GEMs
GOOD EVIDENCE MATTERS

GEMs of the Week

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What's in this week's issue?

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SPOTLIGHT: Can the Addition of L-Methyl/Folic Acid to Antidepressant Therapy Improve Outcomes?

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GEMs GOOD EVIDENCE MATTERS SPOTLIGHT

Folate as Adjunct Therapy to SSRI/SNRI for Major Depressive Disorder: Systematic Review and Meta-Analysis

Altaf R, Gonzalez I, Rubino K, Nemec EC 2nd. Folate as adjunct therapy to SSRI/SNRI for major depressive disorder: Systematic review & meta-analysis. *Complement Ther Med.* 2021;61:102770. doi:10.1016/j.ctim.2021.102770

KEY TAKEAWAY: The addition of L-methylfolic acid to selective serotonin reuptake inhibitor/serotonin-norepinephrine reuptake inhibitor (SSRI/SNRI) monotherapy for the treatment of major depressive disorder yields clinically and statistically significant improvement in symptom reduction and overall remission.

STUDY DESIGN: Systematic review and meta-analysis of six randomized control trials (N=566)

LEVEL OF EVIDENCE: STEP 2 (downgraded due to small sample size and interstudy variability)

BRIEF BACKGROUND INFORMATION: Major depressive disorder (MDD) is a ubiquitous mental health disorder with an annual incidence in the U.S. of 11 million individuals over 18 years old. The goal of treatment is to achieve an almost complete remission and restoration of function. However, the gold standard of antidepressant monotherapy yields only modest rates of remission and often requires additional psychotropic medication. This study evaluates how folic acid (or its bioavailable derivative, L-methylfolate) may be an effective, well-tolerated, and affordable adjunct to first-line therapies.

PATIENTS: Adults with MDD

INTERVENTION: SSRI/SNRI with L-methylfolic acid

CONTROL: SSRI/SNRI alone or with placebo

PRIMARY OUTCOME: Symptomatic improvement

Secondary Outcome: Adverse effects

METHODS (BRIEF DESCRIPTION):

- Investigators searched study databases for trials evaluating the addition of folate to SSRI/SNRI therapy for MDD.
- Inclusion criteria: Patients at least 18 years old who met the diagnostic criteria for MDD and was receiving treatment with an SSRI/SNRI.
- Exclusion criteria: The presence of severe symptoms (mania, psychosis, suicidality), hypothyroidism, or patients who were pregnant or breastfeeding.
- Patients age ranged from 18–65 years old.
- Intervention groups were supplemented with daily oral folic acid (500 mcg, 2.5 mg, 10 mg) or L-methylfolic acid (7.5 mg, 15 mg).
- Control groups were left on their standard SSRI/SNRI treatment with some studies adding a placebo.
- The primary outcome was symptomatic improvement with responsiveness defined as ≥50% reduction in depression score.
    - Five studies utilized the Hamilton Depression Rating scale (HAM-D), with a higher score indicating greater depression symptom burden.
    - One study used the Becker Depression Inventory (BDI-II), with a higher score indicating worse symptoms.
- The remission rate was defined in three studies as ≤9 on the HAM-D scale.
- A raw mean difference (MD) was calculated for studies using HAM-D and a standardized mean difference (SMD) was used for all six.

INTERVENTION (# IN THE GROUP): 279

COMPARISON (# IN THE GROUP): 287

FOLLOW-UP PERIOD: 4–10 weeks

RESULTS:

Primary Outcome –

- Reduction in depression scores was significantly lower in patients receiving supplemental folic acid (SMD –0.38; 95% CI, –0.55 to –0.22).
- There was a clinically significant improvement in response rate in the supplemental group (relative risk [RR] 1.4; 95% CI, 1.2–1.6).
- The supplemental group experienced higher remission rates (3 studies, N=216; RR 1.4; 95% CI, 1.0–1.9).
- Patients supplemented with folic acid had a 36% increase in response rate (number needed to treat [NNT] of 5) and a 39% increase in remission rate (NNT of 9).

Secondary Outcome –

- The most common adverse effects were gastrointestinal and somatic.

- There appeared to be no increased risk of adverse effects beyond that of SSRI/SNRI or folate alone.

LIMITATIONS:

- The search process was limited by using too few keywords and databases, limiting articles available for review.
- There was a small sample size, limiting generalizability.
- There was considerable heterogeneity, particularly for randomization and missing outcome data regarding one included study.
- There was variance between studies in length of treatment, the form of folate used, the dosage administered, and the depression scales used.

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Improved Outcomes in Ultrasound-Guided IUD Placement

Does Ultrasound Guidance Provide Pain Relief During Intrauterine Contraceptive Device Insertion? A Systematic Review and Meta-Analysis of Randomized Controlled Trials

Baradwan S, Alshahrani MS, Alnoury A, et al. Does Ultrasound Guidance Provide Pain Relief During Intrauterine Contraceptive Device Insertion? A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *J Ultrasound Med.* 2023;42(7):1401-1411. doi:10.1002/jum.16166

KEY TAKEAWAY: Ultrasound-guided intrauterine device (IUD) insertion may provide a non-pharmacological method for improving outcomes related to pain experienced during insertion. Additional benefits include decreased procedure time, better reported patient satisfaction, and decreased complications and misplaced IUDs.

STUDY DESIGN: Systematic review and meta-analysis of seven randomized controlled trials (RCTs) (N=1,267)

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: IUDs offer an effective and long-lasting form of contraception. Pain experienced during the insertion of an IUD and complications thereafter contribute as a barrier to those who may otherwise benefit from IUD contraception.

PATIENTS: Women undergoing IUD placement for contraception

INTERVENTION: Ultrasound-guided IUD insertion

CONTROL: Traditional IUD insertion

PRIMARY OUTCOME: Pain

Secondary Outcome: Insertion time, patient satisfaction, complications during device insertion, incidences of misplaced IUDs

METHODS (BRIEF DESCRIPTION):

- Four investigators reviewed 100 RCTs that compared ultrasound-guided IUD placement with traditional IUD placement.
- The study included RCTs that were completed in Egypt (5), Kuwait (1), and the United States (1).
- Patient characteristics differed between groups including maternal age, body mass index, parity, uterus position, number of previous cesarean sections, and the type of IUD.
- The duration of the procedure was timed in minutes.
- Some of the studies used non-steroidal anti-inflammatory drugs, however, others did not use pharmacological agents for pain.
- Pain scores are based on the VAS, which rates subjective pain on a scale, with higher scores indicating more pain.
- Placement satisfaction was based on a three-point scale: Satisfied, indifferent, or unsatisfied.
- Any complications that occurred during insertion procedures were reported including improper IUD positioning, which was identified by transvaginal ultrasound.

INTERVENTION (# IN THE GROUP): 633

COMPARISON (# IN THE GROUP): 634

FOLLOW-UP PERIOD: Varied, primarily within 30 minutes after IUD placement or one month for subsequent office visits

RESULTS:

Primary Outcome –

- Ultrasound use during IUD insertion improved pain scores compared to control (mean difference [MD] –1.9; 95% CI, –3.1 to –0.73).

Secondary Outcome –

- Ultrasound use significantly decreased insertion time (MD –1.4 minutes; 95% CI, –1.8 to –0.88).
- Women reported significantly increased satisfaction with ultrasound-guided insertion (risk ratio [RR] 3.6; 95% CI, 2.3–5.6).
- Complications significantly decreased with ultrasound use (RR 0.59; 95% CI, 0.36–0.97).
- Improperly placed IUDs significantly decreased with ultrasound use (RR 0.36; 95% CI, 0.16–0.78).

LIMITATIONS:

- Five out of seven RCTs had a high risk for bias.
- The studies were completed in three different countries, so indications for patients in other populations may be limited.
- There was no data for long-term complications due to short follow-up periods.
- Possible confounding factors including anatomical variations or a history of insertion complications could have an impact on results.

- Not all RCTs used medications to reduce pain.

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Keeping the Heart Flowing with Flozins

Dapagliflozin in Heart Failure with Mildly Reduced or Preserved Ejection Fraction

Solomon SD, McMurray JJV, Claggett B, et al. Dapagliflozin in Heart Failure with Mildly Reduced or Preserved Ejection Fraction. *N Engl J Med*. 2022;387(12):1089-1098. doi:10.1056/NEJMoa2206286

KEY TAKEAWAY: Daily treatment with dapagliflozin is shown to reduce the risk of worsening heart failure or cardiovascular death in those who have chronic heart failure with mildly reduced or preserved ejection fraction.

STUDY DESIGN: Parallel-group, event-driven, double-blind, placebo-controlled, randomized controlled trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Sodium glucose cotransporter 2 (SGLT2) inhibitors reduce adverse outcomes and risk of death in patients with chronic heart failure and reduced ejection fraction. However, few studies evaluate the effectiveness of SGLT2 inhibitors in patients with mildly reduced or preserved ejection fraction. The DELIVER trial aims to determine if patients with chronic heart failure and mildly reduced or preserved ejection fraction benefit from daily treatment with dapagliflozin.

PATIENTS: Patients with stabilized heart failure

INTERVENTION: Dapagliflozin

CONTROL: Placebo

PRIMARY OUTCOME: Worsening heart failure or cardiovascular death

Secondary Outcome: Total number of worsening heart failure events and cardiovascular death

METHODS (BRIEF DESCRIPTION):

- Included patients were ≥40 years old with or without type 2 diabetes with left ventricular ejection fraction of >40%, had demonstrated evidence of structural heart disease, and an elevated natriuretic peptide level.
- Exclusion criteria included type 1 diabetes, SGLT2 inhibitor therapy within four weeks prior to trial or previous intolerance to SGLT2 inhibitor, and eGFR <25 mL/min/1.73m2 at first visit.
- Patients were blinded and randomized into two treatments:
    - 10 mg dapagliflozin daily
    - Matching placebo
- Worsening heart failure was defined by either unplanned hospitalization due to heart failure or urgent visits due to heart failure.
- Secondary outcome was measured by a change in symptom score using the Kansas City Cardiomyopathy Questionnaire (KCCQ) with scores from 1–100; higher scores indicating fewer symptoms and physical limitations at month eight.

INTERVENTION (# IN THE GROUP): 3,131

COMPARISON (# IN THE GROUP): 3,132

FOLLOW-UP PERIOD: 39 months

RESULTS:

Primary Outcome –

- Worsening heart failure and cardiovascular deaths were lower in the dapagliflozin group compared to the placebo group in the overall population (rate ratio 0.77; 95% CI, 0.67–0.89).

Secondary Outcome –

- Worsening heart failure events and cardiovascular deaths at month eight showed a benefit in the dapagliflozin group compared to placebo (mean placebo-corrected difference from baseline of 2.4 points; 95% CI, 1.5–3.4).

LIMITATIONS:

- Generalizability may be limited due to specific inclusion and exclusion criteria.
- Less than 5% of patients enrolled were Black, though this was proportional to the population percentage based on region.
- The Covid-19 pandemic limited symptom burden assessment to be performed at month eight, before March 11, 2020.

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Weekly Insulin Injections Increase Compliance and Decrease A1C

Weekly Icodec Versus Daily Glargine U100 in Type 2 Diabetes Without Previous Insulin

Rosenstock J, Bain SC, Gowda A, et al. Weekly Icodec versus Daily Glargine U100 in Type 2 Diabetes without Previous Insulin. *N Engl J Med*. 2023;389(4):297-308. doi:10.1056/NEJMoa2303208

KEY TAKEAWAY: Once weekly icodec offered better glycemic control than once daily insulin glargine in insulin naïve patients with type 2 diabetes without increased hypoglycemic events.

STUDY DESIGN: Randomized, open-label, treat to target, phase 3a trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Insulin injections are a commonly used treatment modality to improve glycemic control if non-insulin methods fail, however, compliance can be difficult for patients. Reduced treatment adherence related to daily injections contributes to suboptimal glycemic control. Once weekly glucagon-like peptide 1 (GLP-1) receptor agonist injections have been more effective in maintaining glycemic control and treatment adherence, so a once weekly insulin injection may have similar results.

PATIENTS: Adults ≥18 years old

INTERVENTION: Once weekly icodec injections

CONTROL: Once daily insulin glargine U100 injections

PRIMARY OUTCOME: Hemoglobin A1c (HbA1c)

Secondary Outcome: Percent of time spent in the target glucose range, percent achieving target A1C, hypoglycemic episodes, adverse events

METHODS (BRIEF DESCRIPTION):

- The study was conducted at 143 sites in 12 countries, including the United States.
- Inclusion criteria:
  - Insulin-naïve adults with type 2 diabetes diagnosed more than six months before the study.
  - HbA1C between 7–11%
  - BMI ≤40
  - Adherence to stable doses of non-insulin diabetes medication (e.g. metformin, GLP-1 receptor agonists, etc) for a minimum of 90 days prior to participation.
- Participants were randomly assigned to receive either weekly icodec (starting at 70 units per week) or daily glargine U100 (starting at 10 units per day).
  - Doses were adjusted to achieve a target fasting glucose between 80–130 mg/dL.
  - At the end of the study, the average icodec dose was between 214U and 224U per week while the average glargine dose was between 222U and 234U total per week.
- Participants were followed for a total of 83 weeks with 52 weeks of the main phase, 26 weeks of an extension phase, and five weeks of follow-up to discontinue trial treatment.
- Each participant was given a glucometer, and continuous glucose monitor and educated on their use. Participants continued all stable non-insulin diabetes treatments, except glinides and sulfonylureas.
- HbA1c was measured at baseline, week 52, and week 78. A double-blind continuous glucose monitor was used to measure the percent of time spent in the target glucose range (70–180 mg/dL) from weeks 48–52, weeks 74–78, and the number and severity of hypoglycemic episodes.

INTERVENTION (# IN THE GROUP): 492

COMPARISON (# IN THE GROUP): 492

FOLLOW-UP PERIOD: 83 weeks

RESULTS:

Primary Outcome –

- At week 52, the icodec group had a greater A1C reduction when compared to the glargine group (–1.6 percentage points vs –1.4 percentage points; between-group difference –0.19; 95% CI, –0.36 to –0.03).
- At week 78, there was no significant difference in A1C between the two groups.

Secondary Outcome –

- From weeks 48–52, the icodec group spent more time in the target glucose range when compared to the glargine group (72% vs 67%; between-group difference 4.3; 95% CI, 1.9–6.6).
  - This difference was sustained from weeks 74–78 (70% with icodec vs 6.5% with glargine; between-group difference 4.4; 95% CI, 1.9–7.0)
- More participants receiving icodec reached a HbA1c of <7% at weeks 52 and 78 compared to glargine.

- Incidences of hypoglycemic events were similar in the two groups at week 52 and week 83, with less than one hypoglycemic event per person-year of exposure at trial completion.
- Although some adverse events occurred (e.g. hypersensitivity, injection-site reactions), most were mild to moderate in severity.

LIMITATIONS:

- The study was not double-blinded due to the investigators' desire to limit the number of injections over a long period of time.
- Continuous glucose monitoring was not maintained throughout the entire trial. Continuous use may have provided more accurate information on glycemic control, dosing adjustments, and hypoglycemic events.

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The opinions and assertions contained herein are those of the authors and are not to be construed as official or as reflecting the views of the US Navy Medical Department, the Navy at large, or the Department of Defense.

SGLT-2 Inhibitor Improves NAFLD

Ipragliflozin Improves the Hepatic Outcomes of Patients with Diabetes with NAFLD

Takahashi H, Kessoku T, Kawanaka M, et al. Ipragliflozin Improves the Hepatic Outcomes of Patients With Diabetes with NAFLD. *Hepatol Commun*. 2022;6(1):120-132. doi:10.1002/hep4.1696

KEY TAKEAWAY: Sodium-glucose cotransporter-2 inhibitor (SGLT-2i) may prevent the development of nonalcoholic fatty liver disease (NAFLD), resolve nonalcoholic steatohepatitis (NASH), and alleviate liver fibrosis.

STUDY DESIGN: Multicenter, open-label, randomized controlled trial

LEVEL OF EVIDENCE: STEP 3 (downgraded due to lack of blinding and small sample size)

BRIEF BACKGROUND INFORMATION: SGLT-2i has been shown to lower blood glucose concentration. However, their effects on liver pathology have not been evaluated.

PATIENTS: Patients with DM2 and NAFLD

INTERVENTION: Ipragliflozin

CONTROL: Lifestyle modification, anti-diabetic medication except for SGLT-2i, glucagon-like peptide-1 receptor agonist (GLP-1), and pioglitazone

PRIMARY OUTCOME: Glycemic control, obesity, liver pathology

METHODS (BRIEF DESCRIPTION):

- Adults 20–80 years old with an A1c of >6%, not currently taking SGLT-2i, pioglitazone, GLP-1, or insulin, were included in the study.
- All participants had biopsy-confirmed diagnoses of NAFLD within the previous six months.
- Excluded from the trials were severe diabetes with end-organ damage including GFR <30, retinopathy, CVD, CHF, CVA, PDA, above-recommended alcohol intake, hepatitis B, hepatitis C, abnormal thyroid, or autoimmune liver disease.
- Patients were randomized into two groups: Ipragliflozin vs control.
- There were two endpoint outcomes measured:
  - Glycemic control and obesity
  - Liver function using laboratory markers of serum fibrosis and re-biopsy of the liver

INTERVENTION (# IN THE GROUP): 27

COMPARISON (# IN THE GROUP): 28

FOLLOW-UP PERIOD: 72 weeks

RESULTS:

Primary Outcome –

- Patients taking ipragliflozin (IPR) decreased A1C significantly compared to the control group (CTR) (log odds ratio –0.31; *P*=.01).
- IPR decreased BMI –1.06 kg/m^2 (*P*<.05 at 72 weeks), visceral fat –20 cm^2 (*P*<.05 at 72 weeks), and subcutaneous fat –10 cm^2 (*P*<.01 at 72 weeks) compared to CTR.
- IPR decreased AST –10 U/L (*P*<.01 at 48 weeks), ALT –20 U/L (*P*<.01 at 48 weeks), and GGT –25 U/L (*P*<.05 at 72 weeks) compared to CTR.
- Liver pathology:
  - 12/21 patients with fibrosis in the IPR group had at least one-stage reduction, compared to 4/25 in the CTR group (*P*=.01).
  - No significant changes in steatosis or inflammation between the two groups.
  - 12/17 patients with fibrosis stage >1 in the IPR group had a reduction of at least one severity stage, compared to 4/18 in the CTR group (*P*=.01).
  - 11/21 patients with ballooning had a one-stage reduction, compared to 6/25 patients in the CTR group (*P*=.02).

LIMITATIONS:

- The mechanism of SGLT-2i improvement in liver fibrosis is unclear.
- The study did not provide complete statistical data or confidence intervals.

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