Mental Health Literature Update

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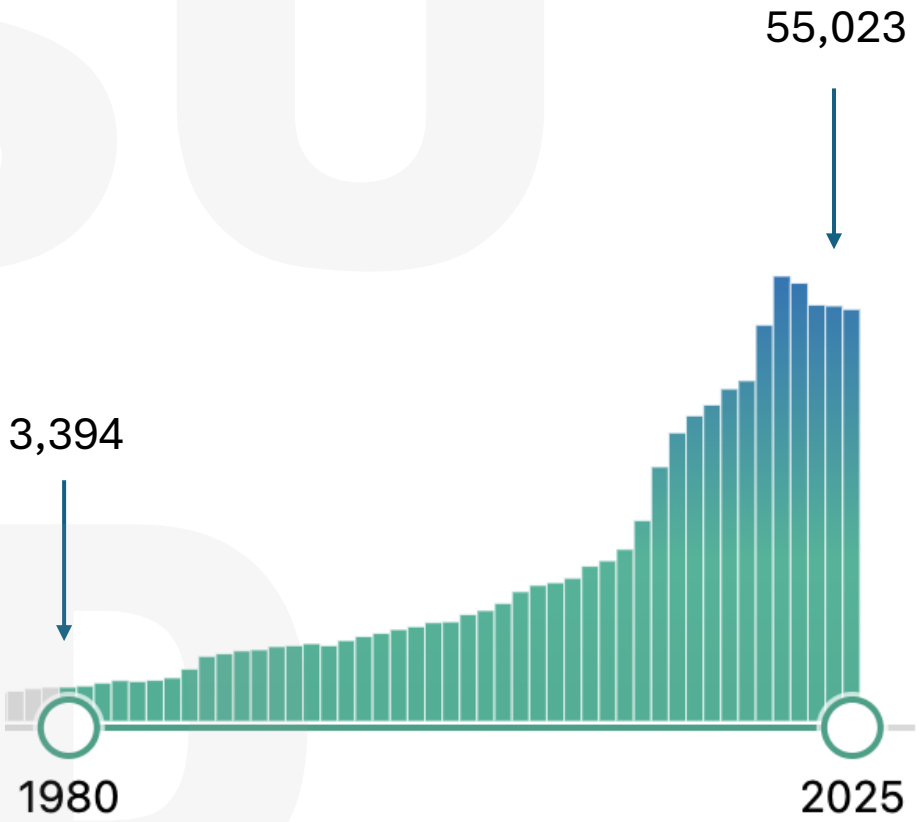
Overview

- Tremendous number of studies published annually
- The number of studies has been growing exponentially
- One study published every 26 seconds[1]
  - Would have to read 5000 articles per day to keep up
- Makes it challenging to stay current



PubMed search: “Psychiatry”

1. Oman Med J. 2010 Oct;25(4):311–314

Overview

- Objective is to review 6 articles published in the past 2 years
- Psychiatry focused, pertinent to primary care
- Covering a range of topics
  - Epidemiology & Population Mental Health
    - Mental-health burden and utilization in primary care
    - Lifestyle and behavioral determinants of cognitive health (step count & dementia risk)
  - Medication Safety & Long-Term Outcomes
    - Stimulants: cardiovascular risk
    - Benzodiazepines: tolerance and dose escalation
  - Treatment Optimization in Psychopharmacology
    - Managing SSRI-associated sexual dysfunction
    - Comparative effectiveness of medications for alcohol use disorder
  - Non-Pharmacologic Therapies
    - Bright light therapy for non-seasonal depression

Overview

- Present a basic case
- Clinical question
- Background on the topic
- Review the article and results
- My take: discuss whether the findings have clinical implications

Case 1

- Picture yourself in your primary care clinic on a typical Monday morning.
- You open your schedule: 22 patients.
- As you scan the chart notes, you notice something striking: 12 of them have active psychiatric conditions: and you are prescribing and adjusting their medications.

- **Question: Is this unusual… or is mental-health care simply a core part of primary care?**

Mental Health and Primary Care

- Primary care is the front door to mental health care
- Patients most often first raise behavioral health symptoms with their PCP
  - Trusting relationships allow PCPs to identify concerns early
  - PCPs initiate much of the evaluation and treatment
- Access barriers limit referrals
  - As a result, PCPs manage the bulk of mental-health care

Study

Article

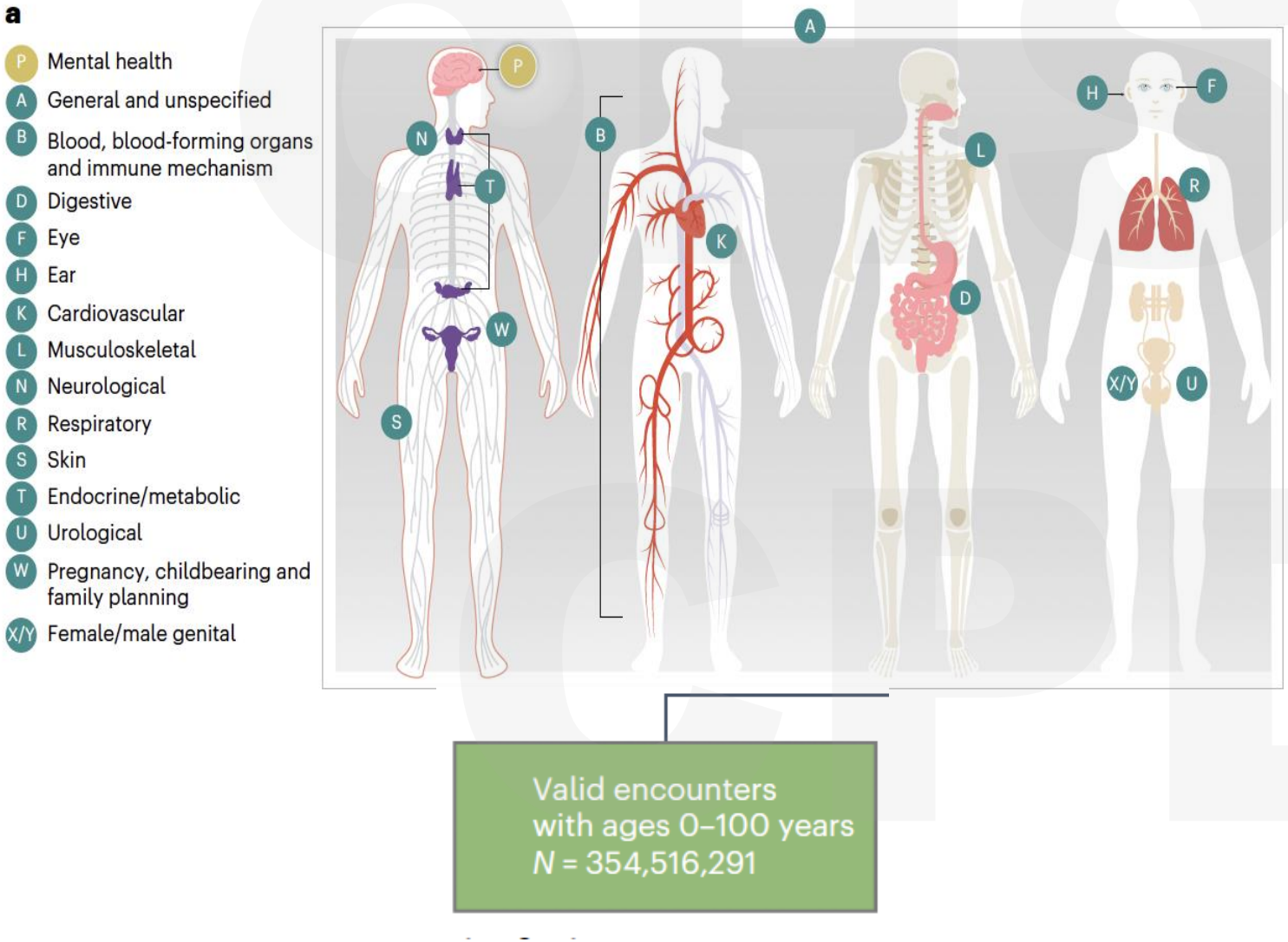
https://doi.org/10.1038/s44220-024-00310-5

A nationwide analysis of 350 million patient encounters reveals a high volume of mental-health conditions in primary care

- **Design:** Population-based registry study using nationwide primary care data in Norway
- **Sample:** 354 million primary-care encounters from 4.9 million individuals, ages 0–100 (2006–2019)
- **Focus:** Volume and types of mental-health conditions addressed by PCPs, compared with other medical conditions

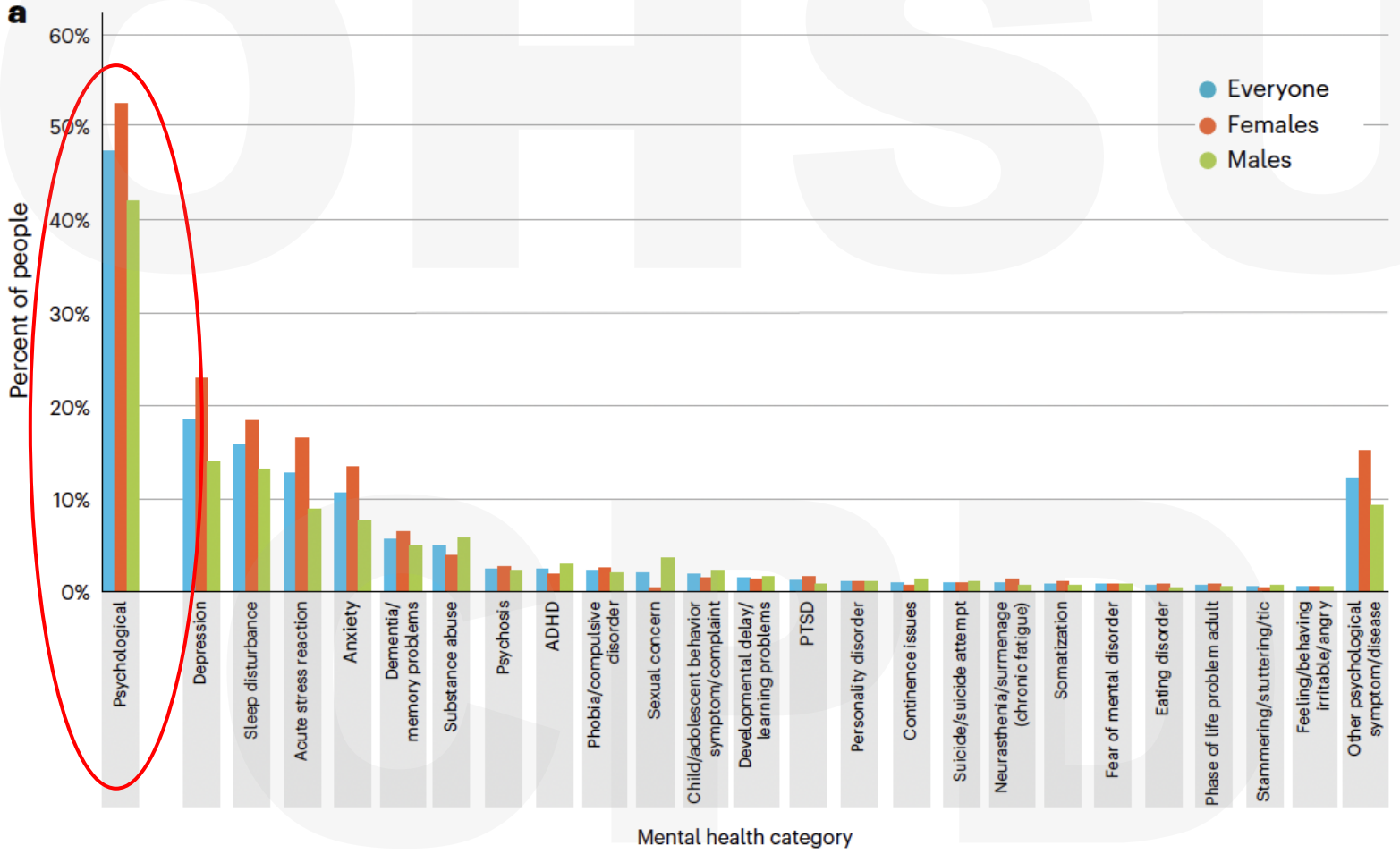
Nature Mental Health | Volume 2 | October 2024 | 1208–1216

Methods



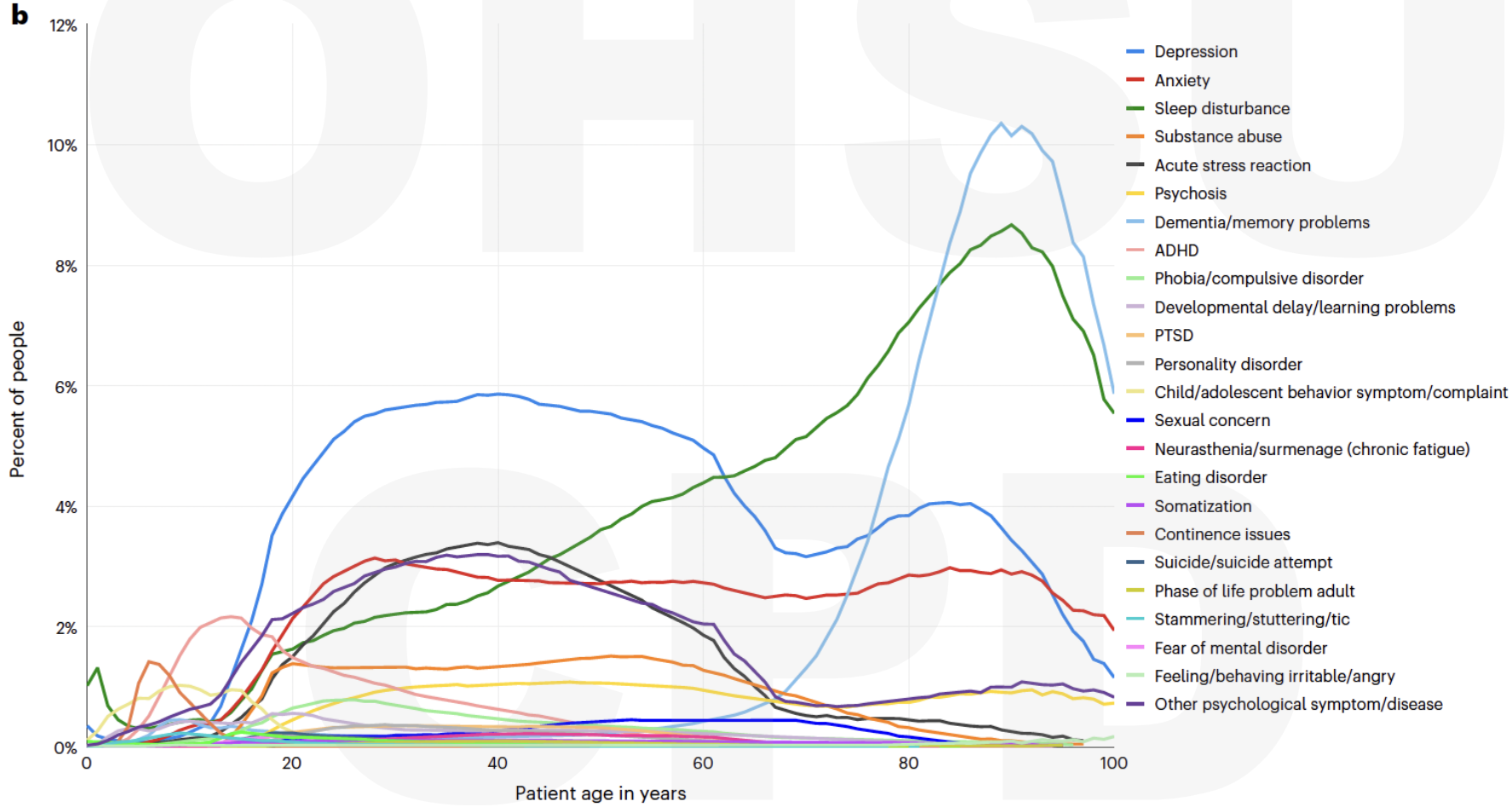
- Extracted all primary-care diagnoses across 15 body systems using the International Classification of Primary Care (ICPC)
- Each encounter was classified by the primary diagnosis or reason for the visit

Results



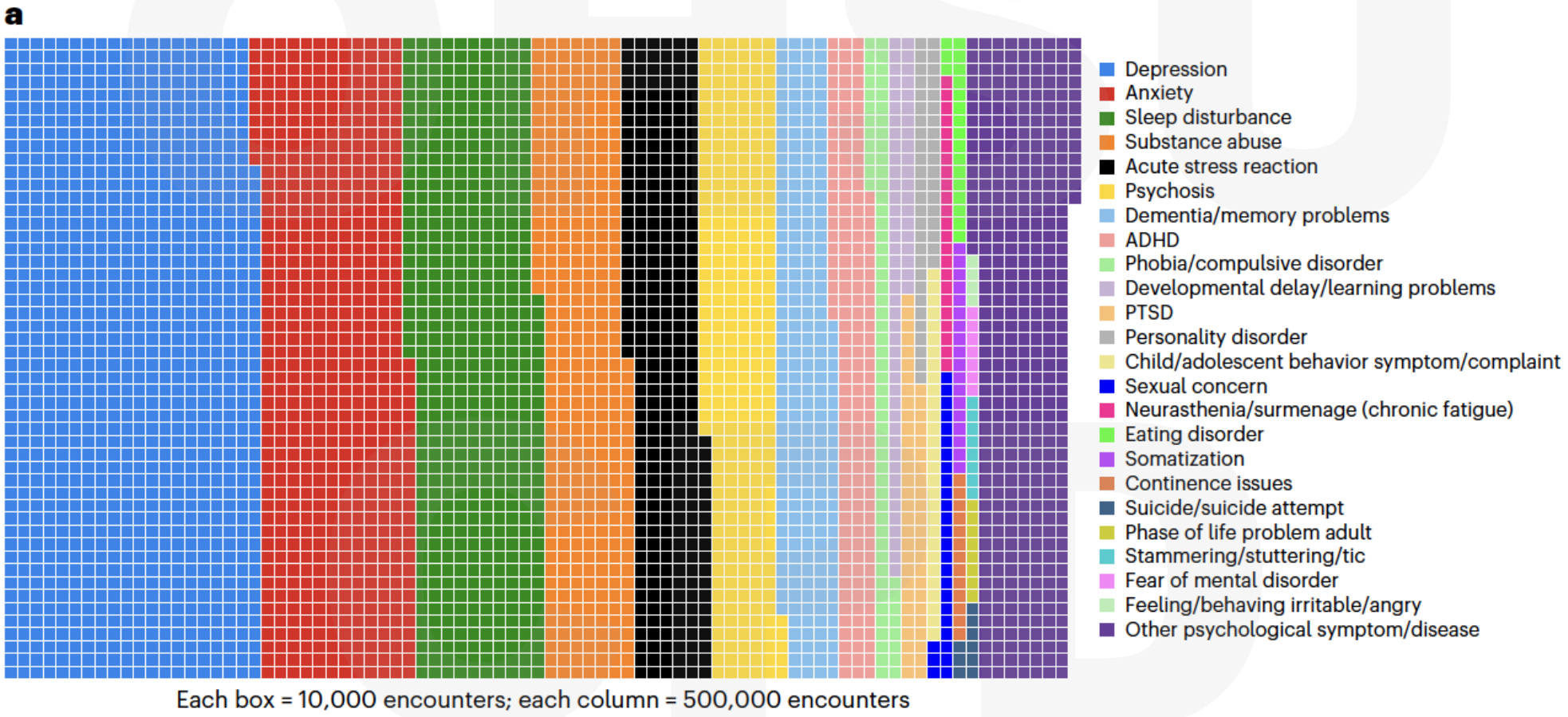
Percentage of patients presenting with a mental health condition between 2006 and 2019

Results



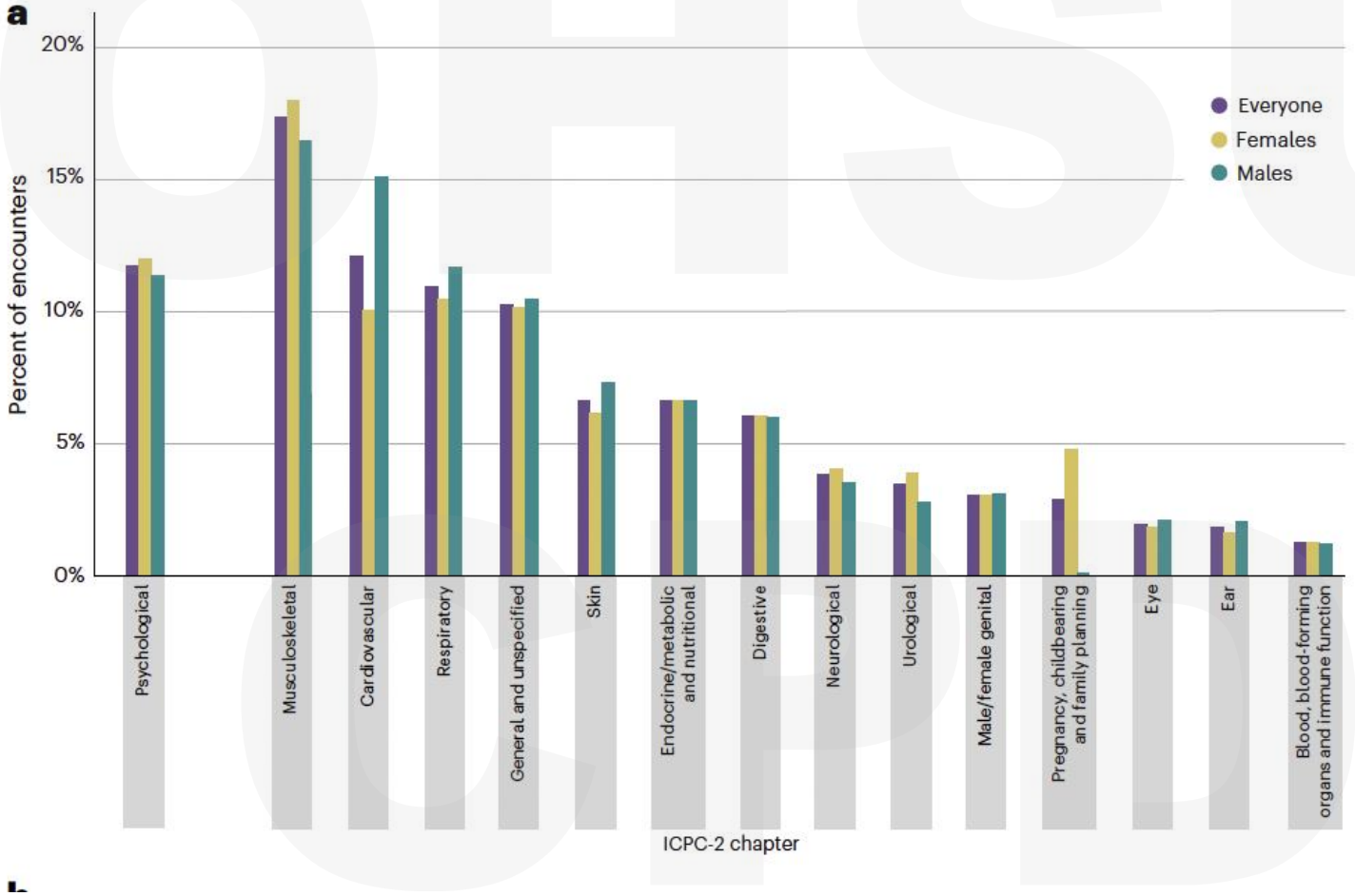
The distribution of mental-health conditions over the lifespan, as a function of age.

Results



The proportion of 41,616,704 mental-health encounters devoted to each of 24 different mental-health conditions

Results



Comparison of the volume of PCPs' mental-health encounters to encounters for medical conditions in 15 different body systems

Discussion

- Mental health is a core component of primary care practice
  - About 1 in 8–9 primary-care encounters involves a mental-health concern, exceeded only by musculoskeletal conditions
- Primary care mental-health work extends well beyond depression and anxiety
  - While common conditions account for about one-third of visits, PCPs manage a wide range of diverse and complex presentations
- Mental-health care in primary care spans the entire lifespan
  - From childhood through older adulthood, patients present with mental-health concerns at every stage of life

My Take

- Study in Norway may not fully generalize to the US
- Primary care is already a frontline mental health system
- PCPs are delivering substantial mental health care, often without specialized support
- This creates a clear need for stronger mental health training and better integration into primary care
  - Integrated care models are likely essential

Case 2

- Your patient is a 32-year old man with moderate major depressive disorder well treated with citalopram 20mg per day
- He has taken citalopram for the last 2 years
- It has been well tolerated except for sexual side effects
- He wants to continue taking it, but would like to find a way to improve sexual satisfaction

- **Question: can taking a “drug holiday” help to improve sexual side effects?**

SSRIs and Sexual Side Effects

- Occur in ~30–70% of patients treated with SSRIs
- Can affect libido, arousal, and orgasm
- A leading cause of nonadherence and discontinuation
- Common management strategies include:
  - Dose reduction
  - Switching antidepressants
  - Adjunctive medications
- Each strategy involves tradeoffs related to efficacy, tolerability, or adding to medication burden

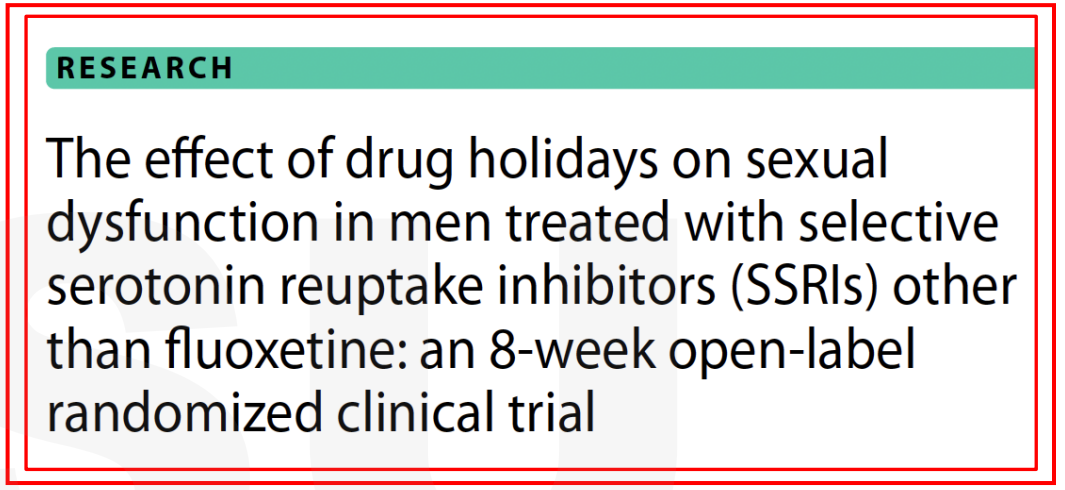
Drug Holiday

A planned, short-term interruption of the medication (typically skipping 1–2 doses) to allow the sexual side effects to diminish

Evidence for this strategy is limited. One small 4-week clinical trial published in 1995 found that planned drug holidays improved sexual function among patients taking sertraline and paroxetine[1]

1. Rothschild AJ. Selective serotonin reuptake inhibitor-induced sexual dysfunction: efficacy of a drug holidays. Am J Psychiatry. 1995;152(10):1514–6.

Study



- Design: 8-week randomized, open-label, controlled outpatient trial (Jan 2022–Mar 2023)
- Participants: Married men aged 18-50 with SSRI induced sexual dysfunction (excluding fluoxetine)
- Objective: To assess whether planned SSRI “drug holidays” improve sexual functioning

Alipour-Kivi et al. BMC Psychiatry (2024) 24:67

Study

- Intervention: Drug-holiday group skipped SSRI doses on two consecutive weekend nights; control group continued daily dosing
- Outcome measure: Between-group change in Male Sexual Health Questionnaire (MSHQ) total and subscale scores from baseline to week 8
  - A validated questionnaire assessing erectile function, ejaculatory function, and sexual satisfaction

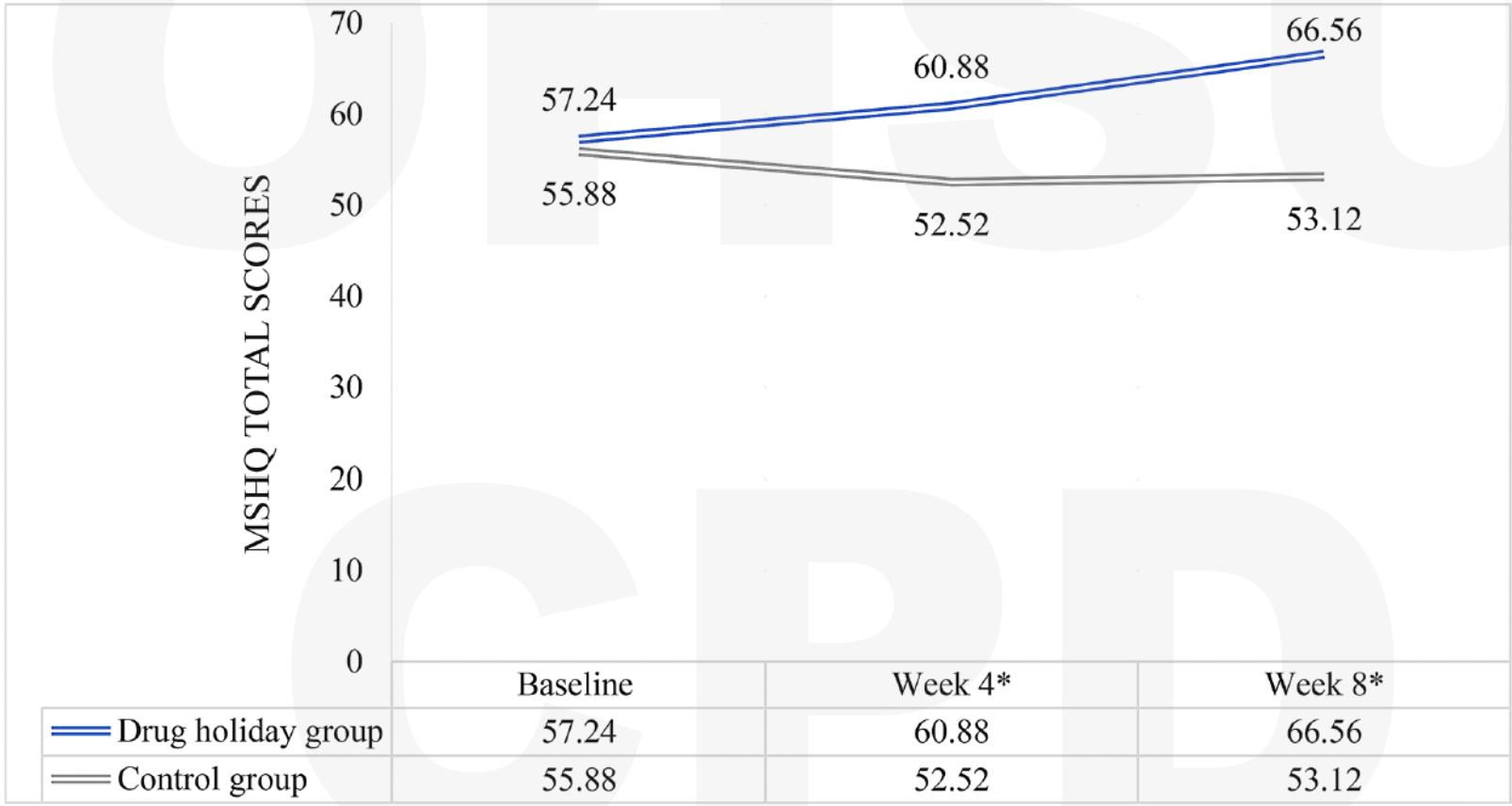
Baseline Participant Characteristics

Table 1 Demographic data of the participants

		Drug holidays group ($N=25$)		Control group ($N=25$)	
		Mean (±SD)	**Count (%)**	**Mean (±SD)**	**Count (%)**
Age (years)		36.44 (±6.049)		35.04 (±6.693)	
Education level	Illiterate		-		1 (4%)
	High school diploma or lower		5 (20%)		10 (40%)
	Higher education		20 (80%)		14 (56%)
Employment status	Employed		20 (80%)		19 (86%)
	Unemployed		5 (20%)		6 (24%)
Medication	Sertraline		11 (44%)		9 (36%)
	Escitalopram		7 (28%)		9 (36%)
	Paroxetine		1 (4%)		1 (4%)
	Citalopram		4 (16%)		4 (16%)
	Fluvoxamine		2 (8%)		2 (8%)
Previous psychiatric diagnosis	Depressive disorders		13 (52%)		6 (24%)
	Anxiety disorders		10 (40%)		12 (48%)
	Obsessive-compulsive and related disorders		2 (8%)		7 (28%)

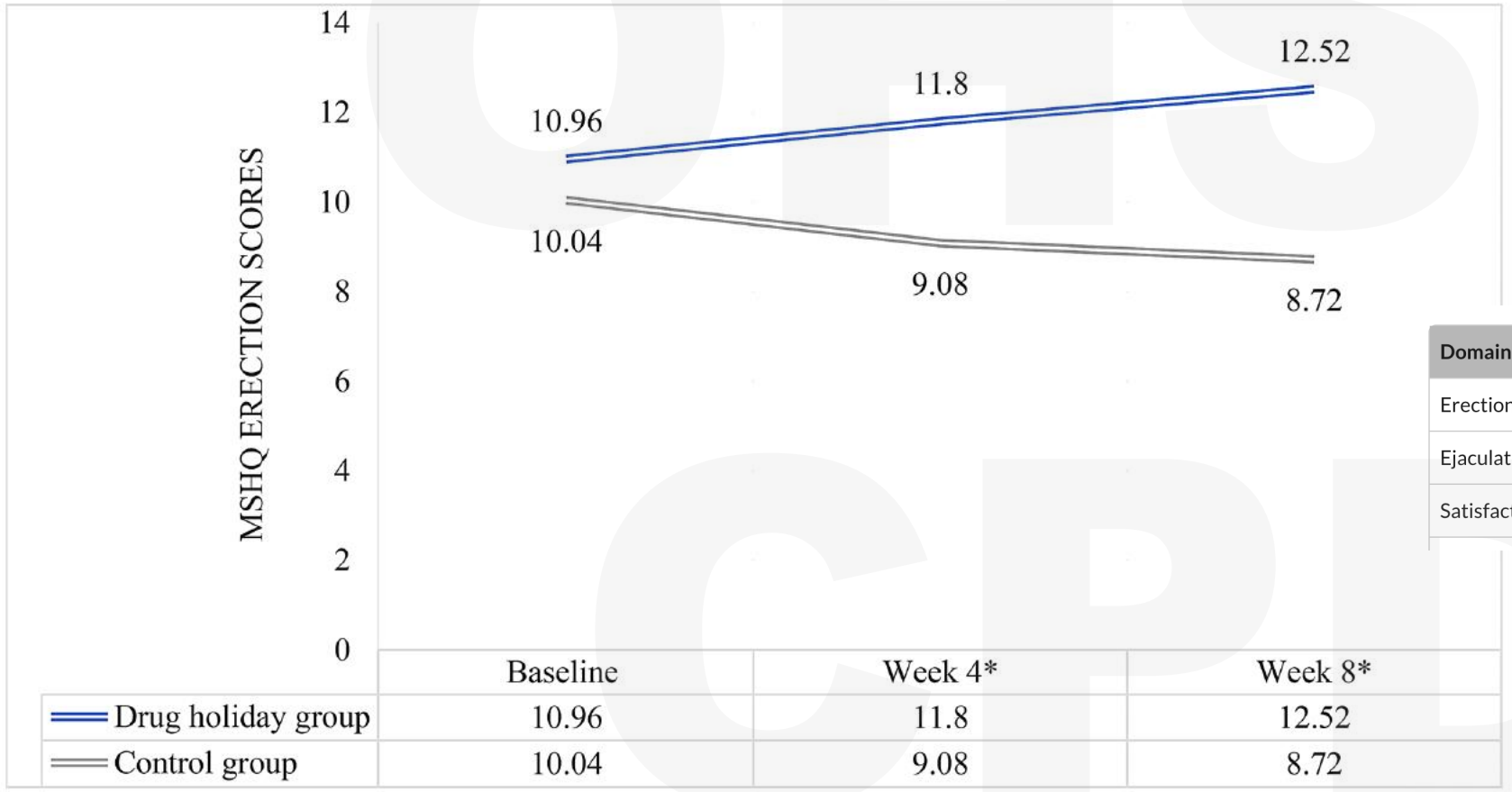
- Maintenance course of treatment, with a stable condition over the past two months and no changes in SSRI dose
- Exclusion: fluoxetine, meds known to cause sexual dysfunction

Results



	Baseline	Week 4*	Week 8*
Drug holiday group	57.24	60.88	66.56
Control group	55.88	52.52	53.12

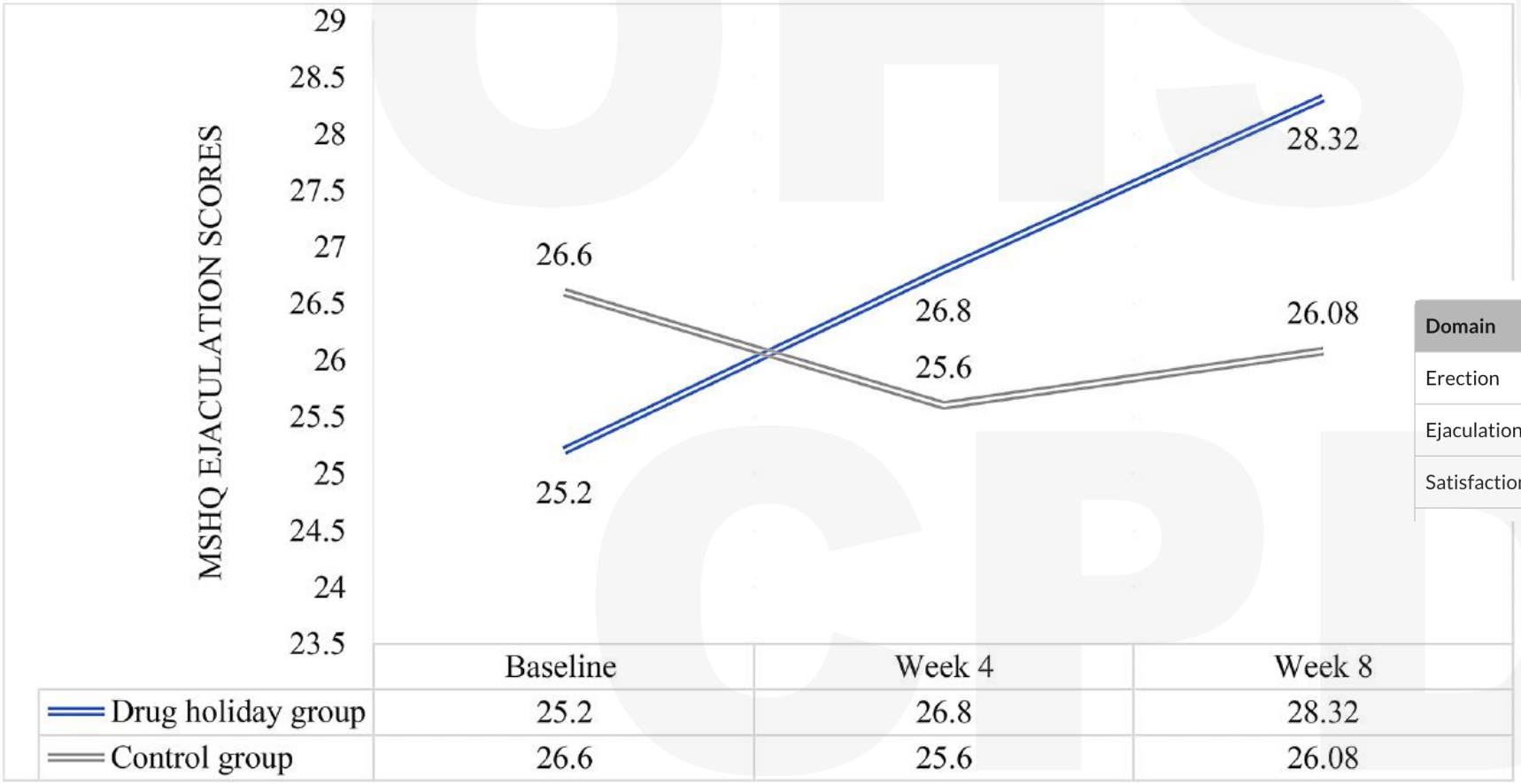
Results: Erectile Function



	Baseline	Week 4*	Week 8*
Drug holiday group	10.96	11.8	12.52
Control group	10.04	9.08	8.72

Domain	Items	Score Range	Higher Scores Indicate
Erection	1-3	0-15	Higher level of sexual functioning
Ejaculation	5-11	1-35	Higher level of sexual functioning
Satisfaction	13-18	6-30	Higher level of satisfaction

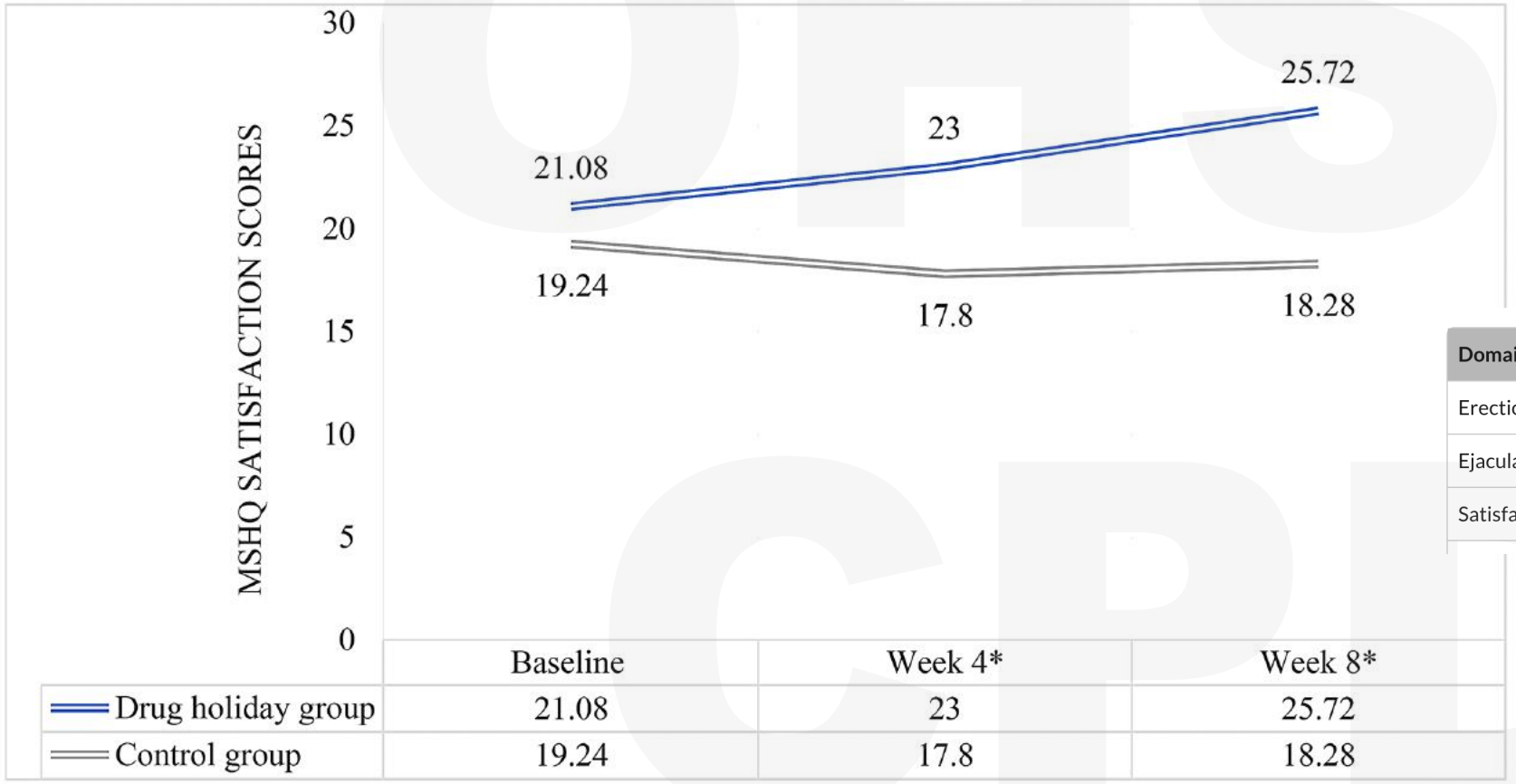
Results: Ejaculation



	Baseline	Week 4	Week 8
Drug holiday group	25.2	26.8	28.32
Control group	26.6	25.6	26.08

Domain	Items	Score Range	Higher Scores Indicate
Erection	1-3	0-15	Higher level of sexual functioning
Ejaculation	5-11	1-35	Higher level of sexual functioning
Satisfaction	13-18	6-30	Higher level of satisfaction

Results: Sexual Satisfaction



	Baseline	Week 4*	Week 8*
Drug holiday group	21.08	23	25.72
Control group	19.24	17.8	18.28

Domain	Items	Score Range	Higher Scores Indicate
Erection	1-3	0-15	Higher level of sexual functioning
Ejaculation	5-11	1-35	Higher level of sexual functioning
Satisfaction	13-18	6-30	Higher level of satisfaction

Results

- Mild, transient symptoms were reported in the drug-holiday group
  - Nausea: 16% (n = 4)
  - Headache: 24% (n = 6)
  - Mild restlessness: 24% (n = 6)

- No additional side effects were reported in the control group

- Mental health measures remained stable, suggesting that short drug holidays did not compromise psychiatric treatment during the study period

Discussion

- Drug holidays were associated with significant within-group improvements in erectile function, ejaculatory function, sexual satisfaction, and total MSHQ scores over time.
- The time course of improvement differed by domain, with erectile function and satisfaction improving by Week 4, and ejaculatory function showing improvement by Week 8.
- Between-group differences were not uniformly significant at each time point, but the pattern of change over time favored the drug-holiday group.
- Overall, the findings suggest a progressive and cumulative benefit of intermittent SSRI interruption for SSRI-related sexual dysfunction, rather than an immediate effect.

My Take

- A small study, limited to men
- MSHQ does not have normative population benchmarks, so score changes reflect relative differenes rather than normalization
- Reasonable to consider in patients on a stable SSRI dose who do not want to switch antidepressants or add an adjunct
- Likely to work better with short half-life SSRIs (e.g., paroxetine, citalopram, sertraline)
- May require time and patient expectation-setting before benefit is seen

Case 3

- Your patient is a 32-year old female with a history of panic disorder.
- She was stable for several years, but a recent stressor led to a recurrence of panic symptoms
- You consider prescribing a short, PRN course of lorazepam, but are reluctant because of the 2020 FDA Black Box Warning (abuse, dependence, and withdrawal)

- **Question: Does starting a benzo meaningfully increase the chance of long-term use or dose escalation?**

Benzodiazepines

- Anxiety is best managed with CBT and SSRI/SNRI therapy; short-term or PRN benzodiazepines may be helpful during acute exacerbations
- Clinical guidelines recommend short-term use due to concerns about dependence
  - In 2020, the FDA issued a boxed warning highlighting risks of abuse, addiction, physical dependence, and withdrawal.
- There is heightened clinician caution and reduced prescribing
- However, the population-level risk of long-term use and dose escalation following initiation has been poorly quantified in real world populations

Study

Long-Term Use of Benzodiazepines and Benzodiazepine-Related Drugs: A Register-Based Danish Cohort Study on Determinants and Risk of Dose Escalation

- Objective: To assess the frequency and predictors of long-term use and dose escalation after initiation of benzodiazepines and benzodiazepine-related drugs (BZRAs).
- Design: Nationwide, population-based, register-based cohort study
- Population: All Danish adults ages 20–80 living in Denmark on Jan 1, 2000 (≈ 4.3 million) followed for redeemed BZRA prescriptions between 2000 and 2020

Am J Psychiatry 181:3, March 2024

Study

- Exposure: Initiation of BZRAs
  - Benzos for anxiety, benzos for sleep, Z-drugs

- Outcomes
  - Long-term use (>1 year and >7 years)
  - Dose escalation to doses above recommended levels

- Analysis: Logistic regression to examine associations between patient characteristics and long-term use or dose escalation

Study Population

TABLE 1. Treatment characteristics of incident users of benzodiazepines and Z-drugs

Measure or Drug	Drug Class							
	Hypnotic Benzodiazepines (ATC N05CD) (N=123,661)		Anxiolytic Benzodiazepines (ATC N05BA) (N=529,235)		Z-Drugs (ATC N05CF) (N=601,802)		Any Benzodiazepine or Z-Drug (N=950,767)	
	Median	IQR	Median	IQR	Median	IQR	Median	IQR
Age (years)	68	51–81	56	45–70	55	43–69	55	43–70
	N	%	N	%	N	%	N	%
Total number of prescriptions								
1	77,031	62.3	250,509	47.3	246,481	40.1	438,317	46.1
2–5	32,177	26.1	175,077	33.1	197,790	32.9	304,939	32.1
>5	14,453	11.7	103,649	19.6	157,531	26.2	297,473	21.8
Length of treatment period								
0–180 days	104,417	84.4	415,273	78.5	437,084	72.6	731,797	77.0
181–365 days	7,212	5.8	44,962	8.5	57,943	9.6	80,008	8.4
366–720 days	5,483	4.4	34,400	6.4	48,061	8.0	65,071	6.8
>720 days	6,549	5.2	34,600	6.5	58,714	9.8	73,811	7.7
Specific drug								
Alprazolam			83,878	15.9			66,683	7.0
Bromazepam			12,969	2.4			10,399	1.1
Brotizolam	1,761	1.4					1,266	0.1
Chlordiazepoxide			26,497	5.0			21,278	2.2
Clobazam			3,399	0.6			2,828	0.3
Diazepam			158,294	29.9			125,081	13.2
Estazolam	3,033	2.5					1,768	0.2
Flunitrazepam	2,156	1.7					876	0.1
Lorazepam			16,954	3.2			11,511	1.2
Lormetazepam	4,589	3.7					2,562	0.3
Midazolam	56,580	45.8					24,716	2.6
Nitrazepam	29,020	23.5					13,353	1.4
Oxazepam			227,244	42.9			166,485	17.5
Triazolam	26,451	21.4					16,455	1.7
Zaleplon					5,853	1.0	5,299	0.6
Zolpidem					211,129	35.1	171,691	18.1
Zopiclone					384,820	63.9	308,516	32.5

- 950,767 persons initiated BZDRs
- Median age of 55

Results: Patterns of Use After Initiation

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- 950,767 persons initiated BZDRs
- Median age of 55
- Most patients had very limited exposure
  - 78% filled only 1-5 prescriptions
  - 77% had treatment duration <6 months

Results: Patterns of Use After Initiation

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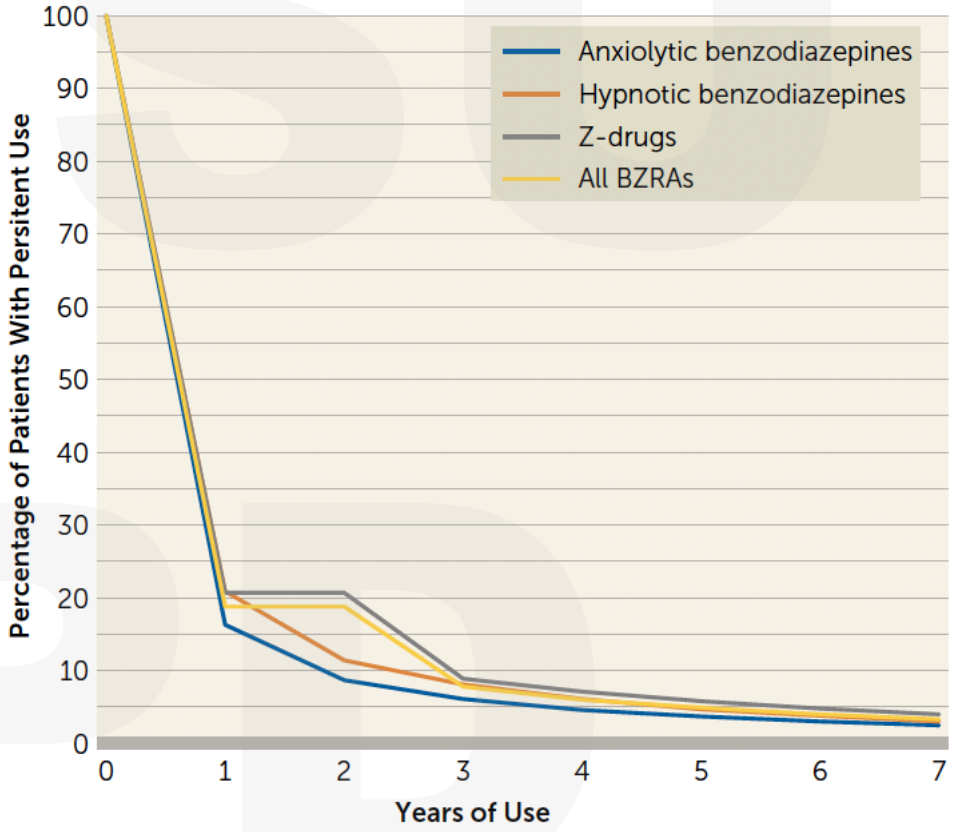
- Median age of 55
- Most patients had very limited exposure
  - 78% filled only 1-5 prescriptions
  - 77% had treatment duration <6 months
- Compared with other benzodiazepines, Z-drugs were more often prescribed repeatedly and over longer treatment periods.

Results

- How often does long-term use occur?
  - 15% of patients used BZDRs for >1 year after initiation
  - 3% remained users for >7 years
  - Long-term use was most common with Z-drugs



Proportion of users with long-term use of benzodiazepines or Z-drugs over 7 years

Results

- Who Is More Likely to Develop Long-Term Use?
  - Psychiatric comorbidity (anxiety, mood disorders) was associated with a modest increase in risk.
  - Substance use disorder showed the strongest and most consistent association
    - Adjusted odds ratios roughly in the 1.4 to 1.7 range across classes
  - Older age was associated with greater persistence
  - Z-drug initiation was associated with higher rates of long-term use than anxiolytic benzodiazepines

Results

- What about dose escalation?
  - Very few patients had prolonged exposure: only about 5% had three or more years of continuous use
  - Dose escalation was rare even among long-term users: ~7% exceeded recommended doses
  - For most long-term users, doses remained stable or declined over time

Results

- Who is most likely to dose escalate?
  - Psychiatric comorbidity was associated with a modest increase in risk
  - Substance use disorder was the strongest and most consistent predictor of escalation
    - 1.4–1.7-fold increase in odds of dose escalation across all classes
  - Risk was slightly higher among women and individuals with lower educational attainment

Discussion

- Over the 20-year study period, roughly one-quarter of adults received at least one benzodiazepine or Z-drug prescription
- Progression to long-term use was uncommon, with most patients discontinuing within the first year of initiation
- Dose escalation was also uncommon, even among patients with sustained use
- Relative risk differed across patient groups, but absolute risk remained low overall
- Psychiatric comorbidity (particularly substance use disorder) identified a higher-risk subgroup for both long-term use and escalation

My Take

- Because this study was conducted in Denmark, absolute risks may be higher in the U.S.; however, overall risk patterns are likely generalizable

- **Most people don’t end up on benzodiazepines long-term**, and dose escalation is uncommon.
- **Risk is not uniform**: patients with substance use disorder are more likely to run into problems.
- **Thoughtful, time-limited prescribing** with follow-up is better than blanket avoidance, especially in lower-risk patients.

Case 4

- You’re seeing a 62-year-old patient for an annual visit.
- Her mother developed dementia in her late 70s, and she’s worried about her own risk.
- She asks, “I don’t really go to the gym—but I do try to stay active. Does walking actually lower my risk of dementia? And how much do I really need to do?”

- **Question: What advice can I give her about step count and speed to lower her dementia risk?**

Activity and Dementia Risk

- Physical activity is one of the most consistently associated modifiable factors linked to lower dementia risk
- Walking is the most common form of physical activity in midlife and older adults
- Step count is intuitive, measurable, and widely available via phones and wearable devices
- The amount and role of walking intensity for dementia risk remain uncertain

Study

JAMA Neurology | Brief Report

Association of Daily Step Count and Intensity With Incident Dementia in 78 430 Adults Living in the UK

- Objective: To examine the dose-response association between daily step count and intensity and incidence of all-cause dementia
- Study design & population: Prospective, population-based cohort of 78,430 adults aged 40–79, with wrist-worn accelerometer data and a median of 6.9 years of follow-up for incident dementia, using UK Biobank data
  - This was a generally healthy, midlife-to-older adult cohort, with most participants in their early 60s at baseline

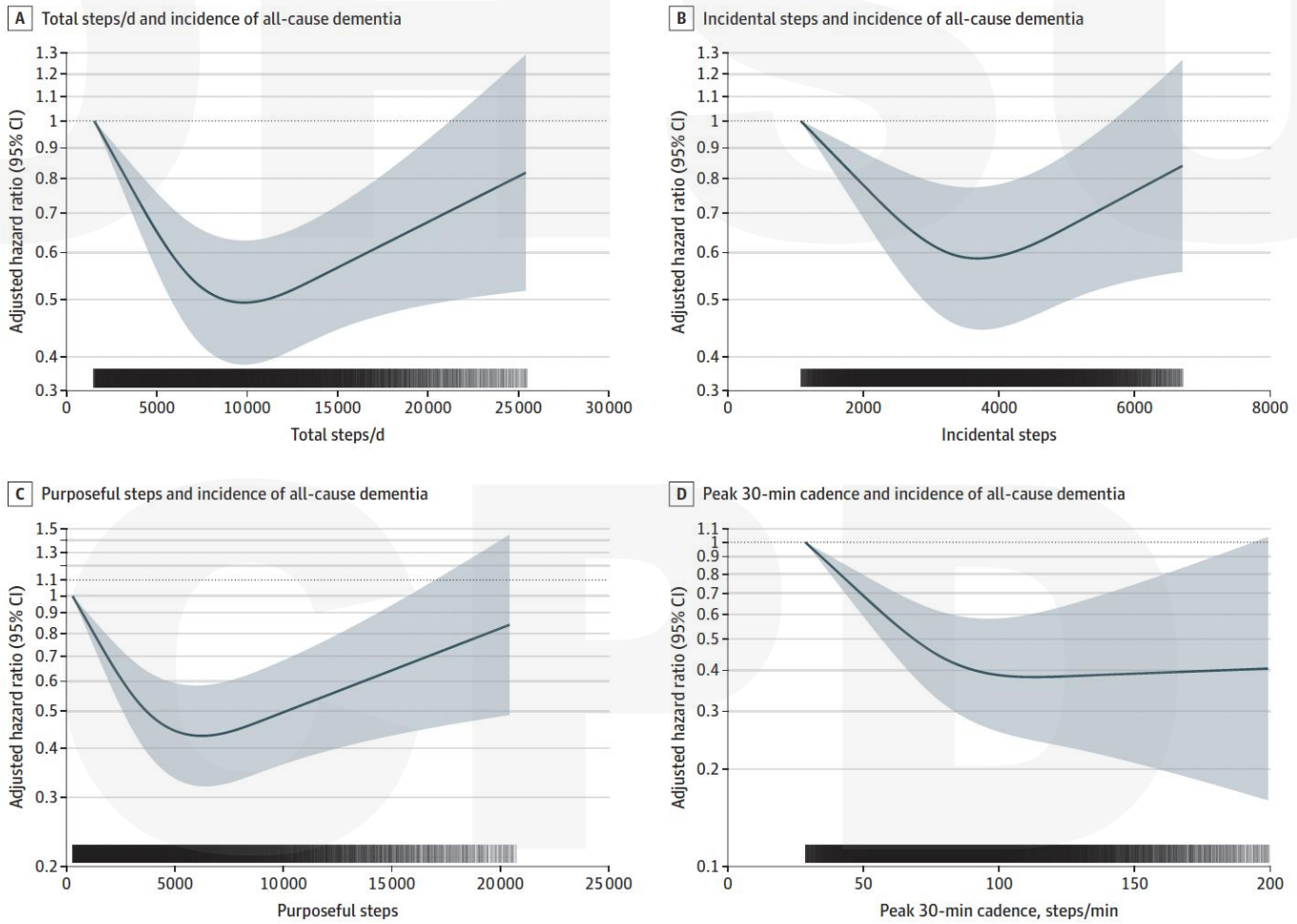
Study

- Exposures: Accelerometer-measured daily step count, including incidental (<40 steps/min), purposeful (≥40 steps/min), and peak 30-minute walking cadence
- Outcome: Incident all-cause dementia (fatal and nonfatal)
- Measure: Identified through linked hospital, primary care, and death records
- Analysis: Cox proportional hazards regression to estimate risk of incident dementia

JAMA Neurol. 2022;79(10):1059-1063.

Results

Figure 2. Dose-Response Association Between Different Accelerometer-Measured Step-Based Metrics and Incidence of All-Cause Dementia



Results

- Dementia risk declined with increasing daily step count
  - 3,500–4,000 steps/day: ~25% lower risk
  - 9,000–10,000 steps/day: ~50% lower risk
- Movement pattern mattered
  - Incidental Steps: ~3,600 steps/day for maximum benefit: ~42% lower risk
  - Purposeful Steps: ~6,300 steps/day for maximum benefit: ~57% lower risk
- Intensity mattered
  - Peak 30-minute cadence: ~110–115 steps/min (brisk walking) for maximum benefit: ~ 62% lower risk

Discussion

- Even modest daily activity levels were associated with meaningful reductions in dementia risk
- Risk reduction was steepest at low–to–moderate step counts, with smaller additional gains at higher levels
- How people walked mattered — purposeful steps and periods of brisk walking showed stronger associations than incidental movement alone
- Findings support focusing on both total movement and walking intensity, not just step counts

My Take

- Limitations: Observational design limits causal inference; the cohort was healthier and less diverse than the general population
- Meaningful activity does not require formal exercise or extreme goals
- Walking is low risk, high yield, with broad health benefits and possible dementia benefit
- It’s not just step count — walking pace and purpose matter
- Bottom line: If patients ask what they can do now for brain health, walking is a reasonable place to start

Case 5

- A 46-year-old man with alcohol use disorder recently stopped drinking after outpatient treatment.
- He’s motivated to stay sober and asks if medication could help reduce relapse.
- You’re deciding between naltrexone and acamprosate.

- **Question: When treating alcohol use disorder, should I reach for naltrexone or acamprosate?**

Background

- Alcohol use disorder (AUD) is common in primary care and frequently co-occurs with hypertension, depression, anxiety, sleep disorders, and chronic pain.
- Most patients are managed (or could be managed) in primary care, rather than specialty addiction treatment settings.
- Evidence-based medications are effective but under prescribed
- Naltrexone and acamprosate are commonly recommended first-line medications, but differ in:
  - Mechanism of action
  - Treatment goals (reduction vs abstinence)
  - Dosing frequency and adherence burden
  - Side-effect profiles
  - Suitability based on liver and renal function

Naltrexone vs Acamprosate: Practical Differences

Naltrexone

- Opioid receptor antagonist
- Reduces heavy drinking and cravings
- Can be started while patients are still drinking
- Once daily oral dosing (or monthly injectable)
- Avoid in active opioid use or acute hepatitis; use caution in advanced liver disease
- Common side effects: nausea, headache

Acamprosate

- Modulates glutamatergic signaling
- Supports maintenance of abstinence
- Requires abstinence at initiation
- Three times daily dosing
- Safe in liver disease; avoid in severe renal impairment
- Common side effects: diarrhea

Choice is often guided by drinking goals, comorbidities, and likelihood of adherence.

Study

- Objective: To compare the effectiveness of medications for alcohol use disorder, with particular focus on naltrexone and acamprosate
- Design: Systematic review and meta-analysis
- Data sources: Randomized controlled trials of medications for AUD with ≥12 weeks of follow-up
  - 118 clinical trials involving 20,976 participants.
- Population: Adults with AUD and on an FDA-approved medication (acamprosate, disulfiram, or naltrexone) or any of 6 off-label medications (baclofen, gabapentin, varenicline, topiramate, prazosin, and ondansetron)

JAMA. 2023;330(17):1653-1665.

Study

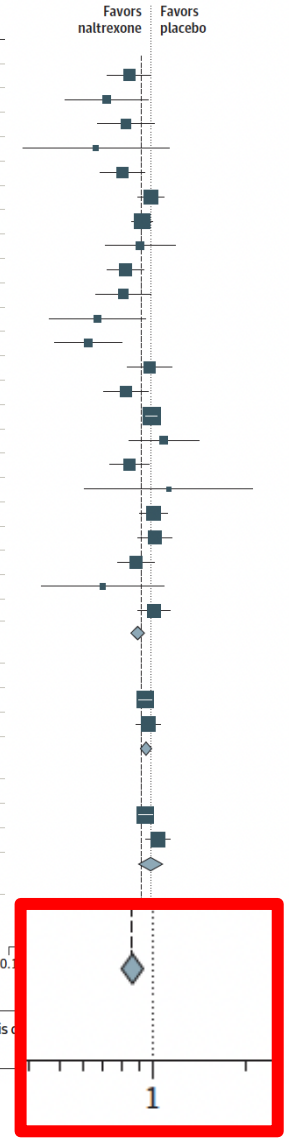
- Interventions: Medications for AUD, including naltrexone, acamprosate, topiramate, and others, compared with placebo
- Primary outcomes: Maintenance of abstinence; relapse to heavy drinking
- Secondary outcomes: Adverse effects
- Analysis: Pooled effect estimates across trials, accounting for between-study differences

Results

- **Question:** Does naltrexone reduce return to heavy drinking?
- **Outcome:** Return to heavy drinking (≥4 drinks/day women; ≥5 drinks/day men)
- **Comparison:** Naltrexone vs placebo across randomized trials
- **Main result:** Pooled estimate shows lower risk with naltrexone (RR=0.86)

Figure 6. Return to Heavy Drinking, Naltrexone vs Placebo

Source	Duration, wk	No./total No. (%) Naltrexone	Placebo	Risk ratio (95% CI)
Naltrexone, 50 mg/d oral				
O'Malley et al,[50] 1992	12	24/52 (46.2)	34/52 (65.4)	0.71 (0.50-1.01)
Volpicelli et al,[63] 1995	12	10/54 (18.5)	17/45 (37.8)	0.49 (0.25-0.96)
Volpicelli et al,[64] 1997	12	17/48 (35.4)	26/49 (53.1)	0.67 (0.42-1.06)
Oslin et al,[54] 1997	12	3/21 (14.3)	8/23 (34.8)	0.41 (0.13-1.35)
Anton et al,[18] 1999	12	26/68 (38.2)	38/63 (60.3)	0.63 (0.44-0.91)
Chick et al,[27] 2000	24	57/85 (67.1)	53/79 (67.1)	1.00 (0.81-1.24)
Krystal et al,[40] 2001	12	183/418 (43.8)	105/209 (50.2)	0.87 (0.73-1.04)
Monti et al,[47] 2001	12	16/64 (25.0)	19/64 (29.7)	0.84 (0.48-1.49)
Morris et al,[49] 2001	12	28/55 (50.9)	43/56 (76.8)	0.66 (0.49-0.89)
Latt et al,[41] 2002	12	19/56 (33.9)	27/51 (52.9)	0.64 (0.41-1.00)
Guardia et al,[34] 2002	12	8/101 (7.9)	19/101 (18.8)	0.42 (0.19-0.92)
Ahmadi and Ahmadi,[15] 2002	12	12/58 (20.7)	33/58 (56.9)	0.36 (0.21-0.63)
Gastpar et al,[31] 2002	12	34/84 (40.5)	36/87 (41.4)	0.98 (0.68-1.40)
Kiefer et al,[37] 2003	12	20/40 (50.0)	30/40 (75.0)	0.67 (0.47-0.95)
Balldin et al,[20] 2003	24	53/56 (94.6)	58/62 (93.5)	1.01 (0.92-1.11)
Killeen et al,[38] 2004	12	21/51 (41.2)	12/36 (33.3)	1.24 (0.70-2.18)
Anton et al,[17] 2005	12	33/80 (41.3)	46/80 (57.5)	0.71 (0.51-0.98)
Huang et al,[36] 2005	14	4/20 (20.0)	3/20 (15.0)	1.33 (0.34-5.21)
Morley et al,[48] 2006	12	39/53 (73.6)	43/61 (70.5)	1.04 (0.83-1.31)
O'Malley et al,[52] 2007	12	39/57 (68.4)	32/50 (64.0)	1.07 (0.81-1.40)
O'Malley et al,[51] 2008	16	22/34 (64.7)	28/34 (82.4)	0.79 (0.59-1.05)
Brown et al,[25] 2009	12	4/20 (20.0)	10/23 (43.5)	0.46 (0.17-1.24)
Mann et al,[45] 2013	12	86/169 (50.9)	41/85 (48.2)	1.05 (0.81-1.38)
Heterogeneity: $\tau^2 = 0.03$, $I^2 = 53.72\%$, $H^2 = 2.42$ Test of $\theta_i = \theta_j$: $Q(22) = 53.29$, $P < .001$				0.81 (0.72-0.90)
Naltrexone, 100 mg/d oral				
Anton et al,[19] 2006	16	207/309 (67.0)	226/309 (73.1)	0.92 (0.83-1.02)
Oslin et al,[53] 2008	24	73/120 (60.8)	76/120 (63.3)	0.96 (0.79-1.17)
Heterogeneity: $\tau^2 = 0.00$, $I^2 = 0.00\%$, $H^2 = 1.00$ Test of $\theta_i = \theta_j$: $Q(1) = 0.17$, $P = .68$				0.93 (0.84-1.01)
Naltrexone, injection				
Kranzler et al,[39] 2004	12	122/158 (77.2)	132/157 (84.1)	0.92 (0.82-1.02)
ALK21-014,[16] 2011	12	90/152 (59.2)	78/148 (52.7)	1.12 (0.92-1.37)
Heterogeneity: $\tau^2 = 0.01$, $I^2 = 66.35\%$, $H^2 = 2.97$ Test of $\theta_i = \theta_j$: $Q(1) = 2.97$, $P = .08$				1.00 (0.82-1.21)
Overall Heterogeneity: $\tau^2 = 0.02$, $I^2 = 54.99\%$, $H^2 = 2.22$ Test of group differences: $Q_b(2) = 5.00$, $P = .08$				0.86 (0.80-0.93)



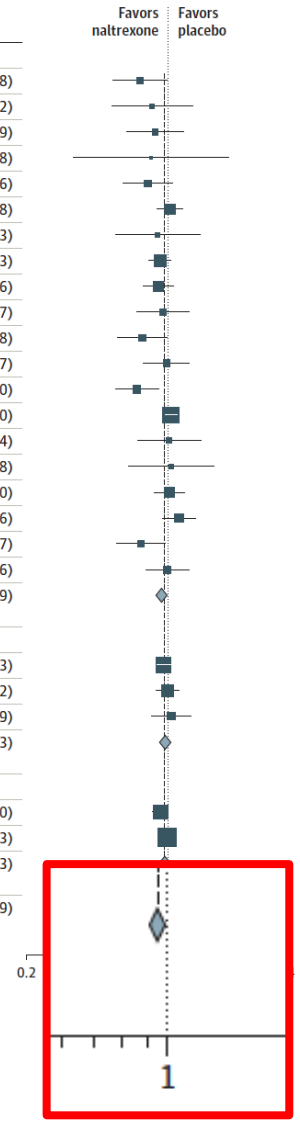
"Overall" refers to pooled estimate for all forms of naltrexone (50 mg/d oral, 100 mg/d oral, and injection). Heavy drinking is d
and ≥5 drinks/d for men.

Results

- **Question:** Does naltrexone reduce return to *any* drinking?
- **Outcome:** Return to any drinking (any alcohol use after abstinence)
- **Comparison:** Naltrexone vs placebo across randomized trials
- **Main result:** Small (RR=0.95) but statistically significant reduction in return to any drinking

Figure 4. Return to Any Drinking, Naltrexone vs Placebo

Source	Duration, wk	No./total No. (%) Naltrexone	Placebo	Risk ratio (95% CI)
Naltrexone, 50 mg/d oral				
O'Malley et al,[50] 1992	12	27/52 (51.9)	38/52 (73.1)	0.72 (0.53-0.98)
Volpicelli et al,[63] 1995	12	21/54 (38.9)	21/45 (46.7)	0.83 (0.53-1.32)
Volpicelli et al,[64] 1997	12	27/48 (56.3)	32/49 (65.3)	0.86 (0.62-1.19)
Oslin et al,[54] 1997	12	6/21 (28.6)	8/23 (34.8)	0.82 (0.34-1.98)
Anton et al,[18] 1999	12	36/68 (52.9)	42/63 (66.7)	0.79 (0.60-1.06)
Chick et al,[27] 2000	12	70/85 (82.4)	64/79 (81.0)	1.02 (0.88-1.18)
Lee et al,[42] 2001	12	19/35 (54.3)	11/18 (61.1)	0.89 (0.55-1.43)
Krystal et al,[40] 2001	12	255/418 (61.0)	140/209 (67.0)	0.91 (0.81-1.03)
Morris et al,[49] 2001	12	43/55 (78.2)	49/56 (87.5)	0.89 (0.75-1.06)
Gastpar et al,[31] 2002	12	41/84 (48.8)	45/87 (51.7)	0.94 (0.70-1.27)
Ahmadi and Ahmadi,[15] 2002	36	32/58 (55.2)	43/58 (74.1)	0.74 (0.56-0.98)
Guardia et al,[34] 2002	12	53/101 (52.5)	54/101 (53.5)	0.98 (0.76-1.27)
Kiefer et al,[37] 2003	12	26/40 (65.0)	37/40 (92.5)	0.70 (0.55-0.90)
Balldin et al,[20] 2003	24	55/56 (98.2)	59/62 (95.2)	1.03 (0.97-1.10)
Killeen et al,[38] 2004	12	30/51 (58.8)	21/36 (58.3)	1.01 (0.70-1.44)
Petrakis et al,[58] 2005	12	21/59 (35.6)	22/64 (34.4)	1.04 (0.64-1.68)
Morley et al,[48] 2006	12	44/53 (83.0)	50/61 (82.0)	1.01 (0.86-1.20)
O'Malley et al,[52] 2007	12	49/57 (86.0)	38/50 (76.0)	1.13 (0.94-1.36)
O'Malley et al,[51] 2008	16	22/34 (64.7)	30/34 (88.2)	0.73 (0.56-0.97)
Baltieri et al,[22] 2008	12	35/49 (71.4)	39/54 (72.2)	0.99 (0.78-1.26)
Heterogeneity: $\tau^2 = 0.01$, $I^2 = 35.07\%$, $H^2 = 1.54$ Test of $\theta_i = \theta_j$: Q(19) = 29.26, $P = .06$				0.93 (0.87-0.99)
Naltrexone, 100 mg/d oral				
Anton et al,[19] 2006	16	241/309 (78.0)	254/309 (82.2)	0.95 (0.88-1.03)
Oslin et al,[53] 2008	24	95/120 (79.2)	96/120 (80.0)	0.99 (0.87-1.12)
Pettinati et al,[59] 2010	14	39/49 (79.6)	30/39 (76.9)	1.03 (0.83-1.29)
Heterogeneity: $\tau^2 = 0.00$, $I^2 = 0.00\%$, $H^2 = 1.00$ Test of $\theta_i = \theta_j$: Q(2) = 0.70, $P = .70$				0.97 (0.91-1.03)
Naltrexone, injection				
Kranzler et al,[39] 2004	12	130/158 (82.3)	141/157 (89.8)	0.92 (0.84-1.00)
Garbutt et al,[30] 2005	24	388/415 (93.5)	198/209 (94.7)	0.99 (0.95-1.03)
Heterogeneity: $\tau^2 = 0.00$, $I^2 = 54.45\%$, $H^2 = 2.20$ Test of $\theta_i = \theta_j$: Q(1) = 2.20, $P = .14$				0.96 (0.90-1.03)
Overall Heterogeneity: $\tau^2 = 0.00$, $I^2 = 25.82\%$, $H^2 = 1.35$ Test of group differences: $Q_b(2) = 0.99$, $P = .61$				0.95 (0.92-0.99)

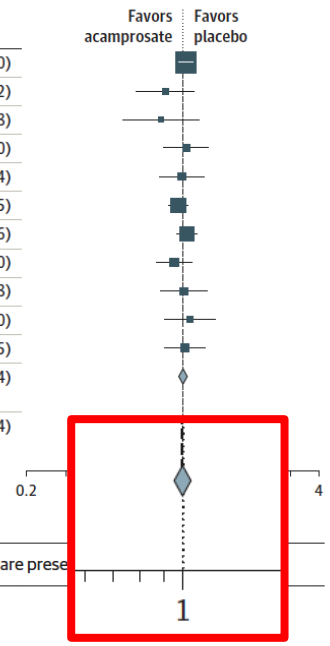


Results

- **Question**: Does acamprosate reduce return to heavy drinking?
- **Outcome**: Return to heavy drinking (≥4 drinks/day for women; ≥5 drinks/day for men)
- **Comparison**: Acamprosate vs placebo across randomized trials
- **Main result**: No reduction in heavy drinking with acamprosate (pooled RR ≈ 1.00)

Figure 5. Return to Heavy Drinking, Acamprosate vs Placebo

Source	Duration, wk	No./total No. (%) Acamprosate	Placebo	Risk ratio (95% CI)
Chick et al,[26] 2000	24	246/289 (85.1)	242/292 (82.9)	1.03 (0.96-1.10)
Kiefer et al,[37] 2003	12	25/40 (62.5)	30/40 (75.0)	0.83 (0.62-1.12)
Kiefer et al,[37] 2003	12	20/40 (50.0)	25/40 (62.5)	0.80 (0.54-1.18)
Morley et al,[48] 2006	12	40/55 (72.7)	43/61 (70.5)	1.03 (0.82-1.30)
Morley et al,[48] 2006	12	40/55 (72.7)	39/53 (73.6)	0.99 (0.79-1.24)
Anton et al,[19] 2006	16	211/303 (69.6)	226/309 (73.1)	0.95 (0.86-1.05)
Anton et al,[19] 2006	16	211/303 (69.6)	207/309 (67.0)	1.04 (0.93-1.16)
Mason et al,[46] 2006	24	143/341 (41.9)	119/260 (45.8)	0.92 (0.76-1.10)
Wölwer et al,[66] 2011	24	65/124 (52.4)	65/125 (52.0)	1.01 (0.79-1.28)
Mann et al,[45] 2013	12	89/172 (51.7)	41/85 (48.2)	1.07 (0.82-1.40)
Mann et al,[45] 2013	12	89/172 (51.7)	86/169 (50.9)	1.02 (0.83-1.25)
Heterogeneity: $\tau^2 = 0.00$, $I^2 = 0.00\%$, $H^2 = 1.00$ Test of $\theta_i = \theta_j$: $Q(10) = 5.90$, $P = .82$				1.00 (0.96-1.04)
Overall Heterogeneity: $\tau^2 = 0.00$, $I^2 = 0.00\%$, $H^2 = 1.00$ Test of group differences: $Q_b(0) = 0.00$				1.00 (0.96-1.04)



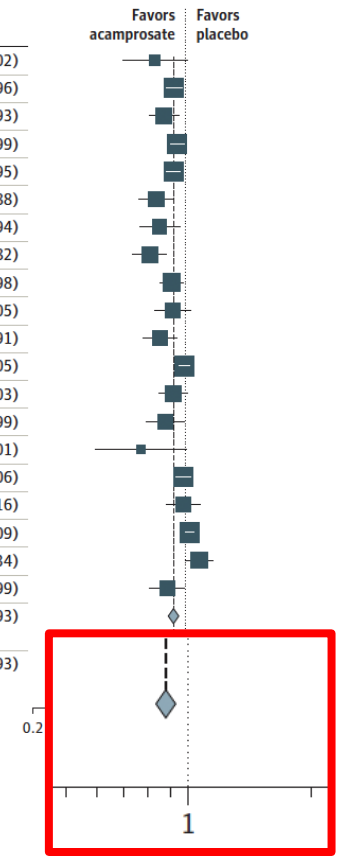
Heavy drinking is defined as ≥4 drinks/d for women and ≥5 drinks/d for men. Multiple comparisons within publications are prese

Results

- **Question**: Does acamprosate reduce return to any drinking?
- **Outcome**: Return to any drinking (any alcohol use after a period of abstinence)
- **Comparison**: Acamprosate vs placebo across randomized trials
- **Main result**: Meaningful reduction in return to any drinking with acamprosate (pooled RR ≈ 0.88)

Figure 2. Return to Any Drinking, Acamprosate vs Placebo

Source	Duration, wk	No./total No. (%)		Risk ratio (95% CI)
		Acamprosate	Placebo	
Lhuintre et al,[43] 1985	13	22/42 (52.4)	31/43 (72.1)	0.73 (0.52-1.02)
Lhuintre et al,[44] 1990	12	208/279 (74.6)	245/291 (84.2)	0.89 (0.81-0.96)
Pelc et al,[56] 1992	26	42/55 (76.4)	45/47 (95.7)	0.80 (0.68-0.93)
Paille et al,[55] 1995	51	294/361 (81.4)	157/177 (88.7)	0.92 (0.85-0.99)
Whitworth et al,[65] 1996	52	183/224 (81.7)	208/224 (92.9)	0.88 (0.82-0.95)
Sass et al,[61] 1996	48	75/136 (55.1)	102/136 (75.0)	0.74 (0.61-0.88)
Poldrugo,[60] 1997	26	63/122 (51.6)	84/124 (67.7)	0.76 (0.62-0.94)
Pelc et al,[57] 1997	13	74/126 (58.7)	53/62 (85.5)	0.69 (0.57-0.82)
Geerlings et al,[32] 1997	26	96/128 (75.0)	116/134 (86.6)	0.87 (0.77-0.98)
Besson et al,[24] 1998	51	41/55 (74.5)	47/55 (85.5)	0.87 (0.72-1.05)
Tempesta et al,[62] 2000	26	87/164 (53.0)	115/166 (69.3)	0.77 (0.64-0.91)
Chick et al,[26] 2000	24	254/289 (87.9)	260/292 (89.0)	0.99 (0.93-1.05)
Gual and Lehert,[33] 2001	26	92/141 (65.2)	109/147 (74.1)	0.88 (0.75-1.03)
Kiefer et al,[37] 2003	12	30/40 (75.0)	37/40 (92.5)	0.81 (0.66-0.99)
Baltieri and De Andrade,[21] 2004	12	15/40 (37.5)	21/35 (60.0)	0.63 (0.39-1.01)
Anton et al,[17] 2005	16	244/303 (80.5)	254/309 (82.2)	0.98 (0.91-1.06)
Morley et al,[48] 2006	12	44/55 (80.0)	50/61 (82.0)	0.98 (0.82-1.16)
Mason et al,[46] 2006	24	328/341 (96.2)	240/260 (92.3)	1.04 (1.00-1.09)
Berger et al,[23] 2013	12	48/51 (94.1)	40/49 (81.6)	1.15 (0.99-1.34)
Higuchi et al,[35] 2015	24	86/163 (52.8)	105/164 (64.0)	0.82 (0.68-0.99)
Heterogeneity: $\tau^2 = 0.01$, $I^2 = 77.64\%$, $H^2 = 4.47$ Test of $\theta_i = \theta_j$: $Q(19) = 84.97$, $P < .001$				0.88 (0.83-0.93)
Overall Heterogeneity: $\tau^2 = 0.01$, $I^2 = 77.64\%$, $H^2 = 4.47$ Test of group differences: $Q_b(0) = 0.00$				0.88 (0.83-0.93)



Results

- Disulfiram
  - Effects on drinking outcomes were inconsistent
  - Benefit largely limited to supervised treatment settings
  - Limited applicability to routine primary care
- Topiramate
  - Associated with reduced drinking outcomes in some trials
  - Evidence base is smaller and more heterogeneous
  - Studied as an off-label option
- Other medications
  - Evidence for primary drinking outcomes was limited or mixed
  - Fewer trials with variable outcome definitions

Results: Tolerability and Adverse Events

- Quality of adverse event data
  - Adverse events were often not collected using standardized measures
  - Methods for systematically capturing adverse events were frequently not reported
- Adverse effects and discontinuation
  - Side-effect profiles varied across medications
  - Discontinuation due to adverse events was more common with some off-label agents (topiramate: cognitive side effects)
- Overall tolerability
  - FDA-approved medications (naltrexone, acamprosate) showed more consistent tolerability data
    - Serious adverse events were uncommon across trials

Discussion

- Highest strength of evidence supports acamprosate and oral naltrexone 50 mg/day
- Naltrexone
  - Moderate strength of evidence for reducing: Return to **heavy drinking** (NNT ≈ 11)
  - Limited data for 100 mg oral and injectable formulations, with no clear benefit for relapse outcomes
- Acamprosate
  - Moderate strength of evidence for reducing: Return to **any drinking** (NNT ≈ 11)
  - No demonstrated benefit for reducing heavy drinking

My Take

- Most participants were treated in specialty addiction or research settings, often with structured psychosocial interventions, rather than routine primary care
  - Efficacy estimates reflect best-case conditions with higher engagement than typical primary care practice
- Trial populations were predominantly middle-aged, male, and drawn from specialty settings, with limited representation of older adults, women, and racially diverse populations

- Medications for AUD work, but they work on different outcomes, benefit depends on what you're trying to change.
  - Naltrexone shifts the odds away from heavy drinking
  - Acamprosate shifts the odds away from relapse
- Everything else is second-line
  - Topiramate can reduce drinking but has cognitive side effects

Case 6

- A 42-year-old woman with nonseasonal major depressive disorder has been on sertraline 100 mg daily for 6 weeks.
- She reports partial improvement in mood but continues to struggle with low energy, morning inertia, and poor concentration.
- She has no history of bipolar disorder, psychosis, or seasonal pattern to her depression.
- She is hoping for an intervention to improve her mood other than a medication change.

- **Question: Does bright light therapy (BLT), used as an adjunct, improve outcomes in nonseasonal major depressive disorder?**

Bright Light Therapy

- BLT: A nonpharmacologic treatment involving scheduled exposure to high-intensity white light
  - Delivered via a commercial light box (not standard indoor lighting)
  - Thought to affect circadian regulation and mood-related neurobiology
- Current Clinical Use
  - Established treatment for seasonal affective disorder
  - In nonseasonal depression, studied as an adjunct to antidepressants
  - Typical protocol:
    - 10,000 lux
    - 30–60 minutes daily
    - Morning exposure
  - Generally well tolerated
    - Common side effects: headache, eye strain, insomnia
    - Activation risk in bipolar disorder

Study

- Objective: To evaluate the effectiveness of BLT as an adjunctive treatment for nonseasonal depressive disorders
- Study Design: Systematic review and meta-analysis of 11 randomized clinical trials (2000–2024)
  - Comparators: BLT (alone or adjunctive) vs placebo, dim red light, or antidepressant monotherapy
- Population: 858 adults with nonseasonal depressive disorders, predominantly unipolar depression; bipolar depression was included in a small subset of trials

JAMA Psychiatry. 2025;82(1):38-46.

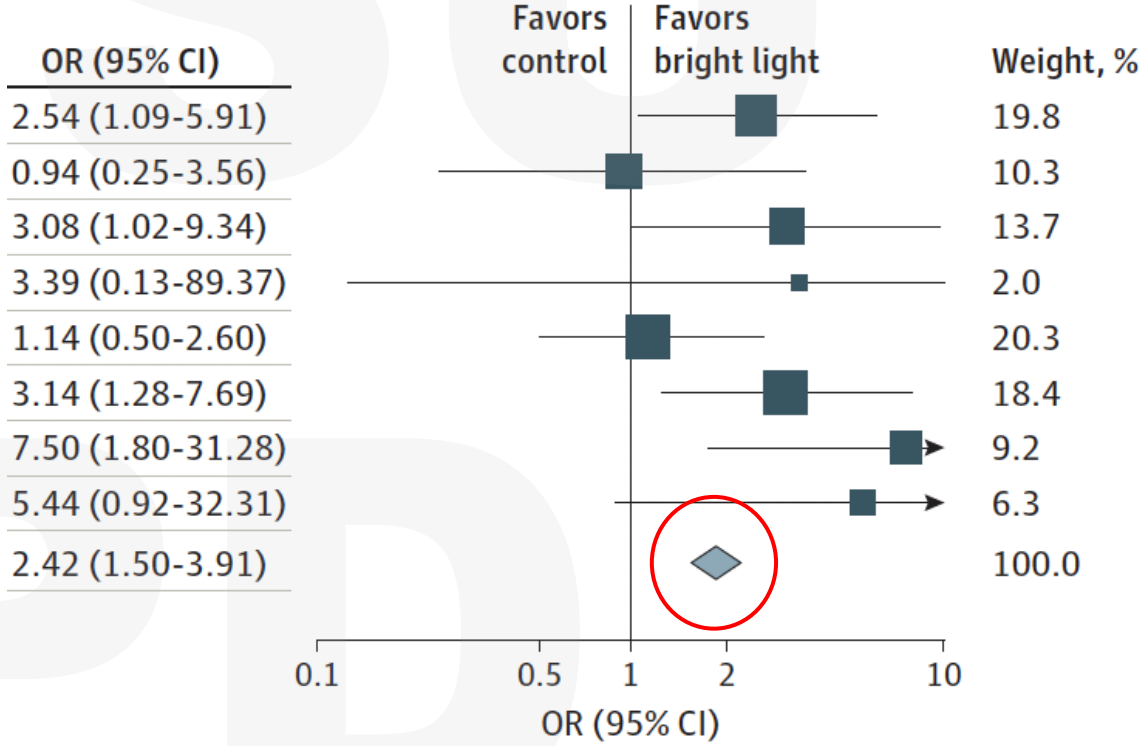
Study

- Outcome Measures:
  - Primary outcomes included remission of symptoms and response to treatment.
  - Exploratory subgroup analyses: outcomes stratified by follow-up duration (eg, <4 weeks vs >4 weeks)

Results

Remission

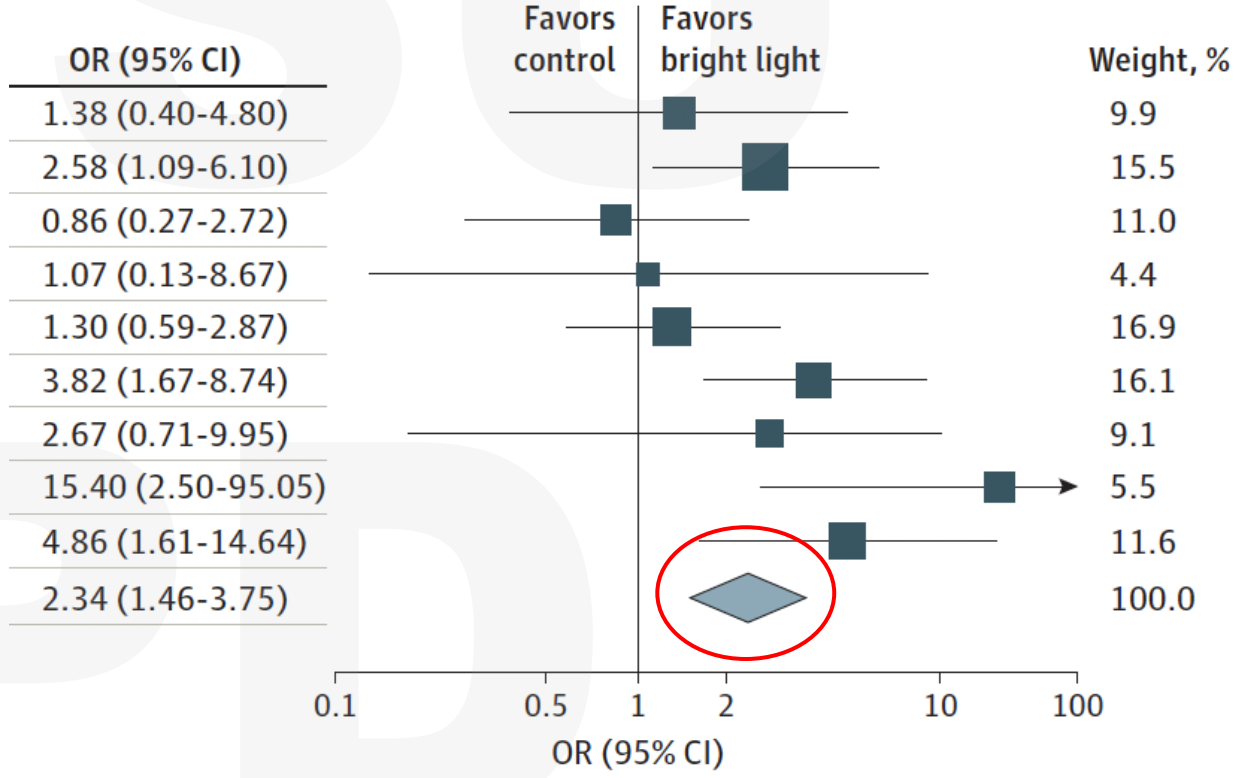
- Eight trials reported remission outcomes
- Remission defined as achieving a specific score threshold on depression scales (eg such as HAM-D ≤7)
- BLT significantly increased remission in nonseasonal depressive disorders
- Remission: 40.7% with BLT vs 23.5% with control
- Pooled effect: OR 2.42



Results

Response

- Eight trials reported response outcomes
- Response was generally defined as a ≥50% reduction in depression scores from baseline, using scales such as HAM-D
- BLT significantly increased response in nonseasonal depressive disorders
- Response: 60.4% with BLT vs 38.6% with control
- Pooled effect: OR 2.34



Results – Exploratory Subgroup Analysis

Remission

- <4 weeks: 27% vs 9% (higher remission with BLT)
- >4 weeks: 47% vs 29% (benefit persists)

Response

- <4 weeks: 56% vs 27% (higher response with BLT)
- >4 weeks: 63% vs 45% (benefit persists)

Discussion

- Adjunctive BLT was associated with higher remission and response rates in nonseasonal depressive disorders
- Effects were clinically meaningful, reflected by absolute increases in remission and response
- Benefits were evident early in treatment, with effects persisting over time
- Larger effects at earlier follow-up suggest BLT may accelerate response, rather than only improving end-point outcomes

My Take

- Key limitations
  - Meta-analysis of heterogeneous RCTs with variability in comparators and outcome measures
  - Limited guidance on optimal duration, maintenance, or patient selection
- Clinical interpretation
  - Signal suggests modest but clinically meaningful benefit
  - Effects may occur earlier than medication adjustments
  - Overall low-risk, nonpharmacologic intervention
- How this affects my practice
  - I would consider BLT as a reasonable adjunct for patients with mild to moderate nonseasonal depression
  - Particularly appropriate for patients who prefer to avoid medication changes
- Bottom line
  - Not a replacement for antidepressants, but a low-harm intervention worth trying in selected patients

Summary

- Mental health in primary care
  - Approximately 1 in 8 primary care encounters involve a mental health condition
  - Mental health encounters exceeded most other body systems except musculoskeletal
- SSRI drug holidays and sexual dysfunction
  - Planned weekend SSRI interruptions were associated with improvements in sexual function and satisfaction
- Benzodiazepine use and dose escalation
  - Long term use and dose escalation were uncommon
  - Higher risk was concentrated among patients with substance use disorder
- Step count and dementia risk
  - More daily walking (especially purposeful and brisk) is associated with lower dementia risk

Summary

- Medications for alcohol use disorder
  - Naltrexone reduced return to heavy drinking
  - Acamprosate reduced return to any drinking, not heavy drinking
  - Medications differed by outcome, rather than overall effectiveness
- Bright light therapy for nonseasonal depression
  - Bright light therapy improves depression outcomes and is a practical, low-risk treatment option

Final Takeaway

- Mental health care is core primary care
- Benefits are often modest, but clinically meaningful
- Impact depends on matching the intervention to the desired outcome
- Many effective strategies are low complexity and low harm
- Small, evidence-based adjustments can meaningfully improve patient care