GEMs
GOOD EVIDENCE MATTERS

GEMs of the Week

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What's in this week's issue?

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SPOTLIGHT: The Role of Micronized Progesterone in the Enhancement of Sleep Quality

The Role of Micronized Progesterone in the Enhancement of Sleep Quality

GEMs GOOD EVIDENCE MATTERS SPOTLIGHT

Efficacy of Micronized Progesterone for Sleep: A Systematic Review and Meta-Analysis of Randomized Controlled Trial Data

Nolan BJ, Liang B, Cheung AS. Efficacy of Micronized Progesterone for Sleep: A Systematic Review and Meta-analysis of Randomized Controlled Trial Data. *J Clin Endocrinol Metab*. 2021;106(4):942-951. doi:10.1210/clinem/dgaa873

KEY TAKEAWAY: Micronized progesterone improves sleep onset latency in studies of mostly postmenopausal women.

STUDY DESIGN: Meta-analysis and systematic review of 10 randomized controlled trials (N=577)

LEVEL OF EVIDENCE: STEP 1

BRIEF BACKGROUND INFORMATION: Preclinical data has demonstrated that progesterone metabolites can produce similar changes to benzodiazepines in sleep architecture. Unlike progestogens generally prescribed as part of postmenopausal therapy, micronized progesterone is bioidentical to human progesterone. This review aimed to analyze current literature in the clinical realm regarding sleep and micronized progesterone and how it could be applicable to providers and patients.

PATIENTS: Adults, primarily postmenopausal women

INTERVENTION: Oral micronized progesterone monotherapy of varying doses

CONTROL: Placebo or active comparator

PRIMARY OUTCOME: Sleep quality and parameters

METHODS (BRIEF DESCRIPTION):

- Meta-analysis and systematic review of English-speaking randomized control trials.
- 577 participants were enrolled, including men and women ≥18 years old.
  - Eight studies included postmenopausal women, one study included perimenopausal women, and one study included men.
- Studies varied in their use of micronized progesterone or intranasal progesterone and placebo or active comparator.
  - Nine studies using micronized progesterone ranging from 100 mg to 300 mg daily
  - One study used intranasal progesterone at 9 mg
  - Seven studies were placebo-controlled
  - Three studies utilized a progestin comparator
  - One study utilized a zolpidem comparator
  - Four studies had concomitant estrogen use
- The primary outcome was subjective self-reported sleep questionnaires and objective sleep outcomes using one-time polysomnography to evaluate improved total sleep time, sleep onset latency, wake and sleep onset, stage two sleep amount, and solve wave sleep.

INTERVENTION (# IN THE GROUP): Not available

COMPARISON (# IN THE GROUP): Not available

FOLLOW-UP PERIOD: 12 weeks

RESULTS:

Primary Outcome –

- Micronized progesterone improved sleep onset latency compared to placebo by polysomnography (effect size 7.1 minutes; 95% CI, 1.3–13)
- Micronized progesterone did not improve total sleep time or sleep efficiency compared to placebo by polysomnography.
  - Total sleep time (effect size 21; 95% CI, –0.16 to 42),
  - Sleep efficiency (effect size 1.3; 95% CI, –2.1 to 4.7)

LIMITATIONS:

- Several studies had small sample sizes, decreasing power, especially regarding self-reported sleep outcomes.
- Studies mostly included postmenopausal women. In several cases, participants were taking concomitant estrogen as well. Therefore, treatment of the vasomotor symptoms of menopause with estrogen could be confounding significant results.
- Moderate heterogeneity between studies evaluating total sleep time.
- Numerical data for sleep quality measures was not presented.
- The total number of trials and patients for each individual result was not available.

Cheyenne Dudenhoeffer, MD
University of Missouri-Columbia
Columbia, MO

Sleep Like a Pro: Progesterone Nasal Spray in Postmenopausal Women

Sleep After Intranasal Progesterone vs Zolpidem and Placebo in Menopausal Women: A Randomized, Double-Blind, Cross Over Study

Schüssler P, Kluge M, Adamczyk M, et al. Sleep after intranasal progesterone vs. zolpidem and placebo in postmenopausal women - A randomized, double-blind cross over study. *Psychoneuroendocrinology*. 2018;92:81-86. doi:10.1016/j.psyneuen.2018.04.001

KEY TAKEAWAY: Intranasal progesterone may provide a dose-dependent improvement in sleep duration and architecture in postmenopausal women.

STUDY DESIGN: Randomized, double-blind, crossover study

LEVEL OF EVIDENCE: STEP 3 (downgraded due to small sample size)

BRIEF BACKGROUND INFORMATION: Insomnia is a common concern among postmenopausal women. One reason may be the decline in progesterone and estrogen; both hormones have demonstrated hypnotic effects in animals and humans. This study examined the relationship between progesterone and sleep in postmenopausal women.

PATIENTS: Healthy, postmenopausal women

INTERVENTION: Intranasal progesterone

CONTROL: Oral and/or intranasal placebos; zolpidem

PRIMARY OUTCOME: Sleep-EEG variables

Secondary Outcome: Subjective sleep variables

METHODS (BRIEF DESCRIPTION):

- Participants included healthy postmenopausal women (11 with natural menopause, 1 with surgical) without chronic diseases, sleep disorders, neuropsychiatric disorders, or stressful life events/shift work from a single center in Germany.
- Each participant received four different regimens on a randomized schedule:
  - 4.5 mg intranasal progesterone and oral placebo
  - 9 mg intranasal progesterone and oral placebo
  - Intranasal placebo with 10 mg oral zolpidem
  - Intranasal and oral placebo
- Patients stayed for four, two-night sessions (7-14 days between sessions) in a sleep lab.
  - One night was an adaptation night and the other was a study night, where they underwent polysomnography for eight hours measuring primary outcome variables including total sleep time, sleep period time, sleep efficiency index, sleep onset latency, and amount of wake after sleep onset.
- Women also completed Leeds Sleep Evaluation Questionnaires and underwent testing of serum hormone concentrations every 20 minutes while asleep including progesterone, cortisol, growth hormone, and melatonin levels
  - Leeds sleep evaluation questionnaire (LSEQ) is a 10-question self-reported questionnaire assessing subjective sleep onset, sleep quality, ease of awakening from sleep, and alertness following wakefulness using a visual analog scale with a score of 0 indicating tired and a score of 100 indicating alert.

INTERVENTION (# IN THE GROUP): 12

COMPARISON (# IN THE GROUP): Self-controlled

FOLLOW-UP PERIOD: Not available

RESULTS:

Primary Outcome –

- The 4.5 mg dose of intranasal progesterone significantly improved the following sleep-EEG variables as compared to placebo:
  - Total sleep time (387 vs. 356 minutes; *P*=.007)
  - Wake after sleep onset (82 vs. 105 minutes; *P*=.024)
  - Length of stage 2 sleep (201 vs. 173 minutes; *P*=.022)
- The 9 mg dose of intranasal progesterone showed statistically significant improvement in the following sleep-EEG variables as compared to placebo:
  - Total sleep time (398 vs. 356 minutes; *P*=.046)
  - Sleep efficiency index (0.88 vs. 0.82; *P*=.029)
  - Wake after sleep onset time (75 vs. 105 minutes; *P*=.03)
  - Awake time (52 vs. 79 minutes; *P*=.024)
  - Length of stage 2 sleep (204 vs. 173 minutes; *P*=.004)
  - Length of non-REM sleep (327 vs. 290 minutes; *P*=.020)

Secondary Outcome –

- Participants reported fewer wake periods with the 4.5 mg dose of intranasal progesterone compared to placebo (LSEQ 61.3 vs 41.8 respectively, *P*=.02)
- Other subjective sleep variables were not significantly different between intranasal progesterone and placebo.

LIMITATIONS:

- Small sample size without described follow-up.
- The intranasal progesterone was a proprietary product of the funding pharmaceutical company, MetP Pharma.
- Progesterone was administered intranasally, which may have less variability in metabolism than oral progesterone.
- Hormone level results were not discussed at length, with no numerical values or statistical analysis provided.

Eliza Owens, MD
University of Missouri – Columbia
Columbia, MO

Is all Progesterone Created Equal? Effect of Progesterone in Postmenopausal Women

The Effect of Different Progestogens on Sleep in Postmenopausal Women: A Randomized Trial

Leeangkoonsathian E, Pantasri T, Chaovisitseree S, Morakot N. The effect of different progestogens on sleep in postmenopausal women: a randomized trial [published correction appears in Gynecol Endocrinol. 2017 Dec;33(12):i. doi: 10.1080/09513590.2017.1364585]. *Gynecol Endocrinol.* 2017;33(12):933-936. doi:10.1080/09513590.2017.1333094

KEY TAKEAWAY: Micronized progesterone and dydrogesterone are equally effective hormonal treatments for insomnia in postmenopausal women.

STUDY DESIGN: Randomized controlled trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Insomnia is a common symptom following menopause with hormonal treatment, estrogen with progesterone, being a standard of care treatment as it is proposed to reduce vasomotor variability and regulate body temperature. This study assesses the comparison between the use of dydrogesterone and micronized progesterone in its efficacy to improve sleep.

PATIENTS: Postmenopausal women with insomnia

INTERVENTION: Oral, micronized progesterone and estradiol valerate

CONTROL: Oral, dydrogesterone and estradiol valerate

PRIMARY OUTCOME: Self-reported sleep

METHODS (BRIEF DESCRIPTION):

- This study was conducted at a tertiary care center in Thailand and included post-menopausal women 40–60 years old.
  - Those with psychiatric or other medical conditions contributing to insomnia, contraindications to hormonal supplementation, or use of hypnotics were excluded from the study.
- All participants received daily estradiol valerate 1 mg
- Participants were randomized 1:1 to the following groups:
  - Oral dydrogesterone 10 mg
  - Micronized oral progesterone 100 mg
- Baseline data was obtained with no reported significant variance in vitals and laboratory work between control and intervention groups.
- Participants in both groups had baseline and monthly self-reported Pittsburgh Sleep Quality Index (PSQI) scores obtained.
  - PSQI is a measure of global sleep quality regarding sleep latency, duration, efficiency, disturbances, and daytime dysfunction with a range of scores of 0–21 with a score of 0–4 indicating quality sleep.

INTERVENTION (# IN THE GROUP): 50

COMPARISON (# IN THE GROUP): 50

FOLLOW-UP PERIOD: Three months

RESULTS:

Primary Outcome –

- Dydrogesterone with estradiol valerate significantly improved sleep quality compared to baseline (4.9 vs 10.5, respectively; *P*<.001).
- Micronized progesterone with estradiol valerate significantly improved sleep quality compared to baseline (6.3 vs 10.2, respectively; *P*=.003).
- Sleep quality between dydrogesterone and micronized progesterone was not statistically different (relative risk 0.91; 95% CI, 0.6–0.14).

LIMITATIONS:

- A large number of participants discontinued the intervention throughout the study (54% dydrogesterone group, 40% micronized progesterone group).
- This study does not investigate whether micronized progesterone alone would improve insomnia.
- The outcomes assessed were self-reported and could have been influenced by biases and limited by memory accuracy of subjective perceptions.

Levi Harris, DO, MPH
University of Missouri Bothwell Regional Medical Center
Columbia, MO

Evaluating the Impact of Bariatric Surgery on Sexual Function

The Relationships Between Bariatric Surgery and Sexual Function: Current Evidence Based Medicine

Liu S, Cao D, Ren Z, et al. The relationships between bariatric surgery and sexual function: current evidence based medicine. *BMC Urol*. 2020;20(1):150. Published 2020 Oct 2. doi:10.1186/s12894-020-00707-1

KEY TAKEAWAY: Bariatric surgery may be effective in improving sexual function in male patients with obesity.

STUDY DESIGN: Meta-analysis and systematic review of 11 randomized controlled trials (N=380)

LEVEL OF EVIDENCE: STEP 1

BRIEF BACKGROUND INFORMATION: Erectile dysfunction is a very common concern for male patients and is expected to impact up to 322 million patients by 2025. Obesity is associated with sexual dysfunction in men, though the mechanism is not well understood. This study investigates the potential impact of bariatric surgery on sexual function.

PATIENTS: Middle-aged men with obesity

INTERVENTION: Bariatric surgery

CONTROL: Baseline

PRIMARY OUTCOME: Postoperative sexual function

METHODS (BRIEF DESCRIPTION):

- Meta-analysis of self-controlled randomized controlled studies that included middle-aged men with obesity who underwent bariatric surgery published in PubMed, Embase, The Cochrane Library, CNKI, and Clinical Trials published in English before May 2019 were included.
  - Studies were excluded if they evaluated only women or were missing pre/postoperative data.
- Each study used at least one sexual function assessment scoring system that was collected in the pre- and post-operative setting to measure the primary outcome.
  - The International Index of Erectile Function (IIEF) score measures erectile function, orgasm function, sexual desire, intercourse satisfaction, and overall satisfaction.
    - A score of zero to five was given to each of the questions in the four areas of sexual function. The sum of the answers (maximum score of 75) is the total score of the questionnaire, with higher scores meaning that the patient is less likely to have experienced sexual dysfunction.
  - The Brief Sexual Function Inventory (BSFI) score measures sex drive, erection, ejaculation, desire, problem assessment, and sexual satisfaction.
    - A five-point scale is used to assign each question a score regarding the areas of sexual function.
    - The sum of the answers is the total score of the questionnaire (maximum score of 45), with higher scores meaning that the patient is less likely to have experienced sexual dysfunction.

INTERVENTION (# IN THE GROUP): 370

COMPARISON (# IN THE GROUP): Self-controlled

FOLLOW-UP PERIOD: Variable (range 2–24 months)

RESULTS:

Primary Outcome –

- Bariatric surgery improved sexual function, measured via IIEF, compared to baseline.
  - Erectile function (8 studies, N=239; mean difference [MD] 5.3; 95% CI, 4.1–6.5)
  - Total erectile function (4 studies, N=109; MD 7.2; 95% CI 4.3–10)
  - Intercourse satisfaction (6 studies, N=190; MD 2.6; 95% CI, 1.2–3.9)
  - Orgasmic function (6 studies, N=190; MD 0.50; 95% CI, 0.60–0.94)
  - Overall satisfaction (6 studies, N=190; MD 1.7; 95% CI, 0.78–2.6)
  - Sexual desire (6 studies, N=190; MD 1.3; 95% CI, 0.61–1.9)
- Bariatric surgery improved sexual function, measured via BSFI, compared to baseline.
  - Erection (2 studies, N=111; MD 2.5; 95% CI, 2.4–2.7)
  - Ejaculation (2 studies, N=111; MD 1.4; 95% CI, 1.3–1.5)
  - Desire (2 studies, N=111; MD 1.4; 95% CI, 1.3–1.5)

- Problem assessment (2 studies, N=111; MD 2.2; 95% CI, 2.1–2.3)
- Sexual satisfaction (2 studies, N=111; MD 0.7; 95% CI, 0.60–0.76)

LIMITATIONS:

- Limited generalizability, given that the results were conducted in seven different countries.
- Limited information about patient populations was provided, other than average BMI, age, and surgery evaluated in each study.
- Data is self-reported and there are variable reporting methods (IIEF score vs BSFI score).
- Small sample sizes with a short length of follow-up in each study.

Elizabeth Sherman, MD
University of Missouri – Columbia
Columbia, MO

Exploring the Impact of Bariatric Surgery on Quality of Life

Surgically Induced Weight Loss Effects on Sexual Quality of Life of Obese Men: A Prospective Evaluation

Arolfo S, Scozzari G, Di Benedetto G, Vergine V, Morino M. Surgically induced weight loss effects on sexual quality of life of obese men: a prospective evaluation. *Surg Endosc*. 2020;34(12):5558-5565. doi:10.1007/s00464-019-07356-y

KEY TAKEAWAY: Bariatric surgery improves sexual function and quality of life (QoL) in men with obesity compared to baseline.

STUDY DESIGN: Prospective cohort study

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: Prior literature has noted that obesity negatively impacts sexual function and overall quality of life in men. There is conflicting data regarding the effect of bariatric surgery on testosterone levels, which subsequently influences sexual quality of life. This study sought to understand the efficacy of bariatric surgery on sexual function and related quality of life in men with obesity.

PATIENTS: Middle-aged men with obesity

INTERVENTION: Bariatric surgery

CONTROL: Baseline

PRIMARY OUTCOME: Sexual quality of life

Secondary Outcome: Weight loss, hormone levels, biochemical levels, general QoL

METHODS (BRIEF DESCRIPTION):

- Men with obesity (median age 43 years old, median BMI 44) who underwent sleeve gastrectomy (91%) and Roux-en-Y gastric bypass (9%) were compared to their baseline measures.
- Initial hormonal levels (testosterone, estradiol), biochemical markers (basal glycemia, HbA1c, lipid profile), and anthropometric parameters (weight, BMI, percentage body fat) were assessed.
- To measure the sexual quality of life, participants completed the International Index of Erectile Function (IIEF) which focused on five sexual function domains including erectile function, orgasmic function, sexual desire, intercourse satisfaction, and overall satisfaction.
    - Scores higher than 22 indicate no erectile dysfunction and scores lower than seven indicate severe erectile dysfunction.
- To measure the general quality of life, participants completed the Short-Form 36 (SF-36) questionnaire as a self-reported measure of eight health domains.
    - An IIEF score of zero indicates maximum disability and a score of 100 indicates no disability.
- These assessments were collected at baseline and 12 months post-surgical procedure.

INTERVENTION (# IN THE GROUP): 44

COMPARISON (# IN THE GROUP): Self-controlled

FOLLOW-UP PERIOD: 12 months

RESULTS:

Primary Outcome –

- Bariatric surgery improved overall sexual function satisfaction compared to baseline (no dysfunction reported in 48% vs 25%, respectively; *P*=.028; NNT=4)

Secondary Outcome –

- Bariatric surgery improved the following as compared to baseline:
    - Weight loss
        - BMI (44 vs 31, respectively; *P*≤.001)
        - Body weight (137 vs 100 kg, respectively; *P*≤.001)
    - Hormonal levels
        - Total testosterone (4.7 vs 2.3 ng/dL, respectively; *P*<0.0)
        - Eugonadism (total testosterone ≥4 ng/dL) (68% vs 10% of participants, respectively; *P*>.001; NNT=2)
    - Biochemical levels
        - HbA1c (35 vs 42.5 mmol/mol, respectively; *P*<.001)
        - Basal glycemia (87 vs 98 mg/dL, respectively; *P*<.004)
        - HDL (51 vs 38 mg/dL, respectively; *P*<.001)
    - General QoL (89 vs 61, respectively; *P*<.001)

LIMITATIONS:

- Most patients involved in this study underwent sleeve gastrectomy limiting generalizability to

patients who undergo alternative weight loss procedures.

- Limited follow-up period of 12 months which may not capture the long-term side effects of the surgery such as malabsorption with RYGB.

Farah Heis, MBBS
University of Missouri-Columbia
Columbia, MO

Revitalizing Reproductive Health: Effects of Roux-en-Y Gastric Bypass

Effect of Roux-en-Y Gastric Bypass Surgery on the Sex Steroids and Quality of Life in Obese Men

Hammoud A, Gibson M, Hunt SC, et al. Effect of Roux-en-Y gastric bypass surgery on the sex steroids and quality of life in obese men. *J Clin Endocrinol Metab.* 2009;94(4):1329-1332. doi:10.1210/jc.2008-1598

KEY TAKEAWAY: Roux-en-Y gastric bypass can improve perceived sexual function and hormone levels in severely obese men.

STUDY DESIGN: Prospective cohort study

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: Severely obese men have higher estradiol levels, lower free and total testosterone, as well as lower perceived sexual function scores. This study sought to understand the effect of weight loss surgery on sexual function and obtain an objective measure of hormone levels.

PATIENTS: Adult men with severe obesity

INTERVENTION: Roux-en-Y gastric bypass surgery

CONTROL: No surgical intervention

PRIMARY OUTCOME: Hormone level and sexual quality of life

METHODS (BRIEF DESCRIPTION):

- Severely obese men (mean age 49 years old, mean BMI 46) who were a part of the Utah Obesity Study underwent Roux-en-Y gastric bypass and were compared to those who were unable to undergo surgery (patient or insurance declined).
- Initial fasting testosterone, insulin, and glucose levels were obtained as well as anthropometric values (height, weight, BMI, percentage body fat) were measured.
- Participants completed an Impact of Weight on Quality of Life-Lite questionnaire (IWQOL-Lite) which focused on four areas: Lack of enjoyment with sexual activity, lack of sexual desire, difficulty with sexual performance, and avoidance of sexual encounters.
    - Four areas were focused on via 31 questions
    - Each question was scored on a 5-point Likert scale with higher scores indicating greater dissatisfaction with sexual quality of life.
- Hormone levels, including serum estradiol and free and total testosterone levels, were measured 12 hours after fasting.
- Scores were measured at baseline and at two years.

INTERVENTION (# IN THE GROUP): 22

COMPARISON (# IN THE GROUP): 42

FOLLOW-UP PERIOD: Two years

RESULTS:

Primary Outcome –

- Roux-en-Y gastric bypass reduced dissatisfaction with sexual quality of life compared to no surgery at two years (mean change –7.5 vs –0.1, respectively; $p<.001$).
- Roux-en-Y gastric bypass decreased serum estradiol levels decreased compared to no surgery at two years (mean change –8.1 vs –0.0 pg/ml, respectively; $P=.003$).
- Roux-en-Y gastric bypass increased total testosterone compared to no surgery at two years (mean change 310 vs 14 ng/dl, respectively; p<.001).

LIMITATIONS:

- Difficult to determine if Roux-en-Y gastric bypass itself as compared to weight loss improved sexual hormones and perceived sexual function.
- Many men were excluded due to a lack of follow-up and unavailable blood samples (142 men from the Utah Obesity Study).
- The study did not investigate the impact of weight loss on hormone levels and sexual function outside of surgical intervention.

Claire Wolber, MD
University of Missouri-Columbia
Columbia, MO