GOOD EVIDENCE MATTERS

GEMs of the Week

SPOTLIGHT: Gloom & Shrooms

Psychedelic Therapies for Treatment of Depressive Symptoms

Pemvidutide

Shrinks More Than Just Waistlines!

Sexual Healing?

Sexual Advice as an Adjunct to Conservative Management of Lumbar Radiculopathy

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Comparative Oral Monotherapy of Psilocybin, Lysergic Acid Diethylamide, 3,4 Methylenedioxymethamphetamine, Ayahuasca, and Escitalopram for Depressive Symptoms: Systemic Review and Bayesian Network Meta-Analysis

Hsu TW, Tsai CK, Kao YC, et al. Comparative oral monotherapy of psilocybin, lysergic acid diethylamide, 3,4-methylenedioxymethamphetamine, ayahuasca, and escitalopram for depressive symptoms: systematic review and Bayesian network meta-analysis. *BMJ*. 2024;386:e078607. Published 2024 Aug 21. doi:10.1136/bmj-2023-078607

KEY TAKEAWAY: High-dose psilocybin may reduce depressive symptoms compared to placebo.

STUDY DESIGN: Systemic review and meta-analysis of 19 randomized controlled trials (RCTs) with parallel group or crossover designs (N=2,779)

LEVEL OF EVIDENCE: STEP 2 (downgraded due to small sample sizes, short follow up periods, and inclusion of differing affective disorders)

BRIEF BACKGROUND INFORMATION: Depressive symptoms are common and associated with increased rates of mortality and disability, and conventional treatments are often unsuccessful in treating affective disorders. Various psychedelic compounds have been studied in the treatment of affective disorders (major depression, bipolar disorder, post-traumatic stress disorder [PTSD]) and shown efficacy, but only one randomized controlled trial has directly compared a psychedelic (psilocybin) to a conventional antidepressant (escitalopram). Placebo-controlled trials of psychedelics have a potential problem with blinding, given the noticeable effects of psychedelics on subjects, and rates of placebo response are lower in studies of psychedelics, leading to the possibility of overestimating the effects of psychedelics.

PATIENTS: Patients with depressive symptoms

INTERVENTION: Psychedelics or escitalopram

CONTROL: Placebo, escitalopram, and psychedelic

PRIMARY OUTCOME: Depressive symptoms

Secondary Outcome: All-cause discontinuation, severe adverse events

METHODS (BRIEF DESCRIPTION):

- RCTs were collated from a comprehensive search of the Medline, Cochrane Central Register of Controlled Trials, Embase, PsycINFO, ClinicalTrial.gov, and World Health Organization's International Clinical Trials Registry databases.
- Studies included adults with clinically diagnosed depression or life-threatening or terminal illness with depressive symptoms
- Various dosages of psychedelics or escitalopram were included:
  - Escitalopram: 10 vs 20 mg
  - Psilocybin: Extremely-low-dose (placebo/negligible) vs low-dose vs high-dose
  - MDMA: Extremely-low-dose (placebo/negligible) vs low-dose vs high-dose
  - Ayahuasca
  - LSD
- The primary outcomes assessed depressive symptoms via the 17-item Hamilton depression rating scale (HAMD-17). Scores range from 0 to 54, with higher scores indicating more severe depression.
  - There can be differing cutoffs for depression scoring depending on the source, but commonly accepted cutoffs are no depression (0–7), mild depression (8–16) moderate depression (17–23), and severe depression (≥24).
  - The minimum change in HAMD-17 score to be deemed as having a clinically meaningful effect was three points.
- The authors converted other scoring tools to HAMD-17 scores for better interpretability.
- Secondary outcomes:
  - All cause discontinuation
  - Severe adverse effects (e.g., death, suicide attempt, admission to hospital, significant persistent incapacity)
- Due to concerns for overestimated effect sizes of placebo in psychedelic groups, placebo responses were treated as distinct interventions for psychedelic trials, escitalopram trials, and extremely-low-dose psychedelic trials.

INTERVENTION (# IN THE GROUP): Not available
COMPARISON (# IN THE GROUP): Not available
FOLLOW-UP PERIOD: Varied (1–18 weeks)

RESULTS:

Primary Outcome –

- High-dose psilocybin improved depressive symptoms compared to placebo in antidepressant trials (mean difference [MD] 6.5; 95% CI, 3.2–9.6).
- High dose psilocybin improved depressive symptoms compared to escitalopram 10 mg and escitalopram 20 mg in antidepressant trials.
  - Escitalopram 10 mg (MD 4.7; 95% CI, 1.4–7.7)
  - Escitalopram 20 mg (MD 4.7; 95% CI, 1.6–7.5)
- No other psychedelic, including ayahuasca, LSD, MDMA, or low-dose psilocybin, significantly improved depressive symptoms compared to placebo in antidepressant trials.
- High dose psilocybin improved depressive symptoms compared to placebo in psychedelic trials (MD 5.1; 95% CI, 1.7–8.4).
- Ayahuasca improved depressive symptoms compared to placebo in psychedelic trials (MD 5.7; 95% CI, 2.3–9.1).
- MDMA, LSD, and low-dose psilocybin did not significantly improve depressive symptoms compared to placebo in psychedelic trials.

Secondary Outcome –

- No interventions were associated with higher risk of all-cause discontinuation or severe adverse events compared to placebo.

LIMITATIONS:

- The follow up periods in the included RCTs were short, therefore long-term effects of interventions are unknown.
- The depressive disorders were not the same amongst all studies which reduces the reliability of comparisons among the different results.

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Sexual Healing? Sexual Advice with Conservative Management of Lumbar Radiculopathy

Manual Therapy Plus Sexual Advice Compared with Manual Therapy or Exercise Therapy Alone for Lumbar Radiculopathy: A Randomized Controlled Trial

Danazumi MS, Adamu IA, Usman MH, Yakasai AM. Manual therapy plus sexual advice compared with manual therapy or exercise therapy alone for lumbar radiculopathy: a randomized controlled trial. *J Osteopath Med*. 2024;125(1):25-34. Published 2024 Sep 12. doi:10.1515/jom-2023-0075

KEY TAKEAWAY: The addition of sexual advice to manual therapy in management of chronic unilateral disc herniation with lumbar radiculopathy decreases leg pain, back pain, activity limitation, sexual disability, and kinesiophobia, compared to manual therapy or exercise therapy alone.

STUDY DESIGN: Single center, outcome assessor blinded, randomized controlled trial

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

BRIEF BACKGROUND INFORMATION: Radiculopathy and associated chronic pain, especially back pain, is an extremely common and difficult condition to condition across socioeconomic groups. Management strategies that improve clinical outcomes, such as pain, functional activity, and quality of life, without the addition of long-term pain medications, are valuable tools for primary care. This study investigated the clinical efficacy of the addition of sexual advice to manual therapy.

PATIENTS: Adults with lumbar radiculopathy

INTERVENTION: Sexual advice and manual therapy

CONTROL: Exercise therapy or manual therapy alone

PRIMARY OUTCOMES: Leg and back pain, activity limitation, sexual disability, kinesiophobia

METHODS (BRIEF DESCRIPTION):

- The authors conducted a single-blind randomized controlled trial comparing conservative behavioral and exercise interventions for disc herniation associated with lumbar radiculopathy.
- Patients were recruited from general and surgical outpatient departments at a single hospital in Nguru, Nigeria.
- Adult patients (18–65 years old) were eligible if they had a diagnosis of chronic (>3 months) unilateral disc herniation at L4/L5 or L5/S1 with radiculopathy, confirmed via MRI and clinical examination.
- Patients were excluded if they had a diagnosis of bilateral radiculopathy, other non-ambulatory status back conditions, or were currently receiving treatments for their disc herniation radiculopathy.
- At baseline, participants were an average age of 41 years old. Most were male (69%), and the average BMI was 21 for males and 24 for females.
- Patients were randomized 1:1:1 to manual therapy and sexual advice (MT+SA), manual therapy (MT), or exercise therapy (ET).
    - All participants attended twice weekly therapy sessions for 12 weeks.
    - Patients receiving MT were rotated every four weeks among three trained physiotherapists to minimize experience bias from variable amounts of expertise.
    - MT and MT+SA groups were treated with Mulligan's Spinal Mobilization with Leg Movement and Dowling's Progressive Inhibition of Neuromuscular Structures.
    - The MT+SA group also received a cognitive-behavioral therapy (CBT)-based educational program focusing on pain neurophysiology, sex neurophysiology, back care, effective communication, sexual intercourse planning, and sexual positioning.
    - The ET group was treated with core stability exercise and neurodynamic mobilization.
- The following were measured as the primary outcomes:
    - Leg and back pain were measured using the Visual Analog Scale (VAS). Scores range from 0–10, with higher scores indicating worse pain.
    - Activity limitation was measured by the Rolland-Morris Disability Questionnaire (RMDQ). Scores range from 0–24, with higher scores indicating increased limitations.
    - Sexual disability due to back pain was measured by the Oswestry Disability Index item 8 (ODI-8) scale. Scores range from 0–5, with higher scores indicating increased sexual disability.

- Kinesiophobia was measured by the Tampa Scale of Kinesiophobia (TSK). Scores range from 11–44, with higher scores indicating worse fear.
- Outcome measures were collected at baseline and six, 12, 26, and 52 weeks post-randomization, with primary outcomes defined as change in scale scores at 12 weeks.

INTERVENTION (# IN THE GROUP): 18

COMPARISON (# IN THE GROUP):

- MT: 18
- ET: 18

FOLLOW-UP PERIOD: 52 weeks

RESULTS:

Primary Outcome –

- MT+SA decreased back pain compared to MT and ET.
  - MT (mean difference [MD] –2.1; 95% CI, –3.2 to –0.93)
  - ET (MD –2.2; 95% CI, –3.3 to –1.1)
- MT+SA decreased leg pain compared to MT and ET.
  - MT (MD –2.0; 95% CI, –3.2 to –0.85)
  - ET (MD –2.5; 95% CI, –3.6 to –1.4)
- MT+SA decreased activity limitations compared to MT and ET.
  - MT (MD –2.8; 95% CI, –5.5 to –0.11)
  - ET (MD –2.7; 95% CI, –4.9 to –0.45)
- MT+SA decreased sexual disability due to back pain compared to MT and ET.
  - MT (MD –1.6; 95% CI, –2.3 to –0.85)
  - ET (MD –1.5; 95% CI, –2.2 to –0.68)
- MT+SA decreased kinesiophobia compared to MT and ET.
  - MT (MD –7.8; 95% CI, –11 to –4.6)
  - ET (MD –7.9; 95% CI, –12 to –4.1)
- At 52 weeks, all primary outcomes remained significantly improved for MT+SA compared to either the MT or ET group, though to a lesser degree.

LIMITATIONS:

- Exercise therapy included instructions for exercises at home, which may have reduced efficacy relative to supervised manual and sexual advice therapy.
- Comorbidities such as heart disease and lifestyle factors such as smoking were not measured. While this may have been mitigated by randomization; unreported health conditions may have led to reduced efficacy of exercise therapy relative to other groups.
- Most of the measures used were self-reported, introducing potential recall bias.
- Due to the nature of the interventions, the trial could not be double-blinded, and any data collected via interview were vulnerable to experimenter bias.
- Study was localized to a single population in Nigeria, limiting generalizability.

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Pemvidutide Shrinks More Than Just Waistlines

Effect of Pemvidutide, A GLP-1/Glucagon Dual Receptor Agonist, on MASLD: A Randomized, Double-Blind, Placebo Controlled Study

Harrison SA, Browne SK, Suschak JJ, et al. Effect of pemvidutide, a GLP-1/glucagon dual receptor agonist, on MASLD: A randomized, double-blind, placebo-controlled study. *J Hepatol*. 2025 Jan;82(1):7-17. doi: 10.1016/j.jhep.2024.07.006.

KEY TAKEAWAY: Pemvidutide, a GLP-1/glucagon dual receptor agonist, significantly reduces liver fat content and reduces body weight compared to placebo in patients with metabolic dysfunction-associated steatotic liver disease (MASLD).

STUDY DESIGN: Randomized, double-blind, placebo-controlled study

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: MASLD, defined as having ≥5% steatosis in the liver in patients with no or minimal alcohol consumption, affects about 25% of adults worldwide. It is associated with type 2 diabetes mellitus (T2DM) and obesity. MASLD can progress to liver fibrosis, raising concern for cardiovascular disease and malignancy. Glucagon-like peptide-1 receptor agonist (GLP-1RA) based treatments can improve MASLD, but there are no GLP-1R receptors on the liver, so the improvement is likely due to weight loss. However, the liver does have glucagon receptors (GCGRs). This study assessed the effects of pemvidutide, a dual GLP-1R and GCGR receptor agonist, on liver fat content (LFC) in patients with overweight or obesity.

PATIENTS: Adults with MASLD and overweight or obesity

INTERVENTION: Pemvidutide

CONTROL: Placebo

PRIMARY OUTCOME: Liver fat content

Secondary Outcome: Serum ALT levels, body weight

METHODS (BRIEF DESCRIPTION):

- Participants in the study included patients 18–65 years old with a BMI ≥28 kg/m^2 and LFC ≥10% measured by magnetic resonance imaging-proton density fat fraction.
- The mean ages of participants in each group ranged from 48–50 years old. 53% were female, and 76% were Hispanic.
- 29% of participants had T2DM with an A1C <9.5. Mean BMI was 35–36 kg/m^2. Mean Baseline LFC was 20–24%.
- Participants with very elevated ALT >75 IU/L or significant hepatic fibrosis were excluded. Those using GLP-1R or insulin therapy were also excluded.
- Patients were randomized 1:1:1:1 to pemvidutide 1.2 mg, 1.8 mg, or 2.4 mg, or placebo (normal saline) administered subcutaneously once weekly for 12 weeks.
- The primary outcomes were the absolute and relative percent reductions in LFC. Proportion of patients who achieved 30% and 50% relative reductions in LFC, as well as those who achieved normalization of LFC, defined as LFC ≤5%.
- Secondary outcome was absolute changes in serum ALT and percent changes from baseline body weight. Serum ALT was measured as a marker of hepatic inflammation.

INTERVENTION (# IN THE GROUP):

- 1.2 mg pemvidutide: 23
- 1.8 mg pemvidutide: 23
- 2.4 mg pemvidutide: 24

COMPARISON (# IN THE GROUP): 24

FOLLOW-UP PERIOD: 12 weeks

RESULTS:

Primary Outcome –

- All doses of pemvidutide decreased the absolute reduction of LFC compared to placebo.
  - 1.2 mg pemvidutide (absolute reduction [AR] 8.9; 95% CI, –12 to –5.4)
  - 1.8 mg pemvidutide (AR 15%; 95% CI, –18 to –11)
  - 2.4 mg pemvidutide (AR 11%; 95% CI, –15 to –7.4)
- All doses of pemvidutide decreased the relative reduction of LFC compared to placebo.
  - 1.2 mg pemvidutide (relative reduction [RR] 47%; 95% CI, –64 to –30)
  - 1.8 mg pemvidutide (RR 68%; 95% CI, –84 to –52)
  - 2.4 mg pemvidutide (RR 57%; 95% CI, –76 to –38)

- All doses of pemvidutide normalized LFC more frequently compared to placebo.
  - 1.2 mg pemvidutide (20% vs 0%, respectively; *P*=.0266).
  - 1.8 mg pemvidutide (56% vs 0%, respectively; P<.0001)
  - 2.4 mg pemvidutide (50% vs 0%, respectively; *P*=.0003).

Secondary Outcome –

- All doses of pemvidutide decreased body weight compared to placebo.
  - 1.2 mg pemvidutide (AR 3.4%; 95% CI, –4.7 to –2.0)
  - 1.8 mg pemvidutide (AR 4.3%; 95% CI, –5.6 to –3.0)
  - 2.4 mg pemvidutide (AR 3.7%; 95% CI, –5.1 to –2.3)
- 1.8 mg and 2.4 mg pemvidutide reduced ALT levels compared to placebo.
  - 1.8 mg pemvidutide (AR –14 IU/L; 95% CI, –20 to –7.9)
  - 2.4 mg pemvidutide (AR –14 IU/L; 95% CI, –20 to –7.4)

LIMITATIONS:

- Participants were unlikely to have advanced fibrosis, which limited the study to investigating the results for MASLD but not fibrosis.
- Participants with ALT >75 were excluded, making it less applicable to more advanced MASLD.
- The study population was predominantly Hispanic, making it less generalizable.

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