GOOD EVIDENCE MATTERS

GEMs of the Week

SPOTLIGHT

Persistent Pains, Elusive Gains

Non-Cancer Chronic Pain Management in Primary Care

Blocking COPD? Beta Not

Are GIP's & GLP-1's the Solution for Alcohol Use Disorder and the Opioid Crisis?

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Persistent Pains, Elusive Gains: Non-Cancer Chronic Pain Management in Primary Care

Multidisciplinary Management of Persistent Pain in Primary Care—A Systematic Review

Huttunen MH, Paananen M, Miettunen J, Kalso E, Marttinen MK. Multidisciplinary Management of Persistent Pain in Primary Care—A Systematic Review. *Eur J Pain*. 2024;28(6):886-900. doi:10.1002/ejp.2240

KEY TAKEAWAY: Research on multidisciplinary management of persistent pain in primary care is limited and heterogeneous, highlighting the urgent need for standardized treatment protocols.

STUDY DESIGN: Systematic review of seven prospective cohort, three retrospective cohort, two observational, five randomized controlled trials (RCTs) (N=5,333)

LEVEL OF EVIDENCE: STEP 3 (downgraded due to lack of meta-analysis, low quality studies, and significant heterogeneity)

BRIEF BACKGROUND INFORMATION: Multidisciplinary pain management has been present since the 1970s and has been considered the gold standard with effectiveness and cost-effectiveness. With the growing population, multidisciplinary pain management in a primary care setting provides an accessible option. This study aimed to find evidence on how to provide an optimal treatment program in the primary care setting as well as defining the health care professionals involved in the care and outcome measures.

PATIENTS: Adult patients with non-cancer pain persisting >3 months

INTERVENTION: Multidisciplinary intervention involving treatment by ≥3 healthcare professions

CONTROL: Usual care or other non-multidisciplinary interventions

PRIMARY OUTCOME: Pain intensity, pain disability, psychological factors, depression, work-related aspects, opioid consumption, physical functioning, economical aspects

METHODS (BRIEF DESCRIPTION):

- The authors conducted a comprehensive search of several databases, including PubMed, Ovid MEDLINE, Scopus, CINAHL, and PsychINFO, from inception to October 2022, with supplementary research conducted in June 2023.
- Adults >18 years old with non-cancer pain persisting >3 months, multidisciplinary interventions involving ≥3 healthcare professions, interventions conducted in a primary care setting, and reports published in English, were included in the study.
- Patients not meeting inclusion criteria or those that did not report empirical data were excluded from the study.
- Intervention group (6–10 weeks): "Multidisciplinary interventions" were defined as care that involved ≥3 unique healthcare professions including psychologists, physical therapists, physicians, occupational therapists, pharmacists, social workers, dieticians, exercise physiologists, behavioral health consultants.
- The control group were patients receiving usual care or routine primary care management for persistent non-cancer pain.
- Pain intensity (6 studies) was measured using the Visual Analogue Scale, Numeric Rating Scale, Chronic Pain Grade Scale, Roland Morris Disability Questionnaire and Oswestry Disability Index.
- Pain disability (6 studies) was measured by Pain Disability Index, Roland Morris Disability Questionnaire, Functional Rating Index, West Haven-Yale Multidimensional Pain Inventory, Oswestry Disability Index, Widespread Pain Index.
- Psychological factors (8 studies) were scored with Arthritis Self-Efficacy Scale (ASES), Pain Catastrophizing Scale, Pain Self-Efficacy Questionnaire, Coping Strategies Questionnaire (CSQ), General Self-Efficacy Scale, Chronic Pain Acceptance Questionnaire and Brief Illness Perceptions Questionnaire.
- Depression and anxiety (7 studies) were measured using the Beck Depression Inventory, PHQ9, and Hospital Anxiety and Depression Scale.
- Work-related aspects (7 studies) were measured by the Working ability Index and number of sickness absences.
- Opioid Consumption (5 studies) was measured by mean opioid use and number of prescriptions.

- Physical Functioning (2 studies) was measured with the Tampa Scale of Kinesiophobia, and the number of sit-to-stands in one minute.
- Economic aspects (6 studies) were measured by the number of clinic visits and cost-effectiveness.

INTERVENTION (# IN THE GROUP): Not available

COMPARISON (# IN THE GROUP): Not available

FOLLOW-UP PERIOD: Varied (3–24 months)

RESULTS:

Primary Outcome –

- Pain intensity significantly decreased in 2/5 studies.
- Pain disability significantly improved in 2/5 studies.
- Psychological factors significantly improved in 3/7 studies.
- Depression significantly improved in 4/6 studies.
- Work-related sickness absences decreased significantly in 5/7 studies.
- Opioid use significantly decreased in 3/5 studies.
- Physical functioning significantly improved in 1/2 studies.
- Economical aspects:
  - Clinic visits significantly decreased in 3/6 studies.
  - Cost-effectiveness significantly improved in 2/6 studies.

LIMITATIONS:

- The quality of the included studies was generally low, with small sample sizes and most studies done using a European health care system.
- There was a lack of standardization in the methodologies used across the studies, including differences in outcome variables and study designs.
- No meta-analysis was done.

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Blocking COPD? Beta Not

Bisoprolol in Patients with Chronic Obstructive Pulmonary Disease at High Risk of Exacerbation: The BICS Randomized Clinical Trial

Devereux G, Cotton S, Nath M, et al. Bisoprolol in Patients With Chronic Obstructive Pulmonary Disease at High Risk of Exacerbation: The BICS Randomized Clinical Trial. *JAMA*. 2024;332(6):462-470. doi:10.1001/jama.2024.8771

KEY TAKEAWAY: Bisoprolol does not decrease number of chronic obstructive pulmonary disease (COPD) exacerbations compared to placebo in patients with moderate COPD.

STUDY DESIGN: Multi-site, placebo-controlled, double-blind randomized trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: In observational studies, beta blocker use has been associated with reduced risk of COPD exacerbations. Studies on metoprolol, however, have shown increased COPD exacerbations requiring hospitalizations. This study aim to investigate if selective beta blockers decrease COPD exacerbations in patients with COPD at high risk of exacerbations.

PATIENTS: Patients with COPD

INTERVENTION: Bisoprolol

CONTROL: Placebo

PRIMARY OUTCOME: COPD exacerbations

Secondary Outcome: COPD exacerbations requiring hospitalization, COPD related mortality, adverse events

METHODS (BRIEF DESCRIPTION):

- This trial was a multisite, double-blind study conducted at 76 centers in the United Kingdon (UK).
- Patients >40 years old who smoked for >10 years, had >2 prior exacerbations requiring oral steroids or antibiotics or both in previous year and with moderate air flow obstruction defined as the ratio of volume of forced expiration in the first second (FEV1) compared to forced vital capacity at (FEV1/FVC) <0.7 and FEV1 post bronchodilator at <80% of predicted were included in the study.
- Patients diagnosed with asthma (before 40 years old), systolic blood pressure (BP) <100 mmHg, resting heart rate <60 beats per minute (BPM), use of any calcium channel blockers or class one antiarrhythmic drugs antihypertension were excluded.
- At baseline, the mean age was 68 years old, 53% were male, 31% were current smokers, and 5% were prescribed long term oxygen therapy.
- The treatment group received oral bisoprolol at 1.25 mg once daily, up titrated as tolerated over four assessments over seven weeks to a maximum dose of 5 mg.
- The comparison group received a matching placebo.
- The primary outcome measured COPD exacerbations, defined as requiring treatment with oral steroid and/or antibiotics, was measured via self-report at 26 and 52 weeks with telephone, video, or face to face.
- The secondary outcomes measured the total number of COPD related hospitalizations, COPD related mortality, and adverse events.

INTERVENTION (# IN THE GROUP): 261

COMPARISON (# IN THE GROUP): 258

FOLLOW-UP PERIOD: 52 weeks

RESULTS:

Primary Outcome –

- Bisoprolol did not significantly affect COPD exacerbations compared to placebo (adjusted incidence rate ratio [aIRR] 0.97; 95% CI, 0.84–1.1).

Secondary Outcome –

- Bisoprolol did not significantly affect COPD exacerbations requiring hospitalization and adverse events compared to placebo.
- Bisoprolol decreased the risk of COPD related mortality compared to placebo (11 vs 13 deaths, respectively; adjusted hazard ratio [aHR] 0.19; 95% CI, 0.04–0.88).

LIMITATIONS:

- The study was interrupted due to the COVID-19 pandemic.
- The primary outcome was a patient-reported which may have allowed for over reporting of outcomes or inability to capture all events.
- Due to loss of funding, the trial did not meet the target sample size, which limits ability to find a difference should one exist.

- There was a high rate of discontinuation of bisoprolol, and multiple doses used of this medication as patients titrated their doses.

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Are GIP's & GLP-1's the Solution for Alcohol Use Disorder and the Opioid Crisis?

The Association Between Glucose-Dependent Insulinotropic Polypeptide and/or Glucagon-Like Peptide-1 Receptor Agonist Prescriptions and Substance-Related Outcomes in Patients with Opioid and Alcohol Use Disorders: A Real-World Data Analysis

Qeadan F, McCunn A, Tingey B. The association between glucose-dependent insulinotropic polypeptide and/or glucagon-like peptide-1 receptor agonist prescriptions and substance-related outcomes in patients with opioid and alcohol use disorders: A real-world data analysis. *Addiction*. 2025;120(2):236-250. doi:10.1111/add.16679

KEY TAKEAWAY: Glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 receptor agonist (GLP-1) prescriptions decrease opioid overdose and alcohol intoxication compared to no prescription in patients with a history of either opioid use disorder (OUD) or alcohol use disorder (AUD) irrespective of a diagnosis of type 2 diabetes mellitus (T2DM) and/or obesity.

STUDY DESIGN: Retrospective cohort study

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: OUD and AUD affect millions each year in the USA, and the rate of associated death has been increasing. Despite medications for treatment, reliable access to medical care remains difficult. Animal studies have shown GLP-1's can reduce alcohol intake and drug-seeking behavior, and small trials have started investigating addiction and substance-related outcomes. There has yet to be any larger scale studies with real world data. This study aimed to determine the strength of the relationship between adverse outcomes in OUD and AUD and GIP/GLP-1's in the general population, and to specifically analyze the relationship in patients with comorbid diabetes and/or obesity.

PATIENTS: Adults with an OUD or AUD diagnosis

INTERVENTION: First GIP or GLP-1 prescription after OUD or AUD diagnosis

CONTROL: Random encounter without a GIP or GLP-1 prescription after an OUD or AUD diagnosis

PRIMARY OUTCOME: Opioid overdose (OUD cohort) and alcohol intoxication (AUD cohort)

Secondary Outcome: OUD cohort and AUD cohort stratified for T2DM and/or obesity

METHODS (BRIEF DESCRIPTION):

- A search was done in the Oracle Cerner Real-World Data electronic medical record (EMR) with the following inclusion criteria: ≥18 years old, a documented code of either OUD or AUD between January 2014 and August 2022.
- The index encounter was defined as either the first prescription code for either a GIP or a GLP-1 that occurred after the OUD/AUD diagnosis or a random encounter after the OUD/AUD diagnosis in those without a prescription.
- Data was analyzed between January 2014 and September 2022 to allow a minimum of 30 days follow up after index encounter.
- GIP/GLP-1's included were abiglutide, dulaglutide, exenatide, liraglutide, lixisenatide, semaglutide, and tirzepatide.
- Outcomes were rates of opioid overdose or rates of alcohol intoxication between seven days and two years of the index encounter.
- Data analysis was performed while accounting for multiple confounders and stratifying for the presence of T2DM and/or obesity.
- Results were reported using person months and compared with incidence rate, incidence rate ratio (IRR), and adjusted incidence rate ratio (aIRR).
    - aIRR was adjusted in both cohorts for the following confounders: age, gender, race, marital status, region, insurance type, year of encounter, Charlson comorbidity index, mental health history, tobacco dependence history, and sleep apnea history.
    - aIRR was adjusted in the OUD cohort for the following confounders: history of SUD (excluding OUD), history of opioid overdose, median opioid prescription MME in year before index encounter, total duration of opioid prescriptions in year before index encounter, history of mental health condition, history of sleep apnea, benzodiazepine prescription in year before index encounter, tobacco dependence history, history of MOUD

treatment, and family history of psychoactive drug abuse.
    - aIRR was adjusted in the AUD cohort for the following confounders: history of SUD (excluding AUD), history of alcohol intoxication, history of mental health condition, history of MAUD treatment, and family history of alcohol abuse.
- A minimum of 30 days after index encounter was included for participants recruited in August 2022.

INTERVENTION (# IN THE GROUP):
- OUD cohort: 8,103
- AUD cohort: 5,621

COMPARISON (# IN THE GROUP):
- OUD cohort: 495,644
- AUD cohort: 811,688

FOLLOW-UP PERIOD: Seven days to two years after index encounter

RESULTS:

Primary Outcome –
- GIP/GLP-1 receptor agonists decreased opioid overdose compared to no GIP/GLP-1 therapy before (IRR 0.34; 95% CI 0.23–0.45) and after adjusting for confounders (aIRR 0.60; 95% CI, 0.43–0.83).
- GIP/GLP-1 receptor agonists decreased alcohol intoxication compared to no GIP/GLP-1 therapy before (IRR 0.39, 95% CI 0.30–0.52) and after adjusting for confounders (aIRR 0.50; 95% CI, 0.40–0.63).

Secondary Outcome –
- After stratifying for T2DM:
    - GIP/GLP-1 receptor agonists decreased opioid overdose compared to control before (IRR 0.45; 95% CI, 0.32–0.63) and after adjusting for confounders (aIRR 0.62; 95% CI, 0.46–0.82).
    - GIP/GLP-1 receptor agonists decreased alcohol intoxication compared to control before (IRR 0.35; 95% CI, 0.25–0.49) and after adjusting for confounders (aIRR 0.51; 95% CI, 0.40–0.65).
- After stratifying for obesity:
    - GIP/GLP-1 receptor agonists decreased opioid overdose compared to control before (IRR 0.49; 95% CI, 0.34–0.72) and after adjusting for confounders (aIRR 0.67; 95% CI, 0.49–0.92).
    - GIP/GLP-1 receptor agonists decreased alcohol intoxication compared to control before (IRR 0.43; 95% CI, 0.31–0.60) and after adjusting for confounders (aIRR 0.58; 95% CI, 0.45–0.75).
- After stratifying for T2DM and obesity:
    - GIP/GLP-1 receptor agonists decreased opioid overdose compared to control before (IRR 0.53; 95% CI, 0.37–0.75) and after adjusting for confounders (aIRR 0.65; 95% CI, 0.48–0.88).
    - GIP/GLP-1 receptor agonists decreased alcohol intoxication compared to control before (IRR 0.39; 95% CI, 0.27–0.56) and after adjusting for confounders (aIRR 0.58; 95% CI, 0.45–0.75).

LIMITATIONS:
- The study design shows correlation and is unable to conclude causation.
- The data was limited to Cerner hospital systems.
- Variability in diagnostic practices across hospitals and clinicians may lead to inconsistent identification of exposures and outcomes which reduces uniformity and potentially introduces bias into the results.
- Medication adherence was unknown which limits certainty of patient classification into “treatment” group.
- Not all alcohol intoxications or opioid overdoses present to hospitals. The outcomes may be undercounted and may not represent the true incidence in the population.
- The timing of events may not align with their documentation in the EMR, which would misclassify exposure timelines or outcome occurrences.
- The study did not clarify whether fatal overdoses of intoxication-related deaths were included, which limits understanding the full severity and scope of outcomes.

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