI).
- The intervention included oral ashwagandha in capsule form. Doses ranged from 120–600 mg per day.

- Comparator was placebo, in capsule form (either starch or rice powder).
- The primary outcome assessed sleep quantity and sleep quality:
 - Measured by subjective assessments:
 - Sleep Quality Scale (SQS): Scores range from 1–7, with lower scores, indicating better perceived sleep quality.
 - Pittsburgh Sleep Quality Index (PSQI) is a questionnaire that measures several components of sleep over one month with summative. Scores range from 0–21, with lower scores indicating better sleep quality.
 - Measured by objective assessments:
 - Actigraphy (wrist devices) also measured movements to provide information on sleep onset latency, total sleep time, wake time after sleep onset, total time in bed, and sleep efficiency.
- Secondary Outcomes:
 - Mental alertness on rising was measured using a rating scale. Scores range from 1–3, with lower scores, indicating better perceived mental alertness upon waking.
 - Anxiety was measured using the Hamilton Anxiety Rating Scale, or HAMA-A, which assesses intensity of anxiety. Scores range from 0–56, with lower scores indicating a lower intensity of anxiety.
 - Quality of Life was measured by World Health Organization Quality of Life self-administered questionnaire with four domains. The higher the score, the better the quality of life.

INTERVENTION (# IN THE GROUP): 972

COMPARISON (# IN THE GROUP): 792

FOLLOW-UP PERIOD: Variable (6–12 weeks)

RESULTS:

Primary Outcome –

- Ashwagandha improved the following components of sleep compared to placebo:
 - Sleep quality (4 trials, n=228; standardized mean difference [SMD] –1.2; 95% CI, –1.7 to –0.66; $I^2=64\%$)

- Sleep onset latency (3 trials, n=281; SMD -0.53; 95% CI, -0.77 to -0.29; I²=0%)
- Total sleep time (3 trials, n=281; SMD -0.45; 95% CI, -0.69 to -0.21; I²=0%)
- Wake time after sleep onset (3 trials, n=281; SMD -0.39; 95% CI, -0.62 to -0.15; I²=0%)
- Sleep efficiency (3 trials, n=281; SMD -0.68; 95% CI, -1.1 to -0.29; I²=55%)
- There was no significant effect of Ashwagandha compared to placebo in improving sleep quality measured via the PSQI (2 trials, n=131; SMD -0.90; 95% CI -2.1 to 0.33; I²=90%), and total time in bed (3 trials, n=281; SMD -0.17; 95% CI, -0.41 to 0.07; I²=0).
- Subgroup analysis revealed that ashwagandha compared to placebo had a more significant effect in overall sleep quality in patients with insomnia (4 trials, n=1,099; SMD -0.63; 95% CI, -0.83 to -0.43; I²=56%) than those without insomnia (2 trials, n=665; SMD -0.84; 95% CI, -1.1 to -0.58; I²=59%).
- Subgroup analysis also revealed more significant improvement in overall sleep quality when treatment duration was ≥8 weeks (4 trials, n=1,014; SMD -0.68; 95% CI, -0.91 to -0.45; I²=67%) compared to <8 weeks (5 trials, N=1,764; SMD -0.37; 95% CI, -0.46 to -0.27; I²=1%).

Secondary Outcome –

- Ashwagandha significantly improved the following compared to placebo:
 - Mental alertness (3 studies, n=170; mean difference [MD] -0.28; 95% CI, -0.45 to -0.11; I²=0%).
 - Anxiety (3 studies, n=189; MD -2.2; 95% CI, -3.4 to -1.0; I²=0%).
- There was no significant difference in quality of life between groups.

LIMITATIONS:

- Inconsistent findings and small sample size
- There was no consistent tool used for assessing sleep quantity/quality.
- Actigraphy is an indirect measure of sleep and could give confounding data in people with movement disorders.

- There was significant heterogeneity present for many outcome measures.

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A History of Recurrent Pregnancy Loss is Associated with Increased Perinatal Complications, But Not Necessarily a Longer Birth Interval: A Population Study Spanning 18 Years

Cho K, Fayek B, Liu YD, et al. A history of recurrent pregnancy loss is associated with increased perinatal complications, but not necessarily a longer birth interval: a population study spanning 18 years. *Hum Reprod.* 2024;39(5):1105-1116. doi:10.1093/humrep/deae029

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KEY TAKEAWAY: After primary recurrent pregnancy loss (RPL), defined as ≥ 2 pregnancy losses before 20 weeks gestation prior to first live birth, there is a shorter time frame between first and second live births compared to people who do not experience RPL. However, individuals with secondary RPL, defined as no or one pregnancy loss before 20 weeks gestation prior to first live birth, have a longer time between first and second live births compared to people who never experienced RPL.

STUDY DESIGN: Retrospective cohort study

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: There is limited information regarding ability to have more than one child for people with RPL. This study primarily aimed to investigate the reproductive prognosis of individuals with a history of RPL, specifically focusing on their ability to have a second child.

PATIENTS: Persons with at least two recorded live births

INTERVENTION: History of RPL

CONTROL: No history of RPL

PRIMARY OUTCOME: Time interval between first and second live births

Secondary Outcome: Cumulative second live birth rates and the prevalence of pregnancy complications including gestational diabetes mellitus (GDM), hypertensive disorders of pregnancy (HDP), and preterm birth (PTB)

METHODS (BRIEF DESCRIPTION):

- 184,241 people with ≥ 2 live births and delivered between 2000–2018 were included in the study.
- 12,321 people with RPL: 4,302 primary RPL; 8,019 secondary RPL
- People with incomplete birth history were excluded to make groups more similar for comparison (re: fecundability and pregnancy choices)

- Birthrate analysis was performed by enrolling persons who had at least one live birth between 2000–2010 and then followed until March 31, 2018, or until 49 years old to determine second live birth rates ($n=198,319$).
- This group was divided into pregnancy loss without adverse reproductive outcomes (cohort I) and pregnancy loss with adverse pregnancy outcomes (cohort II), with each of those groups further divided into RPL and no RPL groups for analysis.
- RPL was considered the exposure, and the comparison group included people with no history of RPL.
- Primary Outcomes: Time interval between first and second live births as measured by the average duration, in years, between the date of a participant's first live birth and their subsequent second live birth
- Secondary Outcomes:
 - Prevalence of pregnancy complications including GDM, HDP, PTB were measured by comparing the frequency of specific adverse outcomes occurring during the first and second live births among the RPL and non-RPL groups.
 - Cumulative Second Live Birth Rate as measured by probability of an individual having a second live birth within a specific follow-up period (until March 31, 2018, or reaching 49 years old)
- Generalized additive models were used to adjust for maternal age, body mass index (BMI), and other confounders, allowing for a non-linear relationship between maternal age and the birth interval in the measurement of the primary outcome.
- Secondary outcomes were measured using the non-parametric Kruskal-Wallis H test for continuous data and Fisher's exact test for categorical data.
- In order to ascertain cumulative second live birth rates, an additional cohort analysis was undertaken with 198,319 persons with first live births between 2000–2010, and these were analyzed in two cohorts ("cohort I" and "cohort II") which were further subdivided into RPL and no RPL groups.

INTERVENTION (# IN THE GROUP):

- Main RPL group: 12,321

- Cohort I RPL group: 4,531
- Cohort II RPL group: 1,069

COMPARISON (# IN THE GROUP):

- Main no RPL group: 171,920
- Cohort I no RPL group: 161,895
- Cohort II no RPL group: 30,824

FOLLOW-UP PERIOD: Median follow-up was not provided for main study cohort, but participants were followed from study entry until March 31, 2018, or 49 years old, whichever came first.

- Cohort I median follow up: 5.5 years
- Cohort II median follow up: 7.3 years

RESULTS:

Primary Outcome –

- In the adjusted analysis, the time interval from first to second live birth after primary RPL was shorter compared to no RPL:
 - Primary RPL interval (3.1 years; 95% CI, 2.8–3.3)
 - No RPL interval (3.2 years; 95% CI, 3.0–3.4)
- However, the time interval to second live birth with secondary RPL was increased compared to no RPL
 - Secondary RPL interval (4.3 years; 95% CI, 4.1–4.6)
 - No RPL interval (3.2 years; 95% CI, 3.0–3.4)

Secondary Outcome –

- In cohort I, the overall cumulative rate of a second live birth was significantly lower for those with primary RPL compared to the non-RPL group (52% vs 69%, respectively; adjusted hazard ratio [aHR] 0.86; 95% CI, 0.83–0.90).
- In cohort II, individuals who had other adverse outcomes in addition to RPL, the second live birth rate dropped further compared to the non-RPL group (44% vs 59%, respectively; aHR 0.88; 95% CI, 0.80–0.97).
- Prevalence in first live birth was significantly higher in primary RPL compared to those without RPL for the following secondary outcomes:
 - HDP without RPL (6.5% vs with RPL 7.7%; $P=.004$)
 - GDM without RPL (6.2% vs with RPL 9.8%; $P<.001$)
 - PTB without RPL (1.1% vs with RPL 2.0% ($P<.001$))

- Analyses of cohorts I and II supported these findings with similar secondary outcomes.

LIMITATIONS:

- Incidence of RPL in this study was increased compared to previous studies, possibly due to inaccurate patient recall of pregnancy loss (both self-reported loss and clinically diagnosed loss were included in this study).
- The study did not account for family-planning intention.
- The study was not powered to account for effect modification of multiple gestations at first live birth and how that may have influenced interval to second live birth outcomes.

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When Lactobacillus Loses Ground: Vaginal Microbiomes and Shorter Gestation

Microbial Diversity in the Vaginal Microbiota and its Link to Pregnancy Outcomes

Baud A, Hillion KH, Plainvert C, et al. Microbial Diversity in the Vaginal Microbiota and its Link to Pregnancy Outcomes. *Sci Rep*. 2023;13(1):9061. Published 2023 Jun 4. doi:10.1038/s41598-023-36126-z

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KEY TAKEAWAY: Vaginal dysbiosis characterized by high overall microbial diversity and loss of *Lactobacillus* dominance is associated with shorter gestation and preterm birth.

STUDY DESIGN: Prospective observational cohort

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: Preterm birth is a leading cause of infant morbidity, and its underlying mechanisms are often multifactorial and incompletely understood. During pregnancy, the vaginal microbiome is typically *Lactobacillus*-dominant, and reductions in *Lactobacillus* predominance, often described as dysbiosis, have been hypothesized to increase susceptibility to infection and adverse pregnancy outcomes. While healthy pregnancies are commonly associated with lower microbial diversity, the significance of altered diversity patterns remains unclear. This study evaluated whether vaginal microbiome features, specifically overall diversity and dominant-community patterns, are associated with gestational length and risk of preterm birth.

PATIENTS: Pregnant persons delivering at three Paris-region hospitals in France

INTERVENTION: Higher-diversity, “other”-dominant vaginal microbiome patterns at delivery

CONTROL: *L. crispatus*, *L. iners*, or *G. vaginalis*-dominant vaginal microbiome patterns

PRIMARY OUTCOME: Gestational length

Secondary Outcome: Admission for risk of preterm birth

METHODS (BRIEF DESCRIPTION):

- Included participants were ≥18 years old and at least 22 weeks’ gestation.
- Vaginal swabs collected at the time of delivery were matched to completed maternal and neonatal clinical data.
- Metagenomic sequencing was used to characterize vaginal microbiome composition by Faith’s

phylogenetic diversity and dominant-community type, and samples with poor DNA extraction or insufficient sequencing data were excluded.

- Vaginal microbiome patterns at delivery were identified from metagenomic sequencing of vaginal swabs and categorized by Faith’s phylogenetic diversity and dominant-community types, comparing patterns dominated by “other” species to those dominated by *Lactobacillus crispatus*, *Lactobacillus iners*, or *Gardnerella vaginalis*.
- The primary outcome measured gestational length, including preterm birth defined as delivery before 37 weeks’ gestation, was assessed by comparing phylogenetic diversity across four cohort groups, term control, term with membrane rupture (PROM) >24 hours before birth, preterm, and preterm with membrane rupture >24 hours before birth, and dominant-community patterns across gestational-length groupings.
- The secondary outcome measured preterm birth risk and was assessed by comparing the dominant-community patterns between pre-term admissions and full-term controls.
- The primary outcome was reported using Faith’s phylogenetic diversity (PD), which is a measure of diversity within the vaginal microbiome community.

INTERVENTION (# IN THE GROUP): 293

COMPARISON (# IN THE GROUP): 456

FOLLOW-UP PERIOD: Not available

RESULTS:

Primary Outcome –

- Faith’s phylogenetic diversity did not differ significantly between control, term PROM, preterm, and preterm with PROM suggesting that diversity score alone did not separate these groups (mean PD 20, 19, 22, and 21, respectively; results presented via figure).
- Shorter gestation was associated with movement away from dominance by *L. crispatus* and toward “other-dominant” communities. Across gestational age groupings from earliest to latest (22–34, 35–36, 36–37, 37–38, 38–39, and 39–40 weeks), “other-dominant” counts were 65, 39, 22, 16, 28, 22, whereas *L. crispatus* were 25, 38, 63, 43, 43, 39, *L.*

iners was 19, 29, 28, 24, 24, 33, and *G. vaginalis* were 16, 16, 24, 17, 16, 15; $P<.001$). There was a stronger association after excluding less-common *Lactobacillus*-dominant community types.

Secondary Outcome –

- Patients admitted for risk of preterm delivery were more likely than full term controls to have “other-dominant” communities. Relative to full-term spontaneous controls, counts for *L. crispatus* were 53 vs 10, *L. iners* 44 vs 7, *G. vaginalis* 40 vs 4, and other-dominant communities 48 vs 27; $P=.00079$.

LIMITATIONS:

- Vaginal swabs were collected only at the time of delivery, limiting the ability to determine whether microbiome patterns preceded the outcomes.
- The observational design allows for potential confounding, such as peripartum antibiotic use, labor management practices, and maternal comorbidities.
- The study population was drawn from three hospitals within a single geographic region, which may limit generalizability.

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Is Six Weeks of Doxycycline Overkill? Azithromycin Rivals Doxycycline for Treatment of Meibomian Gland Dysfunction

Pulsed Oral Azithromycin vs Six-Week Oral Doxycycline for Moderate to Severe Meibomian Gland Dysfunction: A Randomized Clinical Trial

Upaphong P, Tangmonkongvoragul C, Phinyo P. Pulsed Oral Azithromycin vs 6-Week Oral Doxycycline for Moderate to Severe Meibomian Gland Dysfunction: A Randomized Clinical Trial. *JAMA Ophthalmol.* 2023;141(5):423-429.

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KEY TAKEAWAY: Azithromycin provides similar improvement in meibomian gland function and symptoms compared to doxycycline in adults with moderate-to-severe meibomian gland dysfunction (MGD).

STUDY DESIGN: Double blind randomized controlled trial
LEVEL OF EVIDENCE: STEP 3 (downgraded due to short follow-up duration, single-center design, and long-term applicability)

BRIEF BACKGROUND INFORMATION: MGD is a common cause of evaporative dry eye, and moderate-to-severe disease is often managed with oral doxycycline for its anti-inflammatory properties. However, doxycycline often requires a prolonged course and is associated with gastrointestinal intolerance, photosensitivity, and poor adherence. Azithromycin, with its long half-life and anti-inflammatory properties, may offer a shorter and better-tolerated alternative, but comparative randomized data are limited.

PATIENTS: Adults with moderate-to-severe MGD refractory to conservative therapy

INTERVENTION: Oral azithromycin 1 g once weekly for three weeks

CONTROL: Oral doxycycline 100 mg twice daily for six weeks

PRIMARY OUTCOME: Gland dysfunction and symptom severity

Secondary Outcome: Gastrointestinal (GI) side effects

METHODS (BRIEF DESCRIPTION):

- 137 patients with moderate to severe MGD were included in the study.
- Participants with atopic keratoconjunctivitis, rosacea, altered eyelid anatomy, pterygium, trichiasis, previous punctal occlusion, ocular

adnexal surgery, allergy to tetracycline or macrolide drugs, known heart, liver, or kidney disease, contact lens use within three months, pregnancy, or the use of antibiotics, steroids antiglaucoma medications, or cyclosporin use within one month were excluded from the study.

- There were no differences in patient demographics, stage MGD, or Ocular Surface Disease Index (OSDI) scores at study initiation.
- Participants were randomized in a double-blinded 1:1 ratio to azithromycin or doxycycline.
 - The intervention group received oral azithromycin 1 g weekly for three weeks; placebo tablets matched the doxycycline regimen.
 - The usual care group received oral doxycycline 100 mg twice daily for six weeks.
- Both treatment groups received matching pills and schedules to maintain masking.
- Assessments occurred at study initiation, six weeks, and eight weeks using the following scores:
 - MGD Score: Composite clinical score assessing meibomian gland function. Scores range from 0–28, with higher scores indicating worse dysfunction
 - Minimal clinically important difference (MCID): ± 2
 - Patient-reported symptom severity was measured using the OSDI questionnaire. Scores range from 0–100, with higher scores indicating more severe symptoms
 - MCID: ± 9
- The secondary outcome assessed GI adverse events; measured by comparing the proportion of patients in each group who reported gastrointestinal side effects during the treatment period.

INTERVENTION (# IN THE GROUP): 68

COMPARISON (# IN THE GROUP): 69

FOLLOW-UP PERIOD: Eight weeks

RESULTS:

Primary Outcome –

- Azithromycin did not significantly improve MGD compared to doxycycline at six and eight weeks:

- Six weeks (adjusted mean difference [aMD] -0.33; 95% CI, -1.7 to 1.0)
- Eight weeks (aMD 0.13; 95% CI, -1.6 to 1.8)
- Azithromycin did not significantly improve symptom severity compared to doxycycline at six and eight weeks:
 - Six weeks (aMD -1.2; 95% CI, -5.3 to 2.9)
 - Eight weeks (aMD -1.6; 95% CI, -5.7 to 2.6)

Secondary Outcome –

- Azithromycin reduced GI adverse events compared to doxycycline (4.4% vs 16%, respectively; absolute risk reduction [ARR] 12%; 95% CI, 1.6–21).

LIMITATIONS:

- The study was conducted at a single referral center, which may limit generalizability to primary care populations.
- Participants had moderate to severe disease unresponsive to conservative therapy, so results may not apply to mild MGD.
- Follow-up was limited to eight weeks, preventing assessment of long-term relapse or sustained benefit.
- The equivalence margins, while prespecified, may not reflect all clinicians' thresholds for clinically meaningful change.

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Tears of Joy? Comparing Oral Antibiotics for Meibomian Gland Dysfunction

Systemic Antibiotic Treatment for Meibomian Gland Dysfunction- A Systematic Review and Meta-Analysis

Ben Ephraim Noyman D, Chan CC, Mimouni M, Safir M. Systemic Antibiotic Treatment for Meibomian Gland Dysfunction-A Systematic Review and Meta-analysis. *Acta Ophthalmol.* 2024;102(1):e1-e10.

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KEY TAKEAWAY: Azithromycin and doxycycline are effective at treating signs and symptoms of meibomian gland dysfunction (MGD). Azithromycin exhibits better efficacy and safety profile for treating MGD compared to doxycycline.

STUDY DESIGN: Systematic review and meta-analysis of three prospective clinical trials and three randomized controlled trials (RCTs) (N=563)

LEVEL OF EVIDENCE: STEP 2 (downgraded due to heterogeneity in medication regimens, incomplete blinding, and inconsistency in signs and symptoms between some studies)

BRIEF BACKGROUND INFORMATION: MGD is a chronic disorder of the meibomian glands that contributes to a range of signs and symptoms that can significantly impair visual function and quality of life. Management of MGD includes conservative measures, systemic antibiotics, and emerging technologic and procedural based therapies. However, uncertainty remains regarding the comparative efficacy and safety of different antibiotic regimens for MGD. This study sought to address the efficacy and safety of oral doxycycline vs oral azithromycin in the treatment of MGD.

PATIENTS: Adolescents and adults ≥12 years old with moderate to severe MGD

INTERVENTION: Oral azithromycin

CONTROL: Oral doxycycline

PRIMARY OUTCOME: Objective clinical signs, subjective symptoms, and adverse events

METHODS (BRIEF DESCRIPTION):

- Six prospective comparative studies from Iran, India, and Spain that utilized standardized MGD assessment tools published from 2015–2022 were included (N=563).
- Participants (12–90 years old, with mean 40–50 years old) had clinically diagnosed moderate to

severe MGD and were treated with either azithromycin, doxycycline, or placebo.

- Individuals were excluded if they had received antibiotic treatment within one month prior to enrollment; had a history of liver disease, pregnancy or breastfeeding; wore contact lenses; had allergy to tested substances; had vernal or atopic keratoconjunctivitis; or had a history of ocular surgery or altered lid anatomy.
- The intervention included oral azithromycin 500 mg on day one followed by 250 mg daily for four days. One study used 500 mg daily for five days.
- The comparator included oral doxycycline 100 mg twice daily for seven days followed by 100 mg daily for 21 days. One study used 100 mg twice daily for one month and one used 200 mg daily for two months.
- All studies assessed seven objective clinical signs and five subjective symptoms; each graded on a 0–3 scale. The subjective symptoms included itching, foreign body sensation, dryness, burning, and eyelid swelling.
- The seven objective signs (by slit-lamp examination) included meibomian gland secretion quality, plugged meibomian gland orifices, bulbar conjunctival redness, eyelid margin redness, eyelid margin debris, tear break-up time, and ocular surface staining score.
- Adverse events were recorded throughout follow-up and pooled.

INTERVENTION (# IN THE GROUP): 282

COMPARISON (# IN THE GROUP): 281

FOLLOW-UP PERIOD: Varied (ranged from 60–270 days)

RESULTS:

Primary Outcome –

- Azithromycin did not significantly improve the following compared to doxycycline:
 - Average total signs and symptoms (6 studies, N=563; standardized mean difference [SMD] – 0.09; 95% CI, –0.32 to 0.14; I²=49%)
 - Average total signs score at follow up (consisting of meibomian gland secretion quality, plugged meibomian gland orifices, bulbar conjunctival redness, eyelid margin redness, eyelid margin

debris, tear break-up time, and ocular surface staining score) (6 studies, n=463; SMD -0.50; 95% CI, -1.1 to 0.08; I²=89%)

- Average total symptoms score (consisting of itching, foreign body sensation, dryness, burning, eyelid swelling) (6 studies, N=563; SMD 0.28; 95% CI, -0.17 to 0.72; I²=86%)
- Plugged meibomian gland score (6 studies, N=563; SMD -0.15; 95% CI, -0.33 to 0.04; I²=18%)
- Eyelid margin redness score (SMD -0.10; 95% CI, -0.30 to 0.11; I²=0%)
- Margin debris score (SMD -0.01; 95% CI, -0.20 to 0.17; I²=0%)
- Azithromycin improved the following compared to doxycycline:
 - Meibomian gland secretion (4 studies, n=363; SMD -0.25; 95% CI, -0.48 to -0.3; I²=14%)
 - Tear break-up time (5 studies, n=463; SMD -0.31; 95% CI, -0.50 to -0.13; I²=0%)
 - Ocular surface staining score (3 studies, n=263; SMD -1.0; 95% CI, -1.7 to -0.29; I²=86%)
 - Bulbar conjunctival redness score (1 study, n=100; SMD -0.47; 95% CI, -0.82 to -0.11; I²=72%)
- Azithromycin decreased risk of adverse events compared to doxycycline (6 studies, n=563; odds ratio [OR] 0.24; 95% CI, 0.16-0.34; I²=45%).

LIMITATIONS:

- Several trials did not adequately blind participants or examiners, increasing the risk for performance and detection bias.
- Some signs and symptoms were reported in only one or two studies, preventing comprehensive pooled analysis.
- Doxycycline dose and duration varied between studies.
- Heterogeneity was high for some outcomes (e.g., total signs score) reducing certainty in the magnitude of benefit.
- Follow-up durations differed between studies, limiting conclusions about long-term durability.

- Most studies were conducted in a limited geographic region (India, Spain, and Iran), which may reduce the generalizability.
- There was a wide age range within the study and MGD in pediatric population appears phenotypically different than MGD in adult/geriatric population.

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CBT-I vs Sleep Hygiene: Which Fixes Insomnia?

Effects of Sleep Hygiene Education for Insomnia: A Systematic Review and Meta-Analysis

Ruan JY, Liu Q, Chung KF, Ho KY, Yeung WF. Effects of sleep hygiene education for insomnia: A systematic review and meta-analysis. *Sleep Med Rev*. 2025;82:102109. doi:10.1016/j.smrv.2025.102109

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KEY TAKEAWAY: Sleep hygiene education (SHE) as a standalone therapy does not improve insomnia severity compared to cognitive behavioral therapy for insomnia (CBT-I) (full or partial), acupuncture therapy, and exercise-based interventions in adults with insomnia.

STUDY DESIGN: Systematic review and meta-analysis of 42 randomized clinical trials (RCTs) (N=4,245)

LEVEL OF EVIDENCE: STEP 2 (downgraded due to high heterogeneity of primary outcome results and high methodological bias)

BRIEF BACKGROUND INFORMATION: Insomnia is a debilitating condition that affects millions of people across the world and increases the risk of chronic disease. Pharmacologic treatment is available but can lead to dependence or adverse side effects. SHE is a simple tool that focuses on modifying routines to improve sleep, while CBT-I is a standardized approach to modifying behaviors to re-establish a normal sleeping pattern. Choosing the right non-pharmacologic treatment plan can be challenging for providers not familiar with the efficacy of the available options. This study aimed to address the most recent evidence on whether sleep hygiene education, used as a stand-alone treatment, is effective for treating insomnia in adults when compared to other active sleep treatments.

PATIENTS: Adults (≥18 years) with insomnia disorder

INTERVENTION: SHE

CONTROL: CBT-I, partial CBT-I, exercise, mindfulness-based therapy, and acupuncture

PRIMARY OUTCOME: Insomnia severity

Secondary Outcome: Sleep quality, sleep parameters

METHODS (BRIEF DESCRIPTION):

- RCT's including adults (≥18 years old) with insomnia disorder or clinically significant insomnia symptoms, that were identified using validated tools were included in the review. Participants with or without comorbid conditions were also included.

- The intervention was SHE alone, consisting of education on sleep-promoting behaviors delivered via printed materials, internet-based applications, and in-person sessions.
- The comparator was CBT-I, partial CBT-I, exercise, mindfulness-based therapy, and acupuncture.
 - CBT-I included behavioral and cognitive practices (sleep restriction, sleep diary, cognitive restructuring) delivered individually or in groups, in-person or digitally. Treatment duration typically 2–12 weeks, most commonly weekly sessions.
 - Exercise included structured interventions such as a two week zero-time program and eight-week Kundalini yoga program.
 - Mindfulness-based treatments included were group mindful awareness practices (MAPs),
 - Acupuncture interventions consisted of self-administered acupuncture protocols for insomnia.
- The primary outcome measured insomnia severity via the Insomnia Severity Index (ISI). Scores range from 0–28, with higher scores indicating more severe insomnia.
- The following were measured as the secondary outcomes:
 - Sleep quality was measured using the Pittsburgh Sleep Quality Index (PSQI). Scores range from 0–21, with higher scores indicating worse sleep quality.
 - Sleep parameters, such as Sleep Onset Latency (SOL), measured subjectively with a sleep diary or objectively with polysomnography.

INTERVENTION (# IN THE GROUP): 1,941

COMPARISON (# IN THE GROUP): 2,304

FOLLOW-UP PERIOD: Variable (ranging from immediate post-treatment assessment to 12 months)

RESULTS:

Primary Outcome –

- CBT-I was superior in reducing insomnia severity compared to SHE (16 studies; mean difference [MD] 3.8; 95% CI, 2.9–4.8; I²=79%).

- Partial CBT-I was superior in reducing insomnia severity compared to SHE (3 studies; MD 4.5; 95% CI, 3.3–5.6; $I^2=28\%$).
- Exercise-based interventions were superior in reducing insomnia severity compared to SHE (2 studies; MD 2.9; 95% CI, 0.81–5.0; $I^2=0\%$).
- Acupressure was superior in reducing insomnia severity compared to SHE (2 studies; MD 1.9; 95% CI, 0.82–3.0; $I^2=0\%$).

Secondary Outcome –

- CBT-I was superior in improving sleep quality compared to SHE (12 studies; MD 2.6; 95% CI, 2.0–3.1; $I^2=53\%$).
- Partial CBT-I was superior in improving sleep quality compared to SHE (3 studies; MD 2.0; 95% CI, 1.3–2.8; $I^2=0\%$).
- Mindfulness-based therapy was superior in improving sleep quality compared to SHE (1 study; MD 1.7; 95% CI, 0.66–2.74; $I^2=0\%$).
- Acupressure was superior in improving sleep quality compared to SHE (1 study; MD 2.0; 95% CI, 0.94–3.1; $I^2=0\%$).
- Exercise-based interventions were not superior in improving sleep quality compared to SHE.
- Compared with CBT-I, SHE was less effective for sleep onset latency (12 studies; MD 13 min; 95% CI, 8.5–17; $I^2=32\%$).
- Compared with CBT-I, SHE was less effective for wake after sleep onset (9 studies; MD 9.3 min; 95% CI, 4.9–14; $I^2=0\%$).
- Compared with CBT-I, SHE was less effective for total sleep time (10 studies; MD 20 min; 95% CI, 8.4–33; $I^2=26\%$).
- Compared with CBT-I, SHE was less effective for sleep efficiency (12 studies; MD 6.4%; 95% CI, 4.2–8.6; $I^2=57\%$).

LIMITATIONS:

- There was high methodological bias in the studies included, meaning not all the studies' active treatment protocols were the same.
- High heterogeneity for primary outcome (79%)
- Differences in baseline insomnia severity across studies limit the universality of the results.
- English-only language studies were included.

More Gains, Less Pain: Utility of Resistance Training in Treating Chronic Low Back Pain

Does Resistance Training Improve Pain Intensity, Quality of Life, and Disability in People with Chronic Nonspecific Low Back Pain?

Rodríguez-Domínguez ÁJ, Moral-Munoz JA, Guzmán-Gómez JD, Valero-Ortiz J, González-Gómez L, Cardellat-González M. Does resistance training improve pain intensity, quality of life, and disability in people with chronic nonspecific low back pain? A systematic review and meta-analysis. *Disabil Rehabil.* 2026;48(6):1532-1545. doi:10.1080/09638288.2025.2566275

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KEY TAKEAWAY: Resistance training improves pain but does not improve disability or quality of life compared to control in adults with chronic nonspecific low back pain (LBP).

STUDY DESIGN: Systematic review and meta-analysis of 10 randomized controlled trials (RCTs) (N=434)

LEVEL OF EVIDENCE: STEP 2 (downgraded due to high heterogeneity and risk of bias among the included trials)

BRIEF BACKGROUND INFORMATION: LBP encompasses a broad differential of etiologies that is difficult to completely and reliably diagnose in many cases and is often non-specific. Management of this non-specific pain is similarly non-specific, and evidence-based guidelines frequently recommend a well-rounded approach in rehabilitation. Resistance training has been thought to play a key role in management and resolution of non-specific LBP, however, lacks thorough study.

PATIENTS: Adults with nonspecific chronic LBP, lasting at least 12 weeks, without secondary cause

INTERVENTION: Resistance training or strength training

CONTROL: Any treatment

PRIMARY OUTCOME: Pain intensity, quality of life, and disability

METHODS (BRIEF DESCRIPTION):

- Studies using resistance training in adults with chronic nonspecific LBP, without secondary cause, were included in the review.
- Studies that included combined treatment regimens of strength/resistance training, with other treatment methods, were excluded.
- Studies published in languages other than English, Spanish, French, Italian, or Portuguese were also excluded.

- Participants engaged in resistance training programs that varied across trials, including lumbar-focused strengthening (e.g., lumbar extension exercises) and global strengthening exercises (e.g., squats and deadlifts).
- Programs were delivered 2–3 times per week over 4–24 weeks, with 12 weeks being the most common duration.
- Comparator groups varied widely by study. Several studies utilized one aerobic exercise, stabilization, core training, and combined therapy to compare efficacy to resistance training. Studies that listed a control group utilized either usual care or no intervention.
- Disability was assessed with the following scales:
 - Roland-Morris Questionnaire: A 24-question survey of symptoms related to the impact of LBP on functional status. Scores range from 0–24, with higher scores indicating higher functional impairment.
 - Oswestry Disability Index: A 10-question survey related to the impact of LBP on functional status. Each question consists of six qualitative answer options, converted to a quantitative score of 0–5 depending on symptom severity, with poorer levels of function corresponding to a higher numeric score. The sum of all 10 question scores is the final score, out of a total of 50 possible points.
 - The minimal clinically importance difference (MCID) was defined as a 15% difference in the disability score.
- Pain was assessed with numeric scores corresponding to the visual analog scale, with higher scores indicating higher levels of pain intensity. While most studies utilized a 0–10 scale, one study utilized a 0–100 scale.
 - The MCID was defined as a 15% difference in the pain score.
- Quality of life was assessed using the Short Form-36 Health Survey (SF-36). A 36-item questionnaire across eight individually scored domains of overall health. Scores range from 0–100, with higher scores indicating better health.

- The MCID was defined as a 15% difference in the quality of life score.

INTERVENTION (# IN THE GROUP): 217

COMPARISON (# IN THE GROUP): 217

FOLLOW-UP PERIOD: Variable (immediately after intervention up to 24 weeks following treatment)

RESULTS:

Primary Outcome –

- Resistance training reduced pain intensity compared to control and achieved MCID (7 studies, n=246; standardized mean difference [SMD] –15; 95% CI, –18 to –12; $I^2=28\%$).
 - Resistance training reduced disability compared to control, but was not clinically significant (7 studies, n=195; SMD –13; 95% CI, –14 to –11; $I^2=66\%$).
 - Resistance training improved quality of life compared to control, but was not clinically significant (5 studies, n=205; SMD 6.7; 95% CI, 4.9–8.5; $I^2=5\%$).
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LIMITATIONS:

- This study lacked rigor, as it was not possible to blind patients and therapists who participated in the study.
 - This study did not distinguish outcomes between men and women.
 - The limited number of included RCTs restricted the robustness of the analysis.
 - This study had significant levels of heterogeneity among primary outcomes.
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