GOOD EVIDENCE MATTERS

GEMs of the Week

SPOTLIGHT

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Cytisinicline, An Alternative Therapy for Smoking Cessation?

Cytisinicline for Smoking Cessation: A Randomized Clinical Trial

Rigotti NA, Benowitz NL, Prochaska J, et al. Cytisinicline for Smoking Cessation: A Randomized Clinical Trial. *JAMA*. 2023;330(2):152-160. doi:10.1001/jama.2023.10042

KEY TAKEAWAY: Cytisinicline increases smoking cessation for up to 24 weeks with behavioral support compared to placebo in adults with daily cigarette use.

STUDY DESIGN: Double-blind, placebo-controlled, randomized control trial (RCT)

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Cytisinicline is a plant-based alkaloid-like varenicline that partially binds to α4β2 nicotinic acetylcholine receptors, which help mediate nicotine dependence. Recent but limited studies have shown cytisinicline aids in smoking cessation. However, it is currently only licensed in some European countries as an over-the-counter medication and the current rationale for the dosing and duration of treatment has never been published and may not be optimal.

PATIENTS: Adults with daily cigarette use

INTERVENTION: Cytisinicline

CONTROL: Placebo

PRIMARY OUTCOME: Smoking cessation during treatment

Secondary Outcome: Continuous smoking cessation, adverse events

METHODS (BRIEF DESCRIPTION):

- Adults ≥18 years old who smoked ≥10 cigarettes per day, had expired air carbon monoxide (CO) ≥10 parts per million (ppm), and were ready to set a quit date were included in the study.
- Individuals were excluded if they used any non-cigarette tobacco product, electronic cigarettes, smoking cessation medication, or marijuana in the last 28 days.
- Other exclusion criteria included chronic cardiovascular, kidney, or liver problems as well as moderate to severe depression.
- Total patients were then randomized 1:1:1 to three treatment groups: 12 weeks of cytisinicline, six weeks of cytisinicline followed by six weeks of placebo, or 12 weeks of placebo.
    - Cytisinicline was given as 3 mg three times daily.
- Patients quit smoking 5–7 days after starting treatment.
- Behavioral support was provided for all groups.
- Follow up assessments were performed at day two, weekly from 1–12 weeks, and at weeks 16, 20, and 24.
- Primary outcome was assessed for continuous smoking abstinence during the last four weeks of both the six (weeks 3–6) and 12 (weeks 9–12) week treatment periods.
- Secondary outcome was verified continuous smoking abstinence from the last four weeks of cytisinicline or placebo treatment to week 24.
- Abstinence was defined as:
    - A self-report indicating not having smoked >5 cigarettes since the last visit.
    - Having <10 ppm of breath CO.
- Safety outcomes were assessed by measuring vital signs and using patients' self-report of adverse events and concomitant use of medications on day two and during weekly visits for the 12-week treatment and through an additional 12-week follow-up.

INTERVENTION (# IN THE GROUP):

- Cytisinicline for 12 weeks: 270
- Cytisinicline for six weeks: 269

COMPARISON (# IN THE GROUP): 270

FOLLOW-UP PERIOD: Up to 24 weeks

RESULTS:

Primary Outcome –

- Participants taking cytisinicline were more likely to achieve continuous smoking abstinence during the latter four weeks of the treatment period compared to placebo.
    - For six-week cytisinicline treatment during weeks 3–6 (25% vs 4.4%, respectively; odds ratio [OR] 8.0; 95% CI, 3.9–16)
    - For 12-week cytisinicline treatment during weeks 9–12 (32% vs 7.0%, respectively; OR 6.3; 95% CI, 3.7–11)

- Among participants who were assigned to either cytisinicline group and who achieved continuous abstinence during weeks 3–6, the individuals who continued cytisinicline for an additional six weeks (12-week cytisinicline group) did not have a significantly different rate of relapse-free abstinence during weeks six to 24 compared with individuals in the six-week cytisinicline group who switched to placebo at week six (10% vs 13%, respectively; OR 1.3; 95% CI, 0.75–2.3).

Secondary Outcome –

- Continuous abstinence from the last four weeks of treatment through 24 weeks was significantly higher at both cytisinicline treatment durations compared to placebo.
    - Six-week cytisinicline treatment during weeks 3–24 (8.9% vs 2.6%, respectively; OR 3.7; 95% CI, 1.5–10)
    - For 12-week cytisinicline treatment during weeks 9–24 (21% vs 4.8%, respectively; OR 5.3; 95% CI, 2.8–11)
- Participants who received cytisinicline did not have an increased risk of serious adverse events compared to placebo.

LIMITATIONS:

- Participants were predominantly White, limiting generalizability to other racial and ethnic groups.
- Participants were excluded for serious mental illness, recent unstable cardiovascular disease, and current marijuana or illicit drug use also limiting the generalizability of the findings to these groups.
- Trial was not large or long enough to detect uncommon adverse events.
- No assessment of efficacy was performed past 24 weeks, thus limiting the known efficacy past this time.
- The behavioral support given in additional to treatment likely exceeds what can be provided to the general population.

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Finerenone Improves Heart Failure: Evaluating the FINEARTS-HF Trial

Finerenone in Heart Failure with Mildly Reduced or Preserved Ejection Fraction

Solomon SD, McMurray JJV, Vaduganathan M, et al. Finerenone in Heart Failure with Mildly Reduced or Preserved Ejection Fraction. *N Engl J Med*. 2024;391(16):1475-1485. doi:10.1056/NEJMoa2407107

KEY TAKEAWAY: Finerenone reduces the risk of worsening heart failure (HF) in patients with heart failure with mildly reduced ejection fraction (HFmrEF) or preserved ejection fraction (HFpEF).

STUDY DESIGN: International, multicenter, double-blind, randomized control trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Steroidal mineralocorticoid receptor antagonists (MRAs), such as spironolactone and epleronone, have proven benefit in patients with heart failure and reduced ejection fraction (HFrEF). Finerenone, a nonsteroidal MRA, has demonstrated significant cardiorenal protective benefits in patients with both chronic kidney disease and type 2 diabetes. This study aims to establish its efficacy in patients with heart failure and mildly reduced or HFpEF.

PATIENTS: Adults with HFpEF

INTERVENTION: Finerenone

CONTROL: Placebo

PRIMARY OUTCOME: HF events and death from cardiovascular (CV) causes

Secondary Outcome: Symptomatic improvement, functional improvement, change in kidney function, all-cause mortality, adverse events

METHODS (BRIEF DESCRIPTION):

- The authors conducted a double-blind, randomized, event-driven study across 654 sites in 37 countries.
- Participants were included in the study if they were ≥40 years old, had a left ventricular ejection fraction (LVEF) ≥40% in the last 12 months, had a New York Heart Association (NYHA) functional class II-IV, elevated pro-B-type natriuretic peptide levels (≥300 pg/mL), evidence of structural heart disease in the last 12 months, and were stable on goal-directed medical therapy (GDMT) including a combination of beta-blockers, angiotensin-converting-enzyme inhibitors, angiotensin-receptor blockers, sodium-glucose cotransporter 2 (SGLT2) inhibitors, or angiotensin receptor-neprilysin inhibitor (ARNI).
- Participants were excluded if they had severe kidney impairment (eGFR <25 mL/min) or baseline hyperkalemia (>5.0 mmol/L), myocardial infarction (MI) < 0 days prior to the start of the study, uncontrolled arrhythmia, or MRA use at least 30 days prior to randomization.
- Participants were 72 years old on average, mean LVEF was 54%, 69% of patients were NYHA functional class II, few participants were on SGLT2 inhibitor or ARNI while most patients were on beta blockers, angiotensin-converting enzyme inhibitor (ACEi) or angiotensin II receptor blocker (ARB).
- Participants were randomly assigned in a 1:1 ratio to receive either finerenone (10–20 mg if baseline eGFR ≤60 mL/min or 20–40 mg if baseline eGFR >60 mL/min) or placebo.
- Participants had an initial one month follow up visit then were evaluated every three months for the first year then every two months until completion.
- The primary composite outcome was measured as the total number of cardiovascular deaths and worsened HF events (defined as the number of unplanned hospital admissions or urgent care visits related to HF).
- Secondary outcomes were measured using the following:
  - All-cause mortality was measured as death from any cause tracked through follow-up visits and verified through medical records and death registries.
  - Functional status was measured as improvement or worsening in NYHA functional class.
  - Quality of life was measured using the Kansas City Cardiomyopathy Questionnaire (KCCQ) at six, nine, and 12 months. Scores range from 0–100, with higher scores indicating fewer symptoms, limitations, and better quality of life.
  - Kidney outcomes were measured as a sustained >50% decline in eGFR, progression to end-stage renal disease requiring initiation of dialysis or

transplantation, or sustained eGFR <15 mL/min/1.73m^2.
    - Adverse events including hyperkalemia were measured as events requiring intervention, hypotension, acute kidney injury.

INTERVENTION (# IN THE GROUP): 3,003
COMPARISON (# IN THE GROUP): 2,998

FOLLOW-UP PERIOD: 32 months

RESULTS:

Primary Outcome –

- Finerenone reduced the total number of worsened HF events and death from CV causes compared to placebo (rate ratio [RR] 0.84; 95% CI, 0.74–0.95).
- Finerenone reduced the total number of worsened HF events compared to placebo (RR 0.82; 95% CI, 0.71–0.94).
- There was no statistically significant difference between the two groups in CV death rates alone (hazard ratio [HR] 0.93; 95% CI, 0.78–1.1).

Secondary Outcome –

- Finerenone did not significantly affect all-cause mortality rates, NYHA functional class, kidney outcomes or quality of life compared to placebo.
- Finerenone was associated with higher incidences of hyperkalemia, hypotension, and acute kidney injury when compared to placebo.

LIMITATIONS:

- Finerenone did not significantly improve kidney outcomes in this HF population, despite its known renal-protective effects in diabetes and chronic kidney disease.
- The study was funded by Bayer, the company that manufactures finerenone.
- Although the trial was double-blind, clinicians adjusted treatment based on lab values such as serum potassium, which could have introduced functional unblinding.
- The trial excluded patients with more severe chronic kidney disease which limits external validity as many patients with HFpEF/HFmrEF have more complex clinical profiles than those enrolled.
- The difference in the primary outcome was driven by reduction in hospitalizations/events, rather than mortality, raising concerns about how clinically meaningful the composite result may be on long-term survival.

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The views expressed herein are those of the author and do not necessarily reflect the official policy of the Department of the Navy, Defense Health Agency, Department of Defense, or the U.S. Government.

Evaluating Prophylactic Antibiotics for Risk Reduction After Retained Placenta Removal

Prophylactic Antibiotics for Manual Removal of Retained Placenta in Vaginal Birth

Kongwattanakul K, Pattanittum P, Jongjakapun A, et al. Prophylactic Antibiotics for Manual Removal of Retained Placenta in Vaginal Birth. *Cochrane Database Syst Rev*. 2024;10(10):CD004904. Published 2024 Oct 30. doi:10.1002/14651858.CD004904.pub4

KEY TAKEAWAY: Prophylactic antibiotics do not reduce the risk of postpartum endometritis compared to non-antibiotic interventions in women with a retained placenta after vaginal delivery.

STUDY DESIGN: Systematic review with meta-analysis of four retrospective cohort studies (N=974)

LEVEL OF EVIDENCE: STEP 2 (downgraded due to quality of source articles)

BRIEF BACKGROUND INFORMATION: Retained placentas can lead to serious complications like infections and excessive blood loss during vaginal delivery. Prophylactic antibiotics are commonly recommended to prevent such complications, but the effectiveness of this approach has not been conclusively proven. This study aimed to compare prophylactic antibiotics to non-antibiotic interventions in reducing the risk of postpartum endometritis.

PATIENTS: Pregnant women who experience retained placenta and require manual removal after vaginal delivery

INTERVENTION: Prophylactic antibiotics

CONTROL: No prophylactic antibiotics

PRIMARY OUTCOME: Postpartum endometritis

Secondary Outcome: Postpartum hemorrhage, sepsis, neonatal intensive care unit (NICU) admission, maternal and neonatal adverse effects

METHODS (BRIEF DESCRIPTION):

- This review systematically identified studies comparing prophylactic antibiotics with either no treatment or another type of antibiotic in women undergoing manual removal of retained placenta.
- Women with retained placenta requiring manual removal after vaginal delivery were included in the study.
- Cases involving cesarean births, prophylaxis for other obstetric procedures, or populations without clear reporting on outcomes of interest were excluded from the study.
- Prophylactic antibiotics administered at the time of manual removal of retained placenta. Reported regimens varied across studies, including intravenous and intramuscular routes, with single-dose administration most described. Specific antibiotic types, dosages, and duration were inconsistently reported and not standardized between studies.
- The control for each study included was placebo.
- Incidence of postpartum endometritis, assessed through clinical diagnosis as reported in the included studies. This was based on maternal signs and symptoms of uterine infection documented in the medical records, though specific diagnostic criteria varied across studies.
- Postpartum hemorrhage was assessed by estimated blood loss recorded in medical charts; definitions varied across studies.
- Sepsis was determined by clinical diagnosis documented in the medical record, typically based on systemic signs of infection; no standardized scale or uniform criteria applied across studies.
- NICU admission was recorded as yes/no based on whether the newborn required NICU admission after delivery.
- Maternal and neonatal adverse effects was reported variably across studies, including puerperal morbidity, perineal infection, and readmission rates; assessed through clinical diagnosis or hospital records.
- Statistical analysis used risk ratios (RR) with 95% confidence intervals to assess the impact of antibiotics on the outcomes.

INTERVENTION (# IN THE GROUP): 284

COMPARISON (# IN THE GROUP): 690

FOLLOW-UP PERIOD: Varied

RESULTS:

Primary Outcome –

- Prophylactic antibiotics did not reduce the risk of postpartum endometritis compared to no antibiotic intervention (4 studies, N=974; risk ratio [RR] 0.94; 95% CI, 0.48–1.9; I^2=41%).

Secondary Outcome –

- There was no significant difference in the risk of postpartum hemorrhage, NICU admission or sepsis for prophylactic antibiotics compared to no antibiotic intervention.
- Maternal and neonatal adverse effects were not consistently reported across studies, precluding meta-analysis.

LIMITATIONS:

- The included studies were retrospective and lacked randomized control, leading to potential confounding factors that could bias the results.
- The risk of bias was high in many studies due to incomplete reporting, particularly regarding how participants were selected and how outcomes were measured.
- The number of studies included was small (only 4), and the overall certainty of evidence was rated as very low.
- There was variability in the types and dosages of antibiotics used, which added heterogeneity to the review.

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