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FPIN
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Prophylaxis or No? That Is the Question

Prophylactic Antibiotics for Upper Gastrointestinal Bleeding in Patients with Cirrhosis: A Systematic Review and Bayesian Meta-Analysis

Prosty C, Noutsios D, Dubé LR, et al. Prophylactic Antibiotics for Upper Gastrointestinal Bleeding in Patients With Cirrhosis: A Systematic Review and Bayesian Meta-Analysis. *JAMA Intern Med*. 2025;185(10):1194-1203. doi:10.1001/jamainternmed.2025.3832

KEY TAKEAWAY: Shorter duration or no antibiotic prophylaxis does not increase the risk of all-cause mortality compared to traditional 5–7-day prophylaxis in adults admitted with cirrhosis and upper gastrointestinal (GI) bleeding.

STUDY DESIGN: Systematic review and Bayesian meta-analysis of 14 randomized controlled trials (RCTs) (N=1,322)

LEVEL OF EVIDENCE: STEP 1

BRIEF BACKGROUND INFORMATION: Current standard of care regarding adults with cirrhosis and upper GI bleeding recommends antibiotic prophylaxis to offset the risk of infection. Patients with upper GI bleeding and cirrhosis have a high mortality rate and high rates of infection, rebleeding, and other complications. Recent smaller studies have not demonstrated benefit from antibiotic prophylaxis, but recent meta-analyses are lacking. This study aimed to address the evidence supporting this standard.

PATIENTS: Adults admitted with cirrhosis and upper GI bleeding

INTERVENTION: Shorter- or no-duration antibiotic prophylaxis

CONTROL: Longer-duration antibiotic prophylaxis

PRIMARY OUTCOME: All-cause mortality

Secondary Outcome: Early rebleed within seven days, bacterial infections

METHODS (BRIEF DESCRIPTION):

- Systematic review and Bayesian meta-analysis including 14 RCTs with Bayesian analysis using a pre-specified 5% risk difference noninferiority margin.
- RCTs in adults with cirrhosis and upper GI bleeding were included, with a post-hoc analysis of only studies done since 2004 to account for therapeutic improvements.
- Patients included adults with cirrhosis and upper GI bleeding.
  - Mean age of 41–62 years old
  - 74% were male
  - 90% had a variceal source of bleeding
- Interventions included antibiotic prophylaxis with fluoroquinolones, 3rd-generation cephalosporins, and β-lactams
- Comparison was antibiotic duration: Short (2–3 days), long (5–7 days), or none.
- All but one study specifically excluded patients with signs of infection on enrollment, and one specifically excluded patients with antibiotic use in the three days prior to enrollment.
- The primary outcome measured all-cause mortality and was reported at varying endpoints, ranging from in-hospital to up to 42 days post-hospitalization, with most studies reporting 30-day mortality.
- The following were measured as the secondary outcomes:
  - Early rebleeding, reported by clinician as a second bleeding event within seven days
  - Bacterial infection, defined variously among included studies but generally using positive culture data and/or imaging data such as chest X-ray results. The studies did not share a uniform definition of bacterial infection.

INTERVENTION (# IN THE GROUP): 1,322

COMPARISON (# IN THE GROUP): 657

FOLLOW-UP PERIOD: In-hospital period or up to 30 days

RESULTS:

Primary Outcome –

- Shorter durations or no-duration antibiotic prophylaxis did not increase mortality compared to longer durations (risk difference [RD] 0.9%; 95% credible interval [CrI], –2.6 to 4.9).

Secondary Outcome –

- Shorter antibiotic durations did not increase the risk of early rebleeding within seven days compared to longer durations.

- Shorter durations or no-duration antibiotic prophylaxis increased the risk of infection compared to longer durations (RD 15%; 95% CrI, 5.0–26).
    - However, in the post-hoc analysis, the probability of noninferiority for bacterial infections was higher (75% vs 0.10%).

LIMITATIONS:

- Trials were unblinded, with some heterogeneity of regimen.
- Infection definitions were inconsistent and some studies' criteria would consider asymptomatic bacteriuria an "infection," thus leading to likely overdiagnosis of infections.
- Most studies had short follow-up and limited long-term outcome assessment.
- The studies to date are small and not adequately powered for appropriate primary and secondary outcomes.
- Most included studies predate restrictive transfusion strategies and the widespread use of the covered transjugular intrahepatic portosystemic shunt (TIPS) procedure, which has significantly reduced cirrhosis-related morbidity.
- Publication bias favored longer antibiotic courses.
- Adverse events were not reported.

Cecil Wright Clarkson, MD
Northwest Washington FMRP
Bremerton, WA

Medication Abortion: Early Action, Equal Endpoint

Randomized Trial of Very Early Medication Abortion

Brandell K, Jar-Allah T, Reynolds-Wright J, et al. Randomized Trial of Very Early Medication Abortion. *N Engl J Med*. 2024;391(18):1685-1695. doi:10.1056/NEJMoa2401646

KEY TAKEAWAY: Very early medication abortion, defined as gestations up to 42 days, was noninferior to delayed medication abortion treatment in regard to complete abortion.

STUDY DESIGN: Multicenter, multinational, noninferiority, randomized, controlled trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: There is minimal evidence of medication abortion efficacy at very early gestations before pregnancies can be visualized on ultrasound. In settings where ultrasound confirmation of an intrauterine pregnancy is routine, some clinicians may delay intervention due to concerns of ectopic pregnancy. Considering recent legal restrictions of abortion after six weeks gestation in some US states, research on providing very early medication abortion is clinically relevant.

PATIENTS: Pregnant women up to an estimated 42 days of gestation that requested medication abortion

INTERVENTION: Early start medication abortion

CONTROL: Delayed start medication abortion

PRIMARY OUTCOME: Complete abortion

Secondary Outcome: Incomplete abortions, surgical intervention for incomplete abortion, infections treated with antibiotics

METHODS (BRIEF DESCRIPTION):

- The Very Early Medication Abortion (VEMA) trial took place at 26 sites located within nine different countries.
- Pregnant women requesting medication abortion up to an estimated 42 days of gestation, which was described as an empty cavity or sac-like structure without a yolk sac or embryonic pole on ultrasound.
- Baseline characteristics of patients included an average age of 29 years old and body mass index (BMI) of 25 kg/m^2.
- Groups were similar at baseline aside from more pathologic pregnancies in the delayed start group largely due to early pregnancy losses.
- The intervention group received medication abortion within a day of trial inclusion. The comparison group delayed medication abortion until intrauterine pregnancy was visualized on ultrasound seven days later.
- If intrauterine pregnancy was not visualized, another ultrasound was performed a total of 14 days later. If a pregnancy was not visualized at that time, the pregnancy was deemed pathologic and subsequently treated based on local guidelines.
- Patients received 200 mg of mifepristone orally followed by 800 ug of misoprostol vaginally, sublingually, or buccally, according to local standards.
- In the early-start group, the primary outcome was defined by an 80% decrease in hCG measurement seven days after medication intake.
- In the standard group, the outcome was assessed depending on local practices, such as urine or blood hCG levels or ultrasound.
- Telephone, in person, or medical record follow up was completed four weeks after abortion.
- The noninferiority margin was three percentage points.

INTERVENTION (# IN THE GROUP): 754

COMPARISON (# IN THE GROUP): 750

FOLLOW-UP PERIOD: Four weeks

RESULTS:

Primary Outcome –

- There was no difference in complete abortion between the early start medication abortion group and delayed medication abortion group (risk ratio [RR] 1.0; 95% CI, 0.98–1.0).

Secondary Outcome –

- Compared to the control group, patients in the intervention group were more likely to have ongoing pregnancy (RR 20; 95% CI, 2.7–151) and less likely to have surgical intervention for incomplete abortion (RR 0.41; 95% CI, 0.21–0.77).
- Patients in the intervention group were less likely to have an infection treated with antibiotics than the control group (RR 0.37; 95% CI, 0.18–0.74).

LIMITATIONS:

- Patients were not blinded given the nature of this study, potentially introducing bias for subjective data gathered.
- Women with irregular bleeding or an unknown date of last menstrual period were either included or excluded at the discretion of the local researcher leading to potential differences in estimated gestational age.
- Countries had varying standard practices as in the route of administration of misoprostol and methods for assessing treatment outcome introducing variation in protocol.

Shannon Cunningham, DO
Advocate Illinois Masonic Medical Center FMRP
Chicago, IL

Can Pharmacologic Interventions Help Improve Liver Markers in Nonalcoholic Fatty Liver Disease?

Efficacy of Pharmacologic Interventions on Magnetic Resonance Imaging Biomarkers in Patients with Nonalcoholic Fatty Liver Disease: Systematic Review and Network Meta-Analysis

Malandris K, Papandreou S, Vasilakou D, et al. Efficacy of Pharmacologic Interventions on Magnetic Resonance Imaging Biomarkers in Patients with Nonalcoholic Fatty Liver Disease: Systematic Review and Network Meta-analysis. *J Gastroenterol Hepatol*. 2024;39(7):1219-1229. doi:10.1111/jgh.16559

KEY TAKEAWAY: Multiple pharmacologic agents appear effective in reducing hepatic steatosis and liver fat content; however, larger randomized-controlled trials with longer durations are needed to establish and confirm efficacy at improving fibrosis.

STUDY DESIGN: Systematic review and meta-analysis (pairwise and network) of 47 randomized-controlled trials (RCTs) (N=8,583)

LEVEL OF EVIDENCE: STEP 2 (downgraded due to most outcomes were determined by very small subsets of the number of trials, significant heterogeneity, high risk of bias in a significant number of trials in the primary outcomes)

BRIEF BACKGROUND INFORMATION: Nonalcoholic fatty liver disease (NAFLD) is widespread and shows increasing prevalence tied to similar trends in obesity, type 2 diabetes mellitus (T2DM), and metabolic syndrome. It is among the leading causes of liver cancer and liver transplantation. Currently, no licensed pharmacologic treatments exist for the treatment of NAFLD. This study aimed to uncover effective pharmacologic treatments for this condition by focusing on MRI biomarkers.

PATIENTS: Adults with NAFLD (confirmed either via biopsy or MRI)

INTERVENTION: Various pharmacologic agents

CONTROL: Placebo or against other treatments

PRIMARY OUTCOME: Absolute change from baseline in liver fat content (LFC)

Secondary Outcome: Absolute change from baseline in liver stiffness (LS), number of patients with relative reduction in liver fat content of ≥30%, and number of patients with relative reduction in MR-elastography (MRE) of ≥15%

METHODS (BRIEF DESCRIPTION):

- Systematic database search revealed 6,095 records and 47 total RCTs met eligibility criteria.
- Studies were included if subjects were adults with biopsy-confirmed or MRI-confirmed NAFLD and the treatment lasted at least 12 weeks.
- Trials were excluded if they assessed non-pharmacological or multiple treatments.
- Over half of patients had T2DM and/or an overweight or obese body mass index (BMI) (unspecified quantity).
- Most patients had NASH with F1-F3 fibrosis on liver biopsy.
- Risk of bias assessment for all trials was conducted using the revised Cochrane Risk of Bias tool 2.0. Risk of bias was stratified as:
  - 1) Low risk if all domains were at low risk,
  - 2) High risk if at least one domain was at high risk, and
  - 3) Trials that didn't fall into either of these two categories were considered to have some concern for bias.
- Interventions varied to include 31 agents from 15 different active drug classes that were compared to each other and to placebo.
- The individual agents included glucagon-like peptide-1 receptor agonists (GLP-1 RAs), thiazolidinediones, vitamin E, fibroblast growth factor (FGF) analogs, sodium-glucose cotransporter 2 inhibitors (SGLT-2is), Farnesoid X receptor (FXR) agonists, thyroid hormone receptor-B agonists, acetyl CoA- carboxylase (ACC) inhibitors, PXL065, gastric inhibitory peptide (GIP)-GLP-1 RA, stearoyl-CoA desaturase (SCD)1 inhibitor, apoptosis signal regulating kinase 1 (ASK1) inhibitors, dipeptidyl peptidase 4 (DPP-4) inhibitors, peroxisome proliferator-activated receptor (PPAR) agonists, and Belapectin.
- The primary outcome measured LFC measured by either MRI – proton density fat fraction (MRI-PDFF) or MR-spectroscopy (MR-S). Data shows a histologic response corresponds to at least a 30% relative reduction in MRI-PDFF.

- Secondary outcomes measured included absolute change in LS from baseline (measured by MRE) number of patients with a relative reduction in LFC of ≥30%, and number of patients with a relative reduction in MRE of ≥15%.
- Results for primary and secondary outcomes were determined via pairwise meta-analysis.
- P-scores were used to rank the treatment. Scores range from 0–1 and indicate the probability of a single treatment being better than another.

INTERVENTION (# IN THE GROUP): Not available

COMPARISON (# IN THE GROUP): Not available

FOLLOW-UP PERIOD: Variable, minimum of 12 weeks; ranged from 13–96 weeks (median duration of treatment across trials was 36 weeks)

RESULTS:

Primary Outcome –

- The following drug classes reduced absolute LFC compared to placebo:
  - Thiazolidinediones (3 studies; p-score 0.87; mean difference [MD] –7.3; 95% CI, −11 to −3.8; I^2=54%), most notably pioglitazone (3 studies; p-score 0.82; MD –7.3, 95% CI, –11 to –3.8; I^2=54%).
  - FGF analogs (6 studies; p-score 0.75; MD −5.9%; 95% CI, −9.2 to −2.6; I^2=93%), most notably aldafermin (2 studies; p-score 0.58; MD –4.6; 95% CI, –8.2 to –0.90; I^2=0%) and pegbelfermin (2 studies; p-score 0.43; MD –3.2; 95% CI, –6.7 to 0.31; I^2=73%).
  - GLP-1 RAs (4 studies; p-score 0.76; MD −5.0%, 95% CI, −7.2 to −2.8; I^2=72%), most notably semaglutide (2 studies; p-score 0.63; MD –5.1; 95% CI, –8.8 to –1.3; I^2=82%).
  - SGLT-2is (4 studies; p-score 0.57; MD −4.5%; 95% CI, −5.6 to −3.4; I^2=72%), most notably dapagliflozin (1 study; p-score 0.58; MD –4.7; 95% CI, –9.4 to –0.1; I^2=not applicable).
  - FXR agonists (4 studies; p-score 0.52; MD −3.7%; 95% CI, −5.4 to −2.0; I^2=20%), including cilofexor (2 studies; p-score 0.45; MD –3.7; 95% CI, –7.2 to 0.38; I^2=0%).

Secondary Outcome –

- No drug class had a statistically significant effect on absolute change in LS compared to placebo.
- The following drug classes were more likely to achieve relative reduction in LFC of ≥30% compared to baseline.
  - GLP-1 RAs (2 studies; p-score 0.76; MD 6.0; 95% CI, 2.6–14; I^2=0%)
  - FGF analogs (7 studies; p-score 0.67; MD 4.5; 95% CI, 2.7–7.6; I^2=0%)
  - FXR agonists (2 studies; p-score 0.56; MD 3.7; 95% CI, 1.8–7.2; I^2=0%)
- Incidence of relative reduction in MRE of ≥15% was similar between drug classes and placebo. The only drug classes tested were GLP-1 RAs and FGF analogs.

LIMITATIONS:

- There was notable heterogeneity among studies with patients with varying co-morbidities (e.g., T2DM, overweight, obesity, etc.).
- There were small sample sizes and short duration of studies which can limit validity and generalizability.
- Of the 47 trials studied in the meta-analysis, nine were open label and one did not specify blinding, which may have introduced bias.
- On risk of bias assessment, of the 47 total trials included in this meta-analysis, 14 trials were considered to have a risk of high overall bias.
- Confidence across comparisons was determined to be low to very low.
- 36 of the 47 trials were sponsored by the pharmaceutical industry.
- Some of the pharmacologic agents studied have not been approved by the FDA for public use in the US which limits the usefulness of the data in this population.

Priyanka Kulkarni, MD
North Side FMRP
Milwaukee, WI

Om vs Opioids: The Impact of Mindfulness-Based Therapy vs Cognitive Behavioral Therapy on Opioid-Treated Chronic Low Back Pain

Mindfulness vs Cognitive Behavioral Therapy for Chronic Low Back Pain Treated with Opioids

Zgierska AE, Edwards RR, Barrett B, et al. Mindfulness vs Cognitive Behavioral Therapy for Chronic Low Back Pain Treated with Opioids: A Randomized Clinical Trial. *JAMA Netw Open*. 2025;8(4):e253204. Published 2025 Apr 1. doi:10.1001/jamanetworkopen.2025.3204

KEY TAKEAWAY: Cognitive behavioral therapy (CBT) and mindfulness based therapy (MBT) significantly improve pain, function, and quality of life among patients with opioid-treated chronic low back pain (CLBP), with no significant difference between the two. MBT, like CBT, should be considered as a treatment option for opioid-treated chronic low back pain.

STUDY DESIGN: Multisite partially masked two-arm randomized clinical trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: CLBP is the most common form of chronic noncancer pain treated with opioids, yet many patients experience inadequate relief and significant risks from long-term opioid use. While CBT is the standard psychological treatment, and MBT shows promise, their long-term effectiveness in opioid-treated CLBP has not been well studied.

PATIENTS: Adults with opioid treated CLBP

INTERVENTION: MBT

CONTROL: CBT

PRIMARY OUTCOME: Pain and functional limitation

Secondary Outcome: Opioid dose and health related quality of life (QOL)

METHODS (BRIEF DESCRIPTION):

- Patients with an average pain intensity of at least three on the Brief Pain Inventory (BPI) and a CLBP-related functional limitations score of at least 21 on Oswestry Disability Index (ODI) were included in the study.
- Patients with previous training in MBT or CBT, who were pregnant, or those with psychotic disorders with a psychotic episode in the past one year were excluded.
- Patients were randomized 1:1 to CBT or MBT groups, participating in eight weekly two-hour therapist led group sessions tailored to the needs of the person with CLBP and recommended home practice of 30 min per day, six days per week.
    - CBT served as the usual treatment.
    - MBT treatment involved training in mindfulness skills aimed toward deconstructing pain into constituent cognitive, emotional, and sensorial components and "adaptively coping with pain and negative emotions."
- The co-primary outcomes measures included:
    - The past week's average pain severity was measured using the BPI scale. Scores range from 0–10, with higher values indicating greater pain.
    - Back-pain related functional limitations were measured using the ODI scale. Scores range from 0–100, with higher values indicating greater limitation.

INTERVENTION (# IN THE GROUP): 385

COMPARISON (# IN THE GROUP): 385

FOLLOW-UP PERIOD: Six and 12 months

RESULTS:

Primary Outcome –

- There were no significant between group differences in pain or function at six and 12 months.
- At 12 months, both groups demonstrated improvements in average pain severity and functional limitation scores:
    - Pain severity
        - MBT (change –0.45; 95% CI, –0.64 to –0.26)
        - CBT (change –0.59; 95% CI, –0.78 to –0.40)
    - Functional limitation:
        - MBT (change –3.2; 95% CI, –0.45 to –1.9)
        - CBT (change –3.5; 95% CI, –4.9 to –2.1)

Secondary Outcome –

- Participants in CBT and MBT groups both experienced improvements in health-related QOL and decreased opioid dose after 12 months of treatment, without significant between-group differences.

LIMITATIONS:

- The study population was predominantly White and non-Hispanic, which may limit applicability to more diverse populations.

- All primary and secondary outcomes were self-reported, which may be subject to recall or social desirability bias.
- Lack of a usual care group may limit efficacy interpretation.
- Transitioning from in-person to remote therapy introduced possible confounding variables.
- Study retention was lower than anticipated and used for sample size calculations, which may suggest the study's sample was not fully powered to detect between group difference.

Greer Russell, DO, MPH
Advocate Health Care Illinois Masonic FMRP
Chicago, IL

From Bloat to Bliss: The Mediterranean Diet for IBS

The Mediterranean Diet for Irritable Bowel Syndrome: A Randomized Clinical Trial

Bamidele JO, Brownlow GM, Flack RM, et al. The Mediterranean Diet for Irritable Bowel Syndrome: A Randomized Clinical Trial. *Ann Intern Med*. 2025;178(12):1709-1717. doi:10.7326/ANNALS-25-01519

KEY TAKEAWAY: A mediterranean diet improves irritable bowel syndrome (IBS) symptoms and has better adherence compared to traditional dietary advice in patients with IBS.

STUDY DESIGN: Block randomized, noninferiority clinical trial

LEVEL OF EVIDENCE: STEP 3 (downgraded due to short study duration)

BRIEF BACKGROUND INFORMATION: Patients with IBS overall have limited evidence-based options regarding dietary advice. This study aimed to explore the clinical response and dietary satisfaction of the mediterranean diet when compared to traditional dietary advice.

PATIENTS: Adults with IBS

INTERVENTION: Mediterranean diet (MD)

CONTROL: Traditional dietary advice (TDA)

PRIMARY OUTCOME: Reduction in IBS-symptom severity
Secondary Outcome: Changes in psychosocial health, quality of life, diet satisfaction and Mediterranean diet Adherence Screener (MEDAS)

METHODS (BRIEF DESCRIPTION):

- Patients were evaluated at accredited teaching hospitals across the United Kingdom (UK).
- There was an assumed response rate of 65% in the MD group as initial data showed uncertainty with an 80% initial response rate.
- A margin of >5% was deemed sufficient to be considered that MD was noninferior to TDA.
- There was an anticipated 10% dropout rate, and 120 patients were needed to have significant power (80%) so 134 patients was the target sample size for the study.
- Patients were block randomized into two diet groups 1:1 and a block size of four according to the severity of IBS (either mild, moderate or severe) as well as IBS subtypes (mixed, diarrhea or constipation dominant).
    - Once randomized, patents attended a group online session of other patients with the same diet to get education from dieticians.
    - The groups only knew their diets and not the diet of the other group.
- The primary outcome was measured using the IBS Symptom Severity Scale (IBS-SSS) and the outcome was a ≥50-point reduction in the IBS-SSS, which is a five question, 500-point visual analog scale (VAS) questionnaire measuring symptoms severity of abdominal distention, interference with quality of life, abdominal pain and frequency of abdominal pain.
    - Included patients had an IBS-SSS score of ≥75.
    - The ≥50 point or greater reduction in the IBS-SSS was also used as the minimal clinically important difference (MCID) and was derived from a prior study referenced.
- Secondary outcomes were measured using the following:
    - Physical and mental quality of life was assessed using a Form 8 Health survey which is an eight-item score. Scores range from 0–100, with higher scores indicating better quality of life.
    - Diet satisfaction assessed with a 10-item questionnaire. Scores range from 1–5, with higher scores indication greater satisfaction.
    - Somatic symptoms were assessed using the Patient Health Questionnaire (PHQ-4). Scores range from 0–12, with higher scores indicating more severe symptoms.
    - MEDAS is a 14-point scale assessing the components of the mediterranean diet. Scores range from 0–14, with higher scores representing greater adherence.

INTERVENTION (# IN THE GROUP): 68

COMPARISON (# IN THE GROUP): 71

FOLLOW-UP PERIOD: Six weeks

RESULTS:

Primary Outcome –

- The ≥50-point reduction in IBS-SSS over six weeks was met by more study participants in the MD group compared to the TDA group:
    - MD (62%; 95% CI, 50–73)

- TDA (42%; 95% CI, 31–55)
- The clinical response favored the MD suggesting noninferiority to TDA (difference 20%; 95% CI, 4–36).

Secondary Outcome –

- Physical and mental quality of life, diet satisfaction, and somatic symptoms were not statistically different between the two groups.
- MEDAS had a significantly greater change in score with the MD group compared to TDA (3.8 vs 1.2, respectively; *P*<.001, suggesting that MD adherence was greater in the MD group than TDA group.

LIMITATIONS:

- Because of the nature of the study design, participants were unable to be blinded to treatment.
- The patients were 19–65 years old with no one <19 years old where IBS is more common.
- Six weeks is a short follow-up.
- The study was performed in the UK where IBS population likely differs to that in other countries, therefore potentially limiting the generalizability of the study outcomes.

George Saboura, MD
Medical College of Georgia
Augusta, GA

Better, But Not Better Than Sham: TTNS for Urgency Urinary Incontinence

Transcutaneous Tibial Nerve Stimulation for Urge Incontinence: A Randomized Clinical Trial

Shah NM, Lukacz ES, Ferrante KL, Menefee SA. Transcutaneous Tibial Nerve Stimulation for Urge Incontinence: A Randomized Clinical Trial. *Urogynecology (Phila)*. 2025;31(3):225-233. doi:10.1097/SPV.0000000000001616

KEY TAKEAWAY: Transcutaneous tibial nerve stimulation (TTNS) is not superior to sham therapy and both groups demonstrated statistically and clinically meaningful improvement from baseline, suggesting a strong placebo or nonspecific treatment effect rather than a true treatment benefit of TTNS.

STUDY DESIGN: Single-center, double-blinded, sham-controlled randomized clinical trial

LEVEL OF EVIDENCE: STEP 3 (downgraded due to small sample size and lack of statistically significant difference between intervention and sham groups)

BRIEF BACKGROUND INFORMATION: Urgency urinary incontinence (UUI) is common in adult women and significantly impairs quality of life, yet many patients do not tolerate or respond adequately to pharmacologic therapies. Neuromodulation techniques such as TTNS have emerged as a low-risk, noninvasive alternative, but existing studies show inconsistent results, with uncertainty regarding whether symptom improvement exceeds placebo effects. This uncertainty underscores the need for well-designed randomized, sham-controlled trials to clarify the true efficacy of TTNS.

PATIENTS: Adult women with either pure UUI or urgency-predominant mixed urinary incontinence

INTERVENTION: TTNS

CONTROL: Sham treatment

PRIMARY OUTCOME: Symptom bother and health related quality of life

Secondary Outcome: Leakage reduction, subjective improvement, voiding frequency

METHODS (BRIEF DESCRIPTION):

- The study included ambulatory women with a mean age of 66 (±12) years old. Most study participants were predominantly postmenopausal (83%) and non-Hispanic White (86%).
- Participants in intervention group self-administered placement of electrodes on medial leg, with units starting at 20 Hz and increased until a big toe motor response occurred or discomfort was felt.
- Participants in sham group self-administered placement of electrodes on lateral leg to avoid stimulating the tibial nerve with an amplitude fixed at 5 mA.
- Both groups completed home treatments for 30 minutes, twice weekly for 12 weeks.
- OAB-q was used to measure changes in "Symptom Severity" and "Health-Related Quality of Life" (HRQOL) scales. Scores range from 0–100.
  - For the Symptom Severity subscale, higher scores indicate greater bother
  - For the HRQOL subscale, higher scores indicate better quality of life.
- Participants maintained three-day diaries to record the frequency of voids and UUI episodes. Success was defined as a ≥50% reduction in leakage episodes.
- The Patient Global Impression of Improvement (PGI-I) was used post-intervention. This scale allows patients to rate their condition from "very much better" to "very much worse".

INTERVENTION (# IN THE GROUP): 65

COMPARISON (# IN THE GROUP): 35

FOLLOW-UP PERIOD: 12 weeks

RESULTS:

Primary Outcome –

- TTNS did not significantly affect symptom severity compared to sham treatment (43 vs 51, respectively; *P*=.08).
- TTNS did not significantly improve HRQOL compared to sham treatment (26 vs 32, respectively; *P*=.20).

Secondary Outcome –

- TTNS significantly decreased the number of daily voids compared to the sham group (11 vs 12, respectively; *P*=.009).
- TTNS did not significantly affect the proportion of participants achieving a ≥50% reduction in urgency urinary incontinence episodes and overall patient impression of improvement compared to sham treatment.

- There were no significant side effects reported.

LIMITATIONS:

- There was no statistical significance seen between groups for primary outcome.
- Participants in both arms experienced meaningful reductions in symptom severity and improvements in quality of life, suggesting a powerful placebo effect or therapeutic benefit from regular clinical engagement.
- Despite the lack of statistical significance, the TTNS group showed a trend toward fewer leakage episodes and better overall improvement, indicating that the trial might have detected a difference with a larger sample size or more frequent treatment.
- Lack of effective masking could lead to detection bias.
- Subjects were recruited from the Kaiser Permanente San Diego system who possess the health literacy and organizational capacity to manage home treatments and complex diaries which suggests a higher socioeconomic status population, which limits how well these results apply to underserved communities.

Simon Youngsahn Lee, DO
Northside Hospital Gwinnett FMRP
Lawrenceville, GA