GOOD EVIDENCE MATTERS

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Sleep Without Sedatives: Review of Non-Pharmacological Interventions in Depressed Populations

Efficacy of Non-Pharmacological Interventions on Improving Sleep Quality in Depressed Patients: A Systematic Review and Network Meta-Analysis

Sun A, Wu X. Efficacy of Non-pharmacological Interventions on Improving Sleep Quality in Depressed Patients: A Systematic Review and Network Meta-analysis. *J Psychosom Res*. 2023;172:111435. doi:10.1016/j.jpsychores.2023.111435

KEY TAKEAWAY: Non-pharmacological interventions have variable effectiveness in significantly improving sleep quality in depressed adults.

STUDY DESIGN: Systematic review and network meta-analysis of 26 randomized controlled trials (RCTs) (N=3,748)

LEVEL OF EVIDENCE: STEP 2 (downgraded due to inconsistent scales, limited sample sizes, and incomplete data for certain interventions)

BRIEF BACKGROUND INFORMATION: The number of adult patients battling simultaneous depression and sleep issues has increased and non-pharmacologic treatments have been encouraged, however, their effectiveness remains unclear. Previous studies have shown mixed results due to small sample sizes, inconsistent methodologies, and different intervention types. This study aimed to clarify the evidence using systematic review and network meta-analysis comparing multiple non-pharmacological interventions aimed at improving sleep quality and depressive symptoms.

PATIENTS: Depressed adults with impaired and/or poor sleep quality

INTERVENTION: Non-pharmacological interventions

CONTROL: Conventional medication, psychoeducation, and the blank group (no-intervention, sham, waitlist-control, placebo)

PRIMARY OUTCOME: Sleep quality

Secondary Outcome: Depression severity

METHODS (BRIEF DESCRIPTION):

- RCTs found in PubMed, Embase, Cochrane, and Web of Science from start of database to 2022 were included in the review.
- The review included RCTs involving patients diagnosed with depression that evaluated non-pharmacological interventions for sleep disorders.
- Eligible studies were required to include a comparison group and report outcomes on sleep quality (primary outcome) and/or depression severity (secondary outcome). Studies were identified through major databases up to November 2022.
- Studies were excluded if they were not RCTs, did not include patients with depression and/or sleep disorders, involved pharmacologic interventions, had insufficient outcome data, or were duplicate publications.
- Demographics characteristics: Mean age of 49 years old, 60% female. 11 studies in Pacific-Asian area, 15 studies in USA/Australia/Europe region.
- Various non-pharmacological interventions were used including cognitive behavioral therapy (CBT) weekly for 6–12 weeks, aromatherapy daily for 2–8 weeks, acupuncture 2–3 times weekly for 4–8 weeks, exercise 3–5 times weekly for 6–12 weeks, mindfulness daily for 6–8 weeks.
- Comparators included usual care (routine, standard clinical management), waitlist control (no active intervention during the study period), placebo/sham interventions, and other active non-pharmacological interventions.
- Comparator effectiveness was determined by changes in validated outcome measures, including sleep quality and depression severity, and analyzed using standardized mean differences within a network meta-analysis framework.
- The primary outcome assessed sleep quality measured via several scoring systems including the Insomnia Severity Index (ISI), Pittsburgh Sleep Quality Index (PSQI), among others.
- The secondary outcome assessed depression severity measured via several scoring systems including the Beck Depression Inventory (BDI), Hamilton Depression Scale (HAMD), among others.

INTERVENTION (# IN THE GROUP): Not available

COMPARISON (# IN THE GROUP): Not available

FOLLOW-UP PERIOD: Variable (ranged from 4–24 weeks)

RESULTS:

Primary Outcome –

- In depressed patients with co-occurring sleep problems, aromatherapy, acupuncture, and CBT most significantly improved sleep quality compared to control:
  - Aromatherapy (standardized mean difference [SMD] 4.0; 95% CI, 0.71–7.2).
  - Acupuncture (SMD 3.5; 95% CI, 0.88–6.1)
  - Cognitive Behavioral Therapy (SMD 2.8; 95% CI, 1.6–4.0).
- There was no significant difference in sleep quality for the following non-pharmacological interventions compared to control:
  - Mindfulness-based interventions
  - Light therapy
  - Music therapy
  - Hyperthermic baths
  - Transcranial magnetic stimulation (TMS)
  - Transcranial direct current stimulation (tDCS)

Secondary Outcome –

- In depressed patients with co-occurring sleep problems, acupuncture, acupressure, exercise, and CBT most significantly improved depressive severity symptoms compared to control:
  - CBT (SMD 2.7; 95% CI, 0.96–3.8)
  - Acupuncture (SMD 3.4; 95% CI, 0.77–6.0)
  - Acupoint massage (SMD 3.7; 95% CI, 0.25–7.1)

LIMITATIONS:

- Variable measurement scales across trials, impacting scoring criteria and sensitivity.
- Inadequate reporting of methods (i.e. blinding) could increase bias and overestimate results.
- Data on aromatherapy's effectiveness for depressive symptoms were insufficient due to incomplete data.
- Heterogeneous patient population (depressed with sleep problems) which could confound results

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Trimethoprim-Sulfamethoxazole and Low Birth Weight

A Trial of Trimethoprim-Sulfamethoxazole in Pregnancy to Improve Birth Outcomes

Chasekwa B, Munhanzi F, Madhuyu L, et al. A Trial of Trimethoprim-Sulfamethoxazole in Pregnancy to Improve Birth Outcomes. *N Engl J Med*. 2025;392(21):2125-2134. doi:10.1056/NEJMoa2408114

KEY TAKEAWAY: Trimethoprim-sulfamethoxazole (TMP-SMX) does not improve infant weight at birth when given to pregnant women of at least 14 weeks' gestation until delivery.

STUDY DESIGN: Double-blind randomized, placebo-controlled trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Worldwide, there is a significant incidence of preterm and low birth weights which are tied to poor outcomes such as infection, inflammation, and morbidity. Some studies have shown no change in these outcomes with initiation of antibiotics (often single or short duration) during second and third trimesters. This trial explored if birth weight could be improved in pregnant women exposed to longer duration of TMP- SMX.

PATIENTS: Zimbabwean women

INTERVENTION: TMP-SMX daily

CONTROL: Placebo daily

PRIMARY OUTCOME: Birth weight

Secondary Outcome: Low birth weight (LBW), duration of gestation, preterm birth, small for gestational age (SGA), weight-for-age z score at six weeks, length-for-age z score at six weeks, head-circumference-for-age z score at six weeks, fetal loss, maternal hospitalization or death, neonatal hospitalization or death.

METHODS (BRIEF DESCRIPTION):

- Pregnant women were recruited from three clinics in central Zimbabwe (not area of endemic malaria). Average age was 25 years old, Median gestational age of enrollment was 20 weeks, and human immunodeficiency virus (HIV) prevalence was 13%.
- Participants were included if they had known HIV status, were not receiving and had no indication for receiving TMP-SMX, could receive all care at trial clinics, if their CD4 count (for those with HIV) was >350 cell/uL.
- Participants were randomized to TMP-SMX or placebo:
  - TMP-SMX: Two 480-mg tablets, each having 400 mg of sulfamethoxazole and 80 mg of trimethoprim to be taken daily.
  - Placebo made to mimic TMP-SMX and taken daily.
  - Participants received the first dose of TMP-SMX or placebo either just after determination of the gestation duration of (if it was already ≥14 weeks) or during clinic visit at 14 weeks' gestation.
  - Participants continued receiving TMP-SMX placebo until delivery or fetal loss.
- The primary outcome (birth weight) was measured in grams immediately after delivery.
- Secondary outcomes were assessed using different approaches or measures:
  - LBW was defined by birth weight <2,500 g.
  - Preterm birth was defined as <37 weeks' gestation).
  - SGA was defined as birth weight <10th percentile based on the INTERGROWTH-21st standard.
  - At six weeks postpartum for infant: Weight for age (based on z score), length for age (based on z score), head circumference (based on z score were determined.
  - Fetal loss was defined as a miscarriage or stillbirth.
  - Maternal hospitalization or death and neonatal hospitalization or death were noted between enrollment and 42 days postpartum.
- Follow-up assessments occurred at gestation weeks 20, 26, 30, 34, 36, 38, and 40.
- During follow-up visits, ultrasounds were done to monitor fetal growth from weeks 26–34.
- From 36 weeks' gestation, participants received telephone calls per week to track delivery.
- Infants were seen for postnatal visits when they were three days and six weeks of age for collection of data such as weight, length, and head circumference.

- Researchers used intention-to-treat and per-protocol analyses to assess the outcomes.

INTERVENTION (# IN THE GROUP): 495
COMPARISON (# IN THE GROUP): 498

FOLLOW-UP PERIOD: Up to six weeks (42 days) postpartum

RESULTS:

Primary Outcome –

- TMP-SMX did not significantly affect birth weight compared to placebo (mean difference [MD] 20 g; 95% CI, –43 to 83).

Secondary Outcome –

- TPM-SMX had no significant difference on weight-for-age z score at six weeks, length -for-age z score at six weeks, and head-circumference-for-age z score at six weeks compared to placebo.
- TPM-SMX decreased percentage of infants with LBW compared to control (MD 0.86; 95% CI, 0.60–1.2).
- TPM-SMX increased the mean duration of gestation compared to control (MD 0.5; 95% CI, 0.2–0.7).
- TPM-SMX decreased percentage of infants with preterm birth compared to control (MD 0.6; 95% CI, 0.39–0.91).
- TPM-SMX decreased percentage of infants with SGA compared to control (MD 1.2; 95% CI, 0.88–1.5).
- TPM-SMX increased percentage of fetal loss compared to control (MD 1.3; 95% CI, 0.66–2.4).
- TPM-SMX decreased percentage of maternal hospitalization or death compared to control (MD 0.84; 95% CI, 0.48–1.5).
- TPM-SMX increased percentage of neonatal hospitalization or death compared to control (MD 1.2; 95% CI, 0.56–2.6).

LIMITATIONS:

- The study was conducted in only one country (Zimbabwe), thus limiting the generalizability of the findings.
- This study was not done in an endemic area of malaria, thus limiting a potential population who may have more favorable outcomes with medication.
- Some participants did not follow up postpartum, thereby limiting the estimates of postnatal growth.
- Mean of starting gestation was later second trimester (22 weeks) making it unclear if earlier intervention could improve outcomes.
- Of those selected and randomized, 7.7% did not start trial regimen, decreasing study size and therefore decreasing its power somewhat.
- The secondary analyses did not include adjustments for potential confounders, and thus the results should be interpreted with caution.

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Weekly Insulin: Can it Hold Up Against the Competition?

Insulin Efsitora vs Degludec in Type 2 Diabetes Without Previous Insulin Treatment

Wysham C, Bajaj HS, Del Prato S, et al. Insulin Efsitora versus Degludec in Type 2 Diabetes without Previous Insulin Treatment. *N Engl J Med*. 2024;391(23):2201-2211. doi:10.1056/NEJMoa2403953

KEY TAKEAWAY: Once weekly efsitora is non-inferior to daily degludec in lowering glycated hemoglobin levels (HbA1c) for patients with type 2 diabetes mellitus (T2DM) initiating insulin, though may cause more episodes of hypoglycemia.

STUDY DESIGN: Open label, treat-to-target, randomized control trial

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

BRIEF BACKGROUND INFORMATION: Many patients with T2DM require the administration of daily insulin for management of hyperglycemia. Adherence to daily insulin injections can be a major barrier for these patients. New weekly insulin formulations have been developed which could serve to improve adherence and blood glucose control. This study assesses if once weekly efsitora insulin injection is as effective and safe as daily degludec insulin for treatment of T2DM.

PATIENTS: Adults >18 years old with T2DM

INTERVENTION: Weekly insulin

CONTROL: Daily insulin

PRIMARY OUTCOME: Change in HbA1c

Secondary Outcome: Addition of glucagon-like peptide-1 (GLP-1), time in target blood sugar range, hypoglycemic episodes

METHODS (BRIEF DESCRIPTION):

- 928 patients were recruited from 10 countries in North and South America, Europe, and Asia at 121 research centers in the Vivli network.
- Included patients were insulin-naïve, ≥18 years old with previously diagnosed T2DM and an A1C of 7.0–11%.
- Patients were excluded if they had a body mass index >45 kg/m^2, type 1 diabetes or latent autoimmune diabetes, recent history of hyperglycemic hospitalizations or severe episodes of hypoglycemia, severe renal or liver dysfunction, recent significant weight gain or loss, or were pregnant.
- Patients were randomly assigned in a 1:1 ratio to receive weekly dosed efsitora or daily dosed degludec.
    - The efsitora group started with a loading dose of 300-units (3 times higher than a usual starting dose) to achieve steady-state more rapidly, then a standard starting dose of 100 units weekly.
    - The degludec group started with 10 units daily (the recommended starting dose of degludec for insulin naïve T2DM patients).
    - Insulin doses were adjusted weekly by the investigator for 12 weeks, then monthly, based on patient reported fasting blood sugars (target of 80 to 120 mg/dl) and reported hypoglycemic events.
        - Continuous glucose monitor (CGM) data was not used for dose adjustments and was blinded from patient and investigator.
- The primary outcome was the change in A1C from baseline to week 52 of efsitora compared to degludec.
- The secondary outcomes measured the effectiveness with and without GLP-1 medications, time in target blood sugar range, and hypoglycemic episodes.
- Key secondary endpoints:
    - GLP-1 use and non-use was assessed for efsitora vs degludec using the difference in A1C over 52 weeks
        - Patients that were stable on GLP-1 agonists remained on the medications throughout the trial (around 50% of patients in each group)
    - The time spent in target blood sugar range was assessed using two methods:
        - Change in A1C over 52 weeks
        - Percentage of time blood glucose was between 70–180 mg/dL weeks 48–52
    - Hypoglycemic episodes were assessed using CGM data and defined as the following:

- Clinically significant hypoglycemia as glucose <54 mg/dL with or without symptoms.
- Severe hypoglycemia included events where the patient had an altered mental state and required assistance to administer treatment.

INTERVENTION (# IN THE GROUP): 466
COMPARISON (# IN THE GROUP): 462

FOLLOW-UP PERIOD: 52 weeks

RESULTS:

Primary Outcome –

- Use of efsitora resulted in a non-inferior change in A1C over 52 weeks compared to degludec (–1.3% vs –1.2%, respectively; between-group difference –0.09; 95% CI, –0.22 to 0.04).

Secondary Outcome –

- Use of efsitora resulted in a non-inferior change in A1C compared to degludec for GLP-1 users (between-group difference –0.06; 95% CI, –0.26 to 0.13).
- Use of efsitora resulted in a non-inferior change in A1C compared to degludec for GLP-1 non-users (between-group difference –0.11; 95% CI, –0.28 to 0.07).
- Use of efsitora resulted in a higher percentage of time in blood glucose target range compared to degludec (64% vs 61%, respectively; between-group difference 3.1%; 95% CI, 0.10–6.1).
- Use of efsitora had a statistically insignificant higher rate of combined clinically significant or severe hypoglycemia compared to the degludec group.

LIMITATIONS:

- The open label design could have led to bias.
- Dose adjustments could not be made in real time due to CGM blinding.
- This study only included insulin naïve T2DM patients.
- Pharmaceutical company designed, administered, and wrote the manuscript.

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Rewriting Withdrawal Care: Is Implementing a Phenobarbital Protocol Effective and Safe?

Hospital-Wide Implementation, Clinical Outcomes, and Safety of Phenobarbital for Alcohol Withdrawal

Wolpaw BJ, Oren H, Quinnan-Hostein L, et al. Hospital-Wide Implementation, Clinical Outcomes, and Safety of Phenobarbital for Alcohol Withdrawal. *JAMA Netw Open*. 2025;8(8):e2528694. Published 2025 Aug 1. doi:10.1001/jamanetworkopen.2025.28694

KEY TAKEAWAY: Implementing a phenobarbital protocol in electronic health record (EHR) across all care locations has faster alcohol withdrawal syndrome (AWS) symptoms resolution after 24 hours of adult patients being at the hospital, less treatment duration, and reduction in hospital stay.

STUDY DESIGN: Retrospective cohort study

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: Benzodiazepines have been the go-to treatment for alcohol withdrawal in hospitals. Phenobarbital has been used but mostly in academic settings and has been shown to carry lesser risks. This study aimed to implement a standardized, weight-based phenobarbital protocol across hospital settings to quicken symptom relief and shorten treatment time and hospital stay.

PATIENTS: Adults hospitalized for AWS

INTERVENTION: Implementation of a weight-based phenobarbital order set in the EHR

CONTROL: The period before the order set when treatment was benzodiazepines with symptom-based protocol without the standardized phenobarbital protocol

PRIMARY OUTCOME: Faster symptom resolution, duration of AWS treatment, and time to hospital discharge

Secondary Outcome: Implementation and potential continual use of phenobarbital order sets

METHODS (BRIEF DESCRIPTION):

- Patients at risk for AWS who were hospitalized for at least 24 hours were included based on CIWA-Ar monitoring orders, alcohol testing, and alcohol related diagnosis.
- Median age was 46 years old, with majority being male (about 70%), and had varied comorbidities including liver disease and psychiatric diagnoses.
- Patients who were pregnant, admitted for psychiatric disorders, transitioning to comfort care or missing encounter data were excluded.
- Post-implementation group received weight based intravenous phenobarbital order set:
  - Loading dose: 10–15 mg/kg IV
  - Maintenance dosing per protocol as needed.
  - Adjunctive benzodiazepines as needed if necessary.
  - Physicians administered medication according to protocol, with adherence monitored via the EHR.
- The comparison group (pre-implementation) received usual care of benzodiazepine symptom-based regimens; dosing and schedule determined by treating physician.
- Symptom resolution was measured using daily maximum Clinical Institute Withdrawal Assessment of Alcohol Scale Revised (CIWA-Ar).
- CIWA-Ar scores were measured at 24h, 48h and 96h, with ow score indicating minimal withdrawal symptoms, and high score indicating severe symptoms.
- Duration of AWS treatment (hours from first dose to last).

INTERVENTION (# IN THE GROUP): 100

COMPARISON (# IN THE GROUP): 154

FOLLOW-UP PERIOD: 11 months before implementation and 12 months after implementation

RESULTS:

Primary Outcome –

- Implementing weight-based phenobarbital order set in the EHR resolved AWS symptoms more rapidly after 24–96 hours of patients being at the hospital, compared to before implementation.
  - Arrival to 24 hours (standardized mean difference [SMD] −1.7; 95% CI, −3.8 to 0.5)
  - 24–48 hours (SMD −4.3; 95% CI, −6.3 to −2.4)
  - 48–72 hours (SMD −4.2; 95% CI, −6.1 to −2.3)
  - 72–86 hours (SMD −5.0; 95% CI, −7.7 to −2.2)
- Post-implementation patients require significantly less time on alcohol withdrawal treatment (30 hours vs 58 hours, respectively; SMD −30; 95% CI, −44 to −17).

- Implementation of the order set shortened hospital length of stay, compared to before implementation (3.2 days vs 4.8 days, respectively; SMD –2.2; 95% CI, –3.7 to –0.7).

Secondary Outcome –

- Post-implementation patients received lower total benzodiazepine doses, compared to before implementation of the order set (1.5 mg vs 12 mg, respectively; SMD –22; 95% CI, –28 to –17).
- Safety/adverse outcomes (intubation, use of prolonged restraints and in-hospital mortality) did not show a statistically significant difference.

LIMITATIONS:

- The study was conducted in a single community hospital with predominantly white population, which may limit the findings' generalization.
- The study is a pre/post design and not a randomized controlled trial. Results may be influenced by selection bias and unmeasured confounders.
- Not all patients in the post-implementation period received the order set.
- The transition to new electronic health record resulted in a short pre-implementation observation period.
- Benzodiazepine shortage may have increased usage of phenobarbital order set.

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Semaglutide Reduces Risk of Alzheimer's Disease-Related Dementias Better Than Other Antidiabetic Medications

Associations of Semaglutide with Alzheimer's Disease-Related Dementias in Patients with Type 2 Diabetes: A Real-World Target Trial Emulation Study

Wang W, Davis PB, Qi X, et al. Associations of Semaglutide with Alzheimer's Disease-related Dementias in Patients with Type 2 Diabetes: A Real-world Target Trial Emulation Study. *J Alzheimers Dis*. 2025;106(4):1509-1522. doi:10.1177/13872877251351329

KEY TAKEAWAY: For patients with type 2 diabetes (T2D), semaglutide is associated with significantly decreased risk of Alzheimer's disease-related dementia (ADRD) incidence compared with other antidiabetic medications during a three-year follow-up. This varies across dementia type, with vascular dementia and "other dementias" seeing significantly decreased risk, while fronto-temporal dementia (FTD) and Lewy body dementia (LBD) see no significant decrease in risk.

STUDY DESIGN: Retrospective cohort study

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: Currently, dementia has no cure or effective treatment, therefore prevention strategies are critical. About 45% of dementia cases have been linked to 14 modifiable risk factors including obesity, T2D, hypertension (HTN), and cardiovascular disease (CVD), which increase dementia risk through inflammation and associated vascular disease. Semaglutide has been shown to reduce these risk factors, in addition to having newly proposed anti-inflammatory and vascular benefits. Semaglutide has already been associated with significant reduction in Alzheimer's disease (AD) incidence compared with other antidiabetic medications. This study aimed to explore whether semaglutide has similar effects on other ADRD's.

PATIENTS: Patients with T2D who are eligible for antidiabetic medication

INTERVENTION: Semaglutide

CONTROL: Other antidiabetic medications, including insulin, metformin, dipeptidyl peptidase 4 inhibitors (DPP-4is), sodium-glucose cotransporter 2 inhibitors (SGLT2is), sulfonylureas, thiazolidinediones (TZDs), and older glucagon-like peptide-1 receptor agonists (GLP-1RAs)

PRIMARY OUTCOME: First diagnosis of ADRDs, vascular dementia, FTD, LBD, or other dementias

Secondary Outcome: Dementia-related medication prescriptions

METHODS (BRIEF DESCRIPTION):

- Data was collected through the TriNetX platform for the study's sample population. TriNetX is a web-based research platform that provides on-demand access to population-level aggregate de-identified data from a broad global network of healthcare organizations.
- Patients of any age with T2D who had recent medical encounters for their T2D diagnosis in the past year, were prescribed antidiabetic medications between December 2017 and December 2021, and were diagnosed with at least one condition based on semaglutide's prescription guidelines were included in the study.
- Patients with history of ADRD or AD, co-prescription of semaglutide and comparison medications at baseline, and certain medical conditions making semaglutide prescription contraindicated were excluded in the study.
- Target trials were run separately comparing semaglutide with insulin, metformin, DPP-4is, SGLT2is, sulfonylureas, TZDs, and the first-generation GLP-1RAs.
- The semaglutide group and seven comparison groups were separately propensity-score matched to 50 baseline covariates, 1:1, to emulate randomization.
- Each eligible patient was followed starting 30 days after being prescribed semaglutide or the comparison group until the occurrence of the outcome, death, loss to follow-up, or three years passing since prescription.
- Primary outcomes were measured using International Classification of Diseases, Tenth Revision (ICD-10) codes based on first diagnosis of ADRD, vascular dementia, FTD, LBD, or other dementias in each patient.
- Secondary outcomes were measured based on new prescriptions for dementia related medication

(donepezil, rivastigmine, galantamine, and memantine).

INTERVENTION (# IN THE GROUP): Semaglutide: 64,267

COMPARISON (# IN THE GROUP):

- Insulin: 1,156,564
- Metformin: 975,761
- DPP-4i: 239,773
- SGLT2i: 189,176
- Sulfonylureas: 409,072
- TZDs: 70,573
- 1st generation GLP-1RAs: 173,573

FOLLOW-UP PERIOD: Three years

RESULTS:

Primary Outcome –

- Semaglutide decreased risk of overall ADRD incidence in patients with T2D compared to:
  - Insulin (hazard ratio [HR] 0.54; 95% CI, 0.49–0.59)
  - Metformin (HR 0.67; 95% CI, 0.61–0.74)
  - DPP-4i (HR 0.60; 95% CI, 0.54–0.67)
  - SGLT2i (HR 0.78; 95% CI, 0.70–0.87)
  - Sulfonylureas (HR 0.64; 95% CI, 0.58–0.71)
  - TZDs (HR 0.67; 95% CI, 0.59–0.75)
  - Other GLP (HR 0.80; 95% CI, 0.72–0.89)
- Semaglutide decreased risk of vascular dementia incidence in patients with T2D compared to:
  - Insulin (HR 0.48; 95% CI, 0.39–0.59)
  - Metformin (HR 0.55; 95% CI, 0.45–0.68)
  - DPP-4i (HR 0.55; 95% CI, 0.45–0.69)
  - SGLT2i (HR 0.68; 95% CI, 0.55–0. 85)
  - Sulfonylureas (HR 0.62; 95% CI, 0.50–0.77)
  - TZDs (HR 0.68; 95% CI, 0.50–0.86)
  - Other GLP (HR 0.67; 95% CI, 0.54–0.84)
- Semaglutide decreased risk of "other dementias" incidence in patients with T2D compared to:
  - Insulin (HR 0.54; 95% CI, 0.49–0.60)
  - Metformin (HR 0.70; 95% CI, 0.63–0.87)
  - DPP-4i (HR 0.60; 95% CI, 0.54–0.67)
  - SGLT2i (HR 0.78; 95% CI, 0.70–0.88)
  - Sulfonylureas (HR 0.65; 95% CI, 0.58–0.72)
  - TZDs (HR 0.66; 95% CI, 0.58–0.75)
  - Other GLP (HR 0.82; 95% CI, 0.73–0.82)
- Semaglutide did not decrease risk of FTD or LBD incidence in patients with T2D compared to insulin, metformin, DPP-4i, SGLT2i, sulfonylureas, TZDs and other GLP.

Secondary Outcome –

- Semaglutide lowered the risk of prescriptions for dementia related medications compared to:
  - Insulin (HR 0.72; 95% CI, 0.64–0.81)
  - Metformin (HR 0.78; 95% CI, 0.69–0.88)
  - DPP-4i (HR 0.74; 95% CI, 0.66–0.84)
  - SGLT2i (HR 0.84; 95% CI, 0.75–0.96)
  - Sulfonylureas (HR 0.85; 95% CI, 0.75–0.96)
  - TZDs (HR 0.69; 95% CI, 0.60–0.79)
  - Other GLP (HR 0.83; 95% CI, 0.74–0.94)

LIMITATIONS:

- Retrospective observational studies using patient electronic health records (EHRs) suffer from inherent limitations including over-, under-, or misdiagnosis; unmeasured or uncontrolled confounders and biases; therefore, causal conclusions cannot be drawn.
- This cohort study could not characterize the underlying mechanisms, and future mechanistic studies are necessary.
- Using the ICD-10 diagnosis code for ADRD as the primary outcome presents inherent limitations with overdiagnosis, misdiagnosis and under-diagnosis, given the ICD-10-based diagnoses are for billing purposes.
- There is potential for socio-economic status to present as a significant confounding variable in this study given semaglutide was expensive, poorly covered by insurance, and highly sought after during the study trial period.
- Small sample sizes of patients who developed FTD and LBD limit the generalizability of the findings to these groups.
- Longer-term follow-up beyond three years could not be achieved due to semaglutide's age on the market.

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