GOOD EVIDENCE MATTERS

GEMs of the Week

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Breaking the Habit Safely: Phenobarbital Steps into the Ring

Current Evidence and Clinical Utility of Phenobarbital for Alcohol Withdrawal Syndrome

Nishimura Y, Choi H, Colgan B, Kistler H, Mercado F. Current evidence and clinical utility of phenobarbital for alcohol withdrawal syndrome. *Eur J Intern Med*. 2023;112:52-61. doi:10.1016/j.ejim.2023.03.006

KEY TAKEAWAY: Phenobarbital (PB) may be a safe alternative to benzodiazepines (BZD) in patients with alcohol withdrawal.

STUDY DESIGN: Systematic review of two double-blind, randomized trials and 18 retrospective studies (N=19,682)

LEVEL OF EVIDENCE: STEP 3 (downgraded due lack of meta-analysis and systematic assessment of included study quality, high heterogeneity)

BRIEF BACKGROUND INFORMATION: Alcohol withdrawal is a common reason for hospitalization and treating withdrawal is important to prevent life threatening sequelae including seizures and delirium tremens. Historically, alcohol withdrawal has been treated with BZDs, however there is risk with use that includes BZD resistance, administration issues secondary to short half-life and oversedation. PB may potentially be a safe alternative to treat alcohol withdrawal.

PATIENTS: Adults with alcohol withdrawal

INTERVENTION: PB

CONTROL: BZD

PRIMARY OUTCOME: Mortality, intensive care unit (ICU) length of stay, emergency department (ED) readmission, delirium, BZD dose, and length of stay

METHODS (BRIEF DESCRIPTION):

- Included studies were peer-reviewed RCTs, case-control studies, cohort studies, or cross-sectional studies assessing phenobarbital use in alcohol withdrawal.
- Most studies sample sizes were small, had heterogeneity in PB dosing and duration of treatment, and features of PB use as sole agent or in adjunct with BZD.
- Excluded studies qualitative studies, review articles, case series/reports, pediatric studies, and studies with poorly described use of PB.
- 20 articles (9 in the ED and 11 in the ICU setting) were included in the systemic review.
- Common ED study characteristics: Comparing PB vs BZD in terms of Clinical Institute Withdrawal Assessment Alcohol (CIWA) scoring and alcohol withdrawal, determine if PB vs BZD could decrease ICU admission in alcohol withdrawal, effectiveness of PB protocols in treatment of alcohol withdrawal, comparing discharge return rates in PB vs BZD treated patients, and assessing safety and efficacy of PB with and without use of concurrent BZN use.
- Common ICU study characteristics: Comparing complications of PB vs BZN use in alcohol withdrawal, to evaluate the safety and efficacy of PB protocol in withdrawal, comparing hospital length of stay for alcohol withdrawal in PB vs BZN protocols, and characterizing PB practice patterns in patients with severe alcohol withdrawal.
- Common ED study outcomes: Hospital admission rates, total medication doses, intubation rates, and time to discharge.
- Common ICU study outcomes: Respiratory complications, CIWA scores, cumulative medication doses, mortality, hospital and ICU length of stay, duration of treatment, mechanical ventilation rates and readmission rates.

INTERVENTION (# IN THE GROUP): Not available

COMPARISON (# IN THE GROUP): Not available

FOLLOW-UP PERIOD: Varied

RESULTS:

Primary Outcome –

- PB reduced 30-day, and 1-year mortality compared to BZD.
  - 30-day mortality (1 study, n=2,428; hazard ratio [HR] 0.25; 95% CI, 0.08–0.78)
  - 1-year mortality (HR 0.51; 95% CI, 0.31–0.86)
- PB reduced ICU length of stay compared to BZD (1 study, n=120; 2.4 vs 4.4 days, respectively; *P*=.004).
- PB reduced ED returns within 3 days from discharge compared to BZD and PB + BZD (1 study, n=470; 13% vs 25% vs 10%, respectively; *P*=.001).
- The median cumulative BZN dose in PB adjuvant treated patients was significantly lower than BZN

alone (1 study, n=21; 25 vs 326 mg, respectively; *P*=.02).

- PB decreased alcohol delirium compared to BAZ (1 study, n=52; 0% vs 48%, respectively; *P*=.0001).
- There was significant heterogeneity in studies looking at length of hospital stay (3 studies, n=814; no statistical analysis completed).

LIMITATIONS:

- This study was unable to statistically combine data for a meta-analysis.
- Several studies had very small study populations.
- There was significant heterogeneity among study comparative groups including PB and BZN dosing, defining alcohol withdrawal symptom severity, and outcomes, making conclusions difficult.
- There was potential for lead time bias with limited follow up time.
- Selection bias could have occurred with use of only peer-reviewed literature.

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"P" is for Probable Pregnancy

Timed Intercourse for Couples Trying to Conceive

Gibbons T, Reavey J, Georgiou EX, Becker CM. Timed intercourse for couples trying to conceive. *Cochrane Database Syst Rev*. 2023;9(9):CD011345. Published 2023 Sep 15. doi:10.1002/14651858.CD011345.pub3

KEY TAKEAWAY: Timed intercourse using urinary ovulation detection (UOD) in couples without infertility improves the rate of pregnancies and live births by about one-third compared to controls not using timed intercourse.

STUDY DESIGN: Meta analysis of seven randomized controlled studies (RCTs) (N=2,464)

LEVEL OF EVIDENCE: STEP 1

BRIEF BACKGROUND INFORMATION: There is a fertile window of approximately six days during an ovulatory cycle in which conception can take place. Timed intercourse consists of prospectively identifying this window to increase (or decrease) the likelihood of conception. Methods to predict it include urinary hormone measurement, fertility awareness-based methods (FABM), and pelvic ultrasound.

FABM may include measurement of basal body temperature, monitoring cervical mucus, or calendar charting or tracking. Timed intercourse may have negative aspects including stress, time consumption, and the cost of ovulation kits and tracking apps. This review evaluated the effects of timed intercourse on pregnancy outcomes.

PATIENTS: Couples without an infertility diagnosis who are trying to conceive

INTERVENTION: Timed intercourse based on UOD, FABM, or pelvic ultrasound

CONTROL: Intercourse without ovulation prediction

PRIMARY OUTCOME: Live births or ongoing pregnancy and adverse events

Secondary Outcome: Clinical pregnancy, pregnancy without ultrasound confirmation, time to pregnancy

METHODS (BRIEF DESCRIPTION):

- Published and unpublished systemic reviews, RCTs, and databases were searched electronically for interventions using timed intercourse (excluding trials of intrauterine insemination, but with no language exclusions).
    - Hand searches of reference lists for included studies and expert contact in the field were also conducted to find additional trials.
- The review included seven parallel-design RCTs evaluating women 18–43 years old in fertile couples desiring pregnancy.
- Two review authors extracted data for analysis, used the Cochrane risk of bias assessment tool, and used intention to treat data analysis.
- The primary outcome measured lived births defined as the delivery of a live fetus after 22 weeks and adverse events measured using various questionaries and scales which included:
    - Perceived Stress Scale (PSS). Scores range from 0–40, with higher scores indicating higher perceived stress.
    - Hospital Anxiety and Depression Scale (HADS). Scores range from 0–21, with higher scores indicating more severe depression and anxiety.
    - International Index of Erectile Function (IIEF). Scores range from 0–30, with higher score indicating no dysfunction.
- The following were measured as the secondary outcomes:
    - Clinical pregnancy was defined as the presence of a gestational sac and fetal heartbeat on ultrasound after 12 weeks.
    - Pregnancy without ultrasound confirmation was assessed via patient report.
    - Time to pregnancy was defined as the time from randomization to a clinical pregnancy.
- The authors presented dichotomous data as risk ratios, and continuous data as mean differences.

INTERVENTION (# IN THE GROUP):

- Live births:
    - UOD: 1,033
    - FABM: 69
- Adverse effects:
    - UOD (stress only): 37
    - FABM: 115

COMPARISON (# IN THE GROUP):

- Live birth controls:
    - UOD: 1,021
    - FABM: 71

- Adverse effect controls:
  - UOD (stress only): 40
  - FABM: 130

FOLLOW-UP PERIOD: Varied (2–12 menstrual cycles)

RESULTS:

Primary Outcome –

- Timed intercourse involving UOD minimally improved the chance of live births compared to intercourse without ovulation in couples trying to conceive (risk ratio [RR] 1.4; 95% CI, 1.02–1.8).
- Timed intercourse involving UOD did not significantly impact adverse stress scores compared to intercourse without ovulation in couples trying to conceive (mean difference [MD] 2.0; 95% CI, −0.87 to 4.8).
- Time intercourse involving FABM did not improve the chance of live births compared to intercourse without ovulation in couples trying to conceive (RR 0.95; 95% CI, 0.76–1.2).
- Timed intercourse involving FABM did not significantly impact the following adverse events compared to intercourse without ovulation in couples trying to conceive:
  - Stress (MD −1.1; 95% CI, −3.9 to 1.7)
  - Anxiety (MD 0.5; 95% CI, −0.52 to 1.5)
  - Depression (MD 0.4; 95% CI, –0.28 to 1.1)
  - ED (MD 1.2; 95% CI, −0.38 to 2.8)

Secondary Outcome –

- Timed intercourse involving UOD minimally improved pregnancy rates compared to intercourse without ovulation prediction in couples trying to conceive (RR 1.3; 95% CI, 1.1–1.5).
- UOD improved rates of clinical pregnancy or pregnancy without ultrasound confirmation compared to intercourse without ovulation prediction (RR 1.3; 95% CI, 1.1–1.5).
- UOD did not affect time to pregnancy compared to intercourse without ovulation prediction.
- FABM had no impact on the rate of clinical pregnancy, pregnancy without ultrasound confirmation, and did not affect time to pregnancy compared to intercourse without ovulation prediction.

LIMITATIONS:

- Differences in outcome measurements between studies limited the number of studies grouped for primary outcome analysis. This precluded performing sensitivity studies for robustness and subgroup analyses.
- RCTs using FBAM had few participants and were underpowered to detect a difference in live birth rates.
- Overall evidence quality varied from moderate to very low, due to selective reporting, corporate funding and performance bias resulting from lack of participant and personnel blinding.

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Stepwise Palliative Care as a Solution to Palliative Care Shortages

Stepped Palliative Care for Patients with Advanced Lung Cancer: A Randomized Clinical Trial

Temel JS, Jackson VA, El-Jawahri A, etal. Stepped Palliative Care for Patients with Advanced Lung Cancer: A Randomized Clinical Trial. *JAMA*. 2024 Aug 13;332(6):471-481. doi: 10.1001/jama.2024.10398. PMID: 38824442; PMCID: PMC11145511

KEY TAKEAWAY: Stepped palliative care improves quality of life for adults with advanced lung cancer compared with early palliative care.

STUDY DESIGN: Multi-site prospective randomized nonblinded non inferiority trial

LEVEL OF EVIDENCE: STEP 3 (downgraded due to lack of blinding)

BRIEF BACKGROUND INFORMATION: Early palliative care has been the recommended care model for decades. However, due to advances in treatment options, patients living longer, and limited palliative care resources, there needs to be a less resource intense and more patient centered model to approaching care. This study assessed a stepped care approach to improve access to specialty palliative providers and reserving intensive treatment for those who are not benefiting from less intensive therapies.

PATIENTS: Adults with advanced lung cancer

INTERVENTION: Stepwise palliative care

CONTROL: Early palliative care

PRIMARY OUTCOME: Quality of life

Secondary Outcome: Palliative care visits, length of stay in hospice, end of life care preferences

METHODS (BRIEF DESCRIPTION):

- Patients ≥18 years old receiving care from one of three large urban academic centers with a diagnosis of advanced, incurable lung cancer (non-small cell, small cell or mesothelioma) were included in the study.
- Patients with documented Eastern Cooperative Oncology Group performance status (ECOG) of 0–2 and ability to read and respond in questions in English or Spanish were included in the study.
    - A score of 0 on the ECOG indicates full activity without restrictions, and a score of 2 being unable to work and in bed <50% of day, with higher scores indicating diminished physical abilities.
- Patients already receiving outpatient palliative care or enrolled in hospice were excluded from the study.
- Patients were 67 years old on average, 51% female, and 11% African American or Black, 84% White, and most had non-small cell lung cancer (78%).
- Participants receiving stepped palliative care were scheduled for visits at four weeks from enrollment and additionally with change in health or hospital admission.
    - They received Functional Assessment of Cancer Therapy-Lung (FACT-L) evaluation for symptoms every six weeks. If their score decreased from baseline >10 points patients progressed to step two with palliative care visits every four weeks. Scores range from 0–136, with higher scores indicating better quality of life.
- The comparison group received early palliative care and scheduled visits every four weeks and seen by inpatient team during hospitalizations.
- The primary outcome was quality of life, measured via FACT-L at 24 weeks.
    - The noninferiority margin is –4.5 on the FACT-L
- Secondary outcomes were number of palliative care visits, length of stay in hospice measured by days of hospice enrollment, and end of life care preferences measured via percent of people who had the discussion.

INTERVENTION (# IN THE GROUP): 146

COMPARISON (# IN THE GROUP): 145

FOLLOW-UP PERIOD: 18 months

RESULTS:

Primary Outcome –

- Stepped palliative care improved quality of life compared to early palliative care (adjusted mean difference [aMD] 2.9; 95% confidence limit [CL], –0.1, p<.001).

Secondary Outcome –

- Patients who received stepped palliative care had significantly fewer visits than those who received early palliative care at 24 weeks (aMD –2.3; 95% CL,

–2.7 to –1.8) and 48 weeks (aMD –3.9; 95% CL, –4.7 to –3.1).

- Patients receiving stepped palliative care had shorter length of stays in hospice compared to early palliative care (aMD –15 days; 95% CL, –25).
- Patients receiving stepped palliative care had similar rates of discussing end of life care preferences compared to early palliative care (aMD –2.6%; 95% CL, –10%).

LIMITATIONS:

- The study did not meet the prespecified sample size and may be underpowered to detect a difference between the interventions.
- The study had a high dropout rate and missing data.
- Hospice enrollment has previously been found to impact mortality, which was not reported in this study.
- There was a primarily White patient population, impacting generalizability.
- This study was conducted at three academic centers, impacting generalizability.
- The study only included advanced lung cancer and thus findings may have limited generalizability.

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Biomarker-Based Prostate Cancer Screening

Biomarker vs MRI-Enhanced Strategies for Prostate Cancer Screening: The STHLM3-MRI Randomized Clinical Trial

Björnebo L, Discacciati A, Falagario U, et al. Biomarker vs MRI-Enhanced Strategies for Prostate Cancer Screening: The STHLM3-MRI Randomized Clinical Trial. JAMA Netw Open. 2024;7(4):e247131. Published 2024 Apr 1. doi:10.1001/jamanetworkopen.2024.7131

KEY TAKEAWAY: Detection rates for clinically significant prostate cancer are comparable between biomarker based prostate cancer screening and magnetic resonance imaging (MRI) based prostate cancer screening.

STUDY DESIGN: Single site, randomized, unblinded trial

LEVEL OF EVIDENCE: STEP 3 (downgraded due to unblinding)

BRIEF BACKGROUND INFORMATION: MRI based studies for prostate cancer screening are complex and difficult to access, with substantial interobserver variability. Studies of biomarker-based screening indicate that these tests could help determine which men should undergo MRI evaluation. The effect of biomarker-based screening alone is unknown. This study investigated the difference in prostate cancer detection rates between biomarker based and MRI based screening.

PATIENTS: Men 50–74 years old

INTERVENTION: Biomarker evaluation with Stockholm3 score

CONTROL: Prostate specific antigen (PSA) then MRI if elevated

PRIMARY OUTCOME: Detection rates of clinically significant prostate cancer

Secondary Outcome: Men referred for biopsy, benign biopsies performed, adverse events

METHODS (BRIEF DESCRIPTION):

- Men 50–74 years old with no history of prostate cancer were included in the study. They were recruited from a random statistical mail selection in Sweden.
- Men with prior prostate cancer diagnosis, prostate biopsy within the previous 60 days, severe illness and/or contraindications to MRI were excluded from the study.
- After recruitment, patients were a median 61 years old, most of whom were not taking five alpha reductase inhibitors. The median PSA was 1.03 in the MRI group and 1.02 in the biomarker group.
- All participants provided samples for PSA and Stockholm3 blood tests and were then randomized to the biomarker or MRI groups.
- The intervention group underwent systematic biopsies for a Stockholm3 risk score ≥0.15 (scores combine age, prior biopsy results, family history of prostate cancer, single-nucleotide variants and PSA, free PSA, human kallikrein 2, beta-microseminoprotein, and growth differentiation factor, reported as a percentage, with higher scores indicating higher risk, and scores ≥11% concerning for cancer).
- The comparison group had PSA and if ≥3 ng/mL had a T2 diffusion weighted bi-parametric MRI.
- Men underwent targeted and systematic biopsies for a PI-RADS score ≥3 on MRI. Scores range from 0–5 with higher scores indicating likelihood of clinically significant prostate cancer.
- Biopsies were performed by experienced urologists and MRIs were read by uroradiologists.
- The detection of clinically significant prostate cancer was measured via Gleason score of ≥7, higher scores indicating more severe cancer, and <6 indicating insignificant cancer).

INTERVENTION (# IN THE GROUP): 5,134

COMPARISON (# IN THE GROUP): 7,609

FOLLOW-UP PERIOD: 200 days

RESULTS:

Primary Outcome –

- The detection rate for clinically significant prostate cancer was similar in the biomarker group compared to the MRI enhanced group (2.3% vs 2.5%, respectively; relative proportion 0.92; 95% CI, 0.73–1.2).

Secondary Outcome –

- The percentage of men referred for biopsy was greater in the biomarker group compared to the MRI enhanced group (6.3% vs 4.4%, respectively; relative proportion 1.4; 95% CI, 1.2–1.7).

- The percentage of men who had benign biopsies performed was greater in the biomarker group than in the MRI enhanced group (2.8% vs 1.4%, respectively; relative proportion 2.1; 95% CI, 1.6–2.6).
- More clinically insignificant cancers were discovered in the biomarker group than in the MRI enhanced group (1.2% vs 0.5%, respectively; relative proportion 2.2; 95% CI, 1.5–3.3).
- Post biopsy hospitalization was similar in the biomarker compared to the MRI enhanced group.

LIMITATIONS:

- The study population was homogenous.
- The study personnel and patients were not blinded.
- There was no information about long-term prostate cancer mortality.
- The patients who were not deemed high risk were not biopsied and may have had undetected cancer.
- More men in the biomarker group did not undergo recommended biopsies as compared to the MRI group.

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Is Semaglutide a Panacea for Alcohol Use Disorder?

Once-Weekly Semaglutide in Adults with Alcohol Use Disorder: A Randomized Clinical Trial

Hendershot CS, Bremmer MP, Paladino MB, et al. Once-Weekly Semaglutide in Adults with Alcohol Use Disorder: A Randomized Clinical Trial. *JAMA Psychiatry*. 2025;82(4):395–405. doi:10.1001/jamapsychiatry.2024.4789

KEY TAKEAWAY: Low dose weekly semaglutide reduces alcohol consumption compared to placebo in patients with alcohol use disorder (AUD).

STUDY DESIGN: Randomized, double blind, controlled trial

LEVEL OF EVIDENCE: STEP 3 (downgraded due to drug company sponsored phase II trial with small sample size)

BRIEF BACKGROUND INFORMATION: Previous animal studies have shown that glucagon-like peptide-1 receptor agonists (GLP-1s) reduce alcohol intake and cravings. Observational cohort studies in individuals with diabetes treated with GLP-1s have also reported a reduction in AUD. This study aimed to evaluate the effects of GLP-1s on alcohol intake and cravings.

PATIENTS: Adults with self-reported AUD

INTERVENTION: Semaglutide

CONTROL: Placebo

PRIMARY OUTCOME: Alcohol self-administration

Secondary Outcome: Daily alcohol consumption, weekly alcohol cravings, daily cigarette use

METHODS (BRIEF DESCRIPTION):

- Patients between 21–65 years old with self-reported AUD per DSM criteria and ability to attend weekly clinic visits were included in the study. Notably, patients were recruited who were not seeking treatment for AUD. Recruitment was via online and public advertisements at a local academic center.
  - Participants were an average age of 40 years old, 71% were female, average BMI of 32, and on average endorsed moderate AUD per DSM criteria.
- The following patients were excluded from the study:
  - Treatment seeking individuals with AUD or active attempt to reduce alcohol intake.
  - Patients with any substance use disorder other than AUD in the past year.
  - Patients with illicit drug use within the past 30 days, except for cannabis.
  - Patients with type 1 or type 2 diabetes.
  - Patients with any severe mental health disorder.
- Patients were randomized to receive either low dose subcutaneous semaglutide (0.25 mg/week for 4 weeks, 0.5 mg/week for 4 weeks, and 1.0 mg for 1 week) or placebo (sham) weekly injections.
- Prior to week one and post treatment (week 8–9), all participants completed an alcohol self-administration visit.
  - Alcohol self-administration was completed at an on-campus laboratory designed to replicate a bar setting.
  - Participants had 120 minutes to drink their preferred beverage at any rate. Breath alcohol concentration was measured at 30 minutes intervals following the onset of drinking.
  - The effect size of medications was categorized as small (β=0.10), medium (β=0.30), and large (β=0.50).
- Primary outcomes included amount of alcohol self-administered during pretreatment and post-treatment visits, measured in grams of alcohol consumed.
- Secondary outcomes included self-reported daily log of alcoholic drinks, weekly self-reported alcohol cravings.

INTERVENTION (# IN THE GROUP): 24

COMPARISON (# IN THE GROUP): 24

FOLLOW-UP PERIOD: 10 weeks

RESULTS:

Primary Outcome –

- Semaglutide significantly reduced alcohol consumption compared to placebo (β –0.48; 95% CI, −0.85 to −0.11).

Secondary Outcome –

- Semaglutide did not affect average drinks per day, or number of drinking days compared to placebo.
- Semaglutide significantly reduced drinks per drinking day compared to placebo (β −0.41; 95% CI, −0.73 to −0.09).

- Semaglutide significantly reduced weekly alcohol craving compared to placebo (β −0.39; 95% CI, −0.73 to −0.06).
- Semaglutide significantly decreased daily cigarette consumption over time compared to placebo, for individuals who reported cigarette use, demonstrating a time-by-treatment interaction (β −0.10; 95% CI, −0.16 to −0.03).

LIMITATIONS:

- Drug-company sponsored phase II trial with small sample size and without power analysis, designed primarily to justify future research.
- Enrolled patients were specifically not seeking treatment, so there may be a different effect in treatment seeking individuals.
- Use of low dose semaglutide in this study is different than standard dosing used in weight loss management; it is not clear if the effects would be similar.
- High cost and limited insurance coverage for GLP-1s limit patient access.

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