Mental Health Literature Update

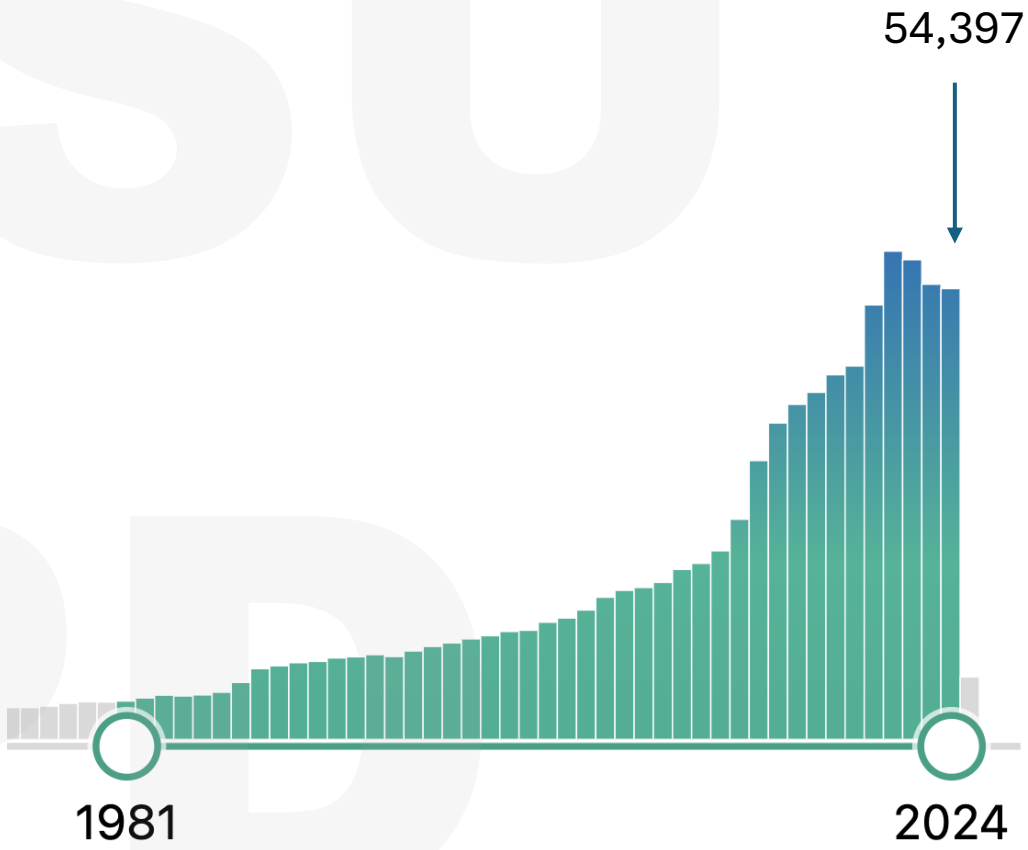
David Mansoor, MD

Associate Professor of Psychiatry

March 2025

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 keep up to keep up and evaluate the quality



PubMed search: “Psychiatry”

1. Oman Med J. 2010 Oct;25(4):311–314

Overview

- Objective is to review 6 interesting articles published in the past 3 years
- Psychiatry focused, pertinent to primary care
- Covering a range of topics
  - Emerging treatments: dementia related agitation and depression
  - Evolving treatment trends: stimulant dosing, antidepressants and weight gain
  - Updates in diagnosis: ADHD
  - Public health issues: social media and mental health

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

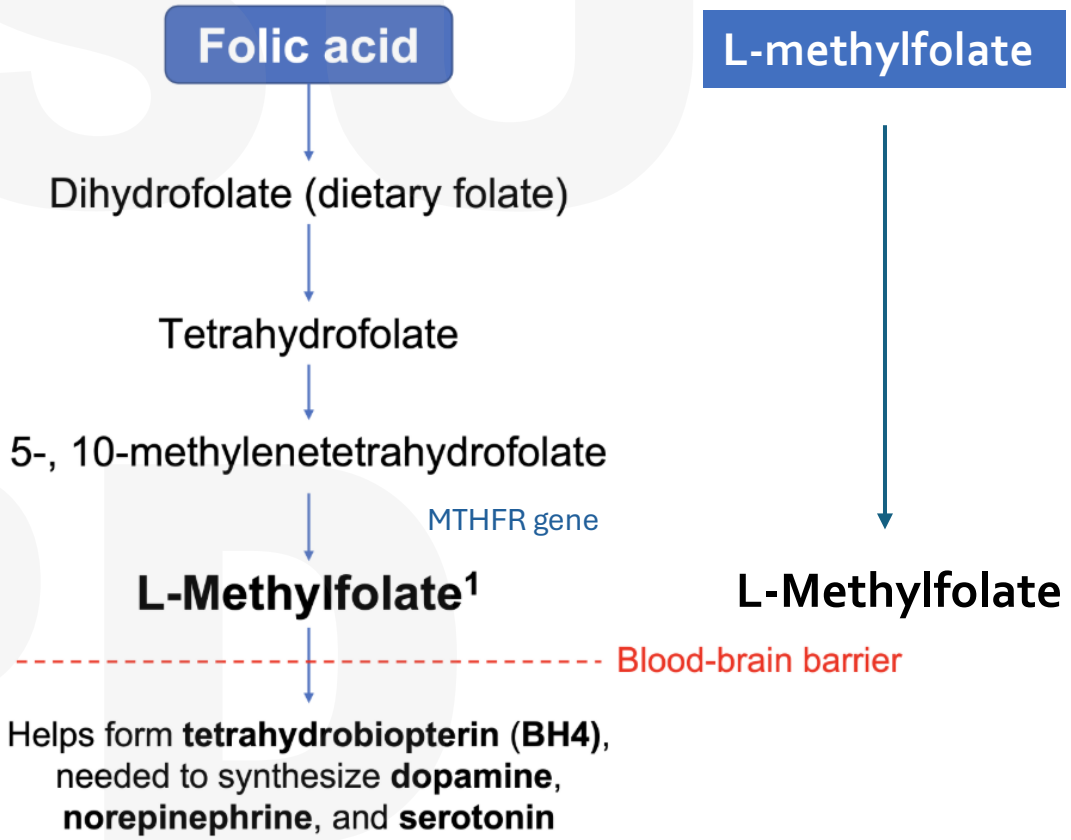
Case 1

- 47-year old woman with a history of depression
- Presents to clinic reporting a recent increase in depression symptoms
- Has been on sertraline 200mg for 6 months without much benefit
- She is interested in a “natural” treatment option

- **Question: Is l-methylfolate an effective adjunct for treatment of depression?**

L-methylfolate

- Vit B9 is an essential nutrient, meaning that it is required for normal body functioning
- Folic acid (synthetic), folate (natural)
- Converted to L-methylfolate in the body
- L-methylfolate crosses the BBB and aids in the synthesis of monoamines
- An association between low folate levels and depression



1. Gibbons RD et al. JAMA Psychiatry 2022

Study

Review

Systematic Review and Meta-Analysis of L-Methylfolate Augmentation in Depressive Disorders

- Systematic review of 9 articles (10 studies; 6,707 patients) and meta-analysis of 3 articles (4 studies; 507 patients)
  - Article inclusion criteria were: (1) examined L-methylfolate adjunctive therapy in depressive disorders, (2) published in a peer-reviewed, English-language journal
- Variety of study designs: RCT, prospective, and retrospective case-control
  - Only RCTs were included in the meta-analysis*

Pharmacopsychiatry 2022; 55: 139–147

Study

Review

Systematic Review and Meta-Analysis of L-Methylfolate Augmentation in Depressive Disorders

- Systematic review of 9 articles (10 studies; 6,707 patients) and meta-analysis of 3 articles (4 studies; 507 patients)
  - Article inclusion criteria were: (1) examined L-methylfolate adjunctive therapy in depressive disorders, (2) published in a peer-reviewed, English-language journal
- Variety of study designs: RCT, prospective, and retrospective case-control
  - Only RCTs were included in the meta-analysis*

Pharmacopsychiatry 2022; 55: 139–147

Characteristics of the studies

Study (First Author, Year)	Sample Size	Subject Characteristics (Age in years, Women %)	Study Design	Treatment	Treatment Duration	Comparator	Primary Outcome Measurement	Result
* Godfrey, 1990	24 (patients with depression)	45.5, 54 %	Double-blinded, randomized controlled trial	L-methylfolate 15 mg + psychotropic medication	6 months	Placebo + psychotropic medication	HAM-D17	The treated group trended towards having a greater reduction in HAM-D versus the comparator
* Kakar, 2017	260	36.9, 53.5 %	Double-blinded, randomized controlled trial	L-methylfolate 15 mg + escitalopram	30 days	Placebo + escitalopram	HAM-D17	Response in the treated was better than the comparator
* Papakostas (Trial 1), 2012	148	47.9, 69.5 %	Double-blinded, randomized controlled trial	L-methylfolate 7.5/15 mg + SSRI	60 days	Placebo + SSRI	HAM-D17	No difference in response between treated and comparator groups
* Papakostas (Trial 2), 2012	75	48.4, 70.6 %	Double-blinded, randomized controlled trial	L-methylfolate 15 mg + SSRI	60 days	Placebo + SSRI	HAM-D17	The treated group had a greater response versus the comparator group

Characteristics of the studies

Study (First Author, Year)	Sample Size	Subject Characteristics (Age in years, Women %)	Study Design	Treatment	Treatment Duration	Comparator	Primary Outcome Measurement	Result
* Godfrey, 1990	24 (patients with depression)	45.5, 54 %	Double-blinded, randomized controlled trial	L-methylfolate 15 mg + psychotropic medication	6 months	Placebo + psychotropic medication	HAM-D17	The treated group trended towards having a greater reduction in HAM-D versus the comparator
* Kakar, 2017	260	36.9, 53.5 %	Double-blinded, randomized controlled trial	L-methylfolate 15 mg + escitalopram	30 days	Placebo + escitalopram	HAM-D17	Response in the treated was better than the comparator
* Papakostas (Trial 1), 2012	148	47.9, 69.5 %	Double-blinded, randomized controlled trial	L-methylfolate 7.5/15 mg + SSRI	60 days	Placebo + SSRI	HAM-D17	No difference in response between treated and comparator groups
* Papakostas (Trial 2), 2012	75	48.4, 70.6 %	Double-blinded, randomized controlled trial	L-methylfolate 15 mg + SSRI	60 days	Placebo + SSRI	HAM-D17	The treated group had a greater response versus the comparator group

Variability in study size

Characteristics of the studies

Study (First Author, Year)	Sample Size	Subject Characteris-tics (Age in years, Women %)	Study Design	Treatment	Treatment Duration	Comparator	Primary Outcome Measurement	Result
* Godfrey, 1990	24 (patients with depression)*	45.5, 54%	Double-blinded, randomized controlled trial	L-methylfolate 15 mg + psychotropic medication	6 months	Placebo + psy-chotropic medication	HAM-D17	The treated group trended towards having a greater reduction in HAM-D versus the comparator
* Kakar, 2017	260 *	36.9, 53.5%	Double-blinded, randomized controlled trial	L-methylfolate 15 mg + escitalopram	30 days	Placebo + escit-alopram	HAM-D17	Response in the treated was better than the comparator
* Papakostas (Trial 1), 2012	148	47.9, 69.5%	Double-blinded, randomized controlled trial	L-methylfolate 7.5/15 mg + SSRI	60 days	Placebo + SSRI	HAM-D17	No difference in response between treated and comparator groups
* Papakostas (Trial 2), 2012	75	48.4, 70.6%	Double-blinded, randomized controlled trial	L-methylfolate 15 mg + SSRI	60 days	Placebo + SSRI	HAM-D17	The treated group had a greater response versus the comparator group

Similar in age, more women than men

Characteristics of the studies

Study (First Author, Year)	Sample Size	Subject Characteristics (Age in years, Women %)	Study Design	Treatment	Treatment Duration	Comparator	Primary Outcome Measurement	Result
* Godfrey, 1990	24 (patients with depression)	45.5, 54 %	Double-blinded, randomized controlled trial	L-methylfolate 15 mg + psychotropic medication	6 months	Placebo + psychotropic medication	HAM-D17	The treated group trended towards having a greater reduction in HAM-D versus the comparator
* Kakar, 2017	260	36.9, 53.5 %	Double-blinded, randomized controlled trial	L-methylfolate 15 mg + escitalopram	30 days	Placebo + escitalopram	HAM-D17	Response in the treated was better than the comparator
* Papakostas (Trial 1), 2012	148	47.9, 69.5 %	Double-blinded, randomized controlled trial	L-methylfolate 7.5/15 mg + SSRI	60 days	Placebo + SSRI	HAM-D17	No difference in response between treated and comparator groups
* Papakostas (Trial 2), 2012	75	48.4, 70.6 %	Double-blinded, randomized controlled trial	L-methylfolate 15 mg + SSRI	60 days	Placebo + SSRI	HAM-D17	The treated group had a greater response versus the comparator group

All double-blinded RCTs

Characteristics of the studies

Study (First Author, Year)	Sample Size	Subject Characteristics (Age in years, Women %)	Study Design	Treatment	Treatment Duration	Comparator	Primary Outcome Measurement	Result
* Godfrey, 1990	24 (patients with depression)	45.5, 54 %	Double-blinded, randomized controlled trial	L-methylfolate 15 mg + psychotropic medication	6 months	Placebo + psychotropic medication	HAM-D17	The treated group trended towards having a greater reduction in HAM-D versus the comparator
* Kakar, 2017	260	36.9, 53.5 %	Double-blinded, randomized controlled trial	L-methylfolate 15 mg + escitalopram	30 days	Placebo + escitalopram	HAM-D17	Response in the treated was better than the comparator
* Papakostas (Trial 1), 2012	148	47.9, 69.5 %	Double-blinded, randomized controlled trial	L-methylfolate 7.5/15 mg + SSRI	60 days	Placebo + SSRI	HAM-D17	No difference in response between treated and comparator groups
* Papakostas (Trial 2), 2012	75	48.4, 70.6 %	Double-blinded, randomized controlled trial	L-methylfolate 15 mg + SSRI	60 days	Placebo + SSRI	HAM-D17	The treated group had a greater response versus the comparator group

Similar treatment interventions:
Placebo vs L-MTHF augmentation

Characteristics of the studies

Study (First Author, Year)	Sample Size	Subject Characteristics (Age in years, Women %)	Study Design	Treatment	Treatment Duration	Comparator	Primary Outcome Measurement	Result
* Godfrey, 1990	24 (patients with depression)	45.5, 54 %	Double-blinded, randomized controlled trial	L-methylfolate 15 mg + psychotropic medication	6 months	Placebo + psychotropic medication	HAM-D17	The treated group trended towards having a greater reduction in HAM-D versus the comparator
* Kakar, 2017	260	36.9, 53.5 %	Double-blinded, randomized controlled trial	L-methylfolate 15 mg + escitalopram	30 days	Placebo + escitalopram	HAM-D17	Response in the treated was better than the comparator
* Papakostas (Trial 1), 2012	148	47.9, 69.5 %	Double-blinded, randomized controlled trial	L-methylfolate 7.5/15 mg + SSRI	60 days	Placebo + SSRI	HAM-D17	No difference in response between treated and comparator groups
* Papakostas (Trial 2), 2012	75	48.4, 70.6 %	Double-blinded, randomized controlled trial	L-methylfolate 15 mg + SSRI	60 days	Placebo + SSRI	HAM-D17	The treated group had a greater response versus the comparator group

30 days to 6 months

Characteristics of the studies

Study (First Author, Year)	Sample Size	Subject Characteristics (Age in years, Women %)	Study Design	Treatment	Treatment Duration	Comparator	Primary Outcome Measurement	Result
* Godfrey, 1990	24 (patients with depression)	45.5, 54 %	Double-blinded, randomized controlled trial	L-methylfolate 15 mg + psychotropic medication	6 months	Placebo + psychotropic medication	HAM-D17	The treated group trended towards having a greater reduction in HAM-D versus the comparator
* Kakar, 2017	260	36.9, 53.5 %	Double-blinded, randomized controlled trial	L-methylfolate 15 mg + escitalopram	30 days	Placebo + escitalopram	HAM-D17	Response in the treated was better than the comparator
* Papakostas (Trial 1), 2012	148	47.9, 69.5 %	Double-blinded, randomized controlled trial	L-methylfolate 7.5/15 mg + SSRI	60 days	Placebo + SSRI	HAM-D17	No difference in response between treated and comparator groups
* Papakostas (Trial 2), 2012	75	48.4, 70.6 %	Double-blinded, randomized controlled trial	L-methylfolate 15 mg + SSRI	60 days	Placebo + SSRI	HAM-D17	The treated group had a greater response versus the comparator group

Same outcome measure

HAMD-17

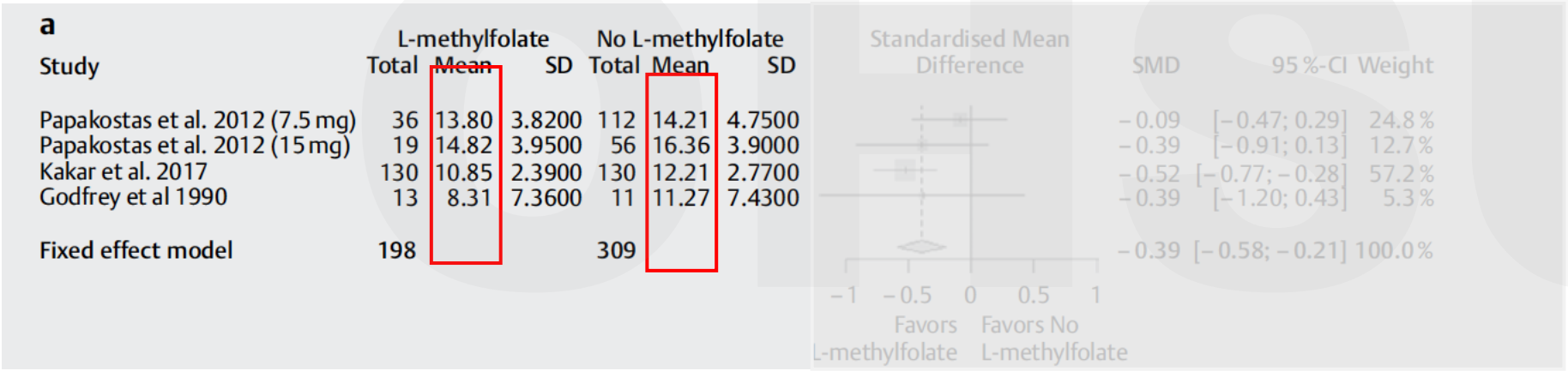
- The Hamilton Rating Scale for Depression (HAMD-17) has been used for several decades to assess the severity of depression
- It is an observer-rated scale
- Assesses presence/severity of 17 depression symptoms
- Score 0-52, higher scores indicate greater severity of depression
  - 0–7: No depression
  - 8–16: Mild depression
  - 17–23: Moderate depression
  - 24 and above: Severe depression

average HAMD score was about 19 on trial entry (mild to moderate)

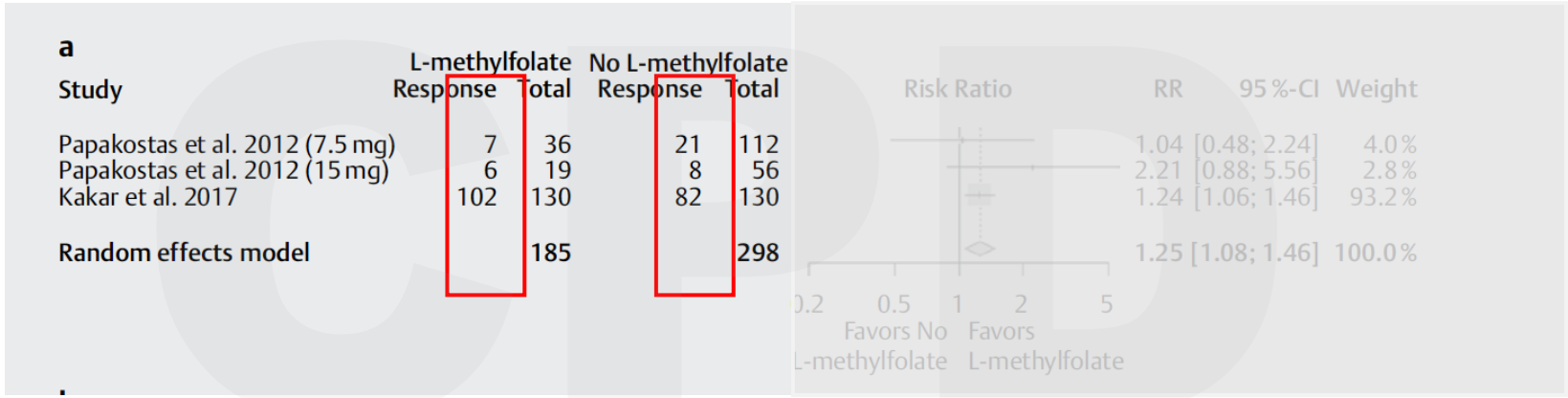
Characteristics of the studies

Study (First Author, Year)	Sample Size	Subject Characteristics (Age in years, Women %)	Study Design	Treatment	Treatment Duration	Comparator	Primary Outcome Measurement	Result
* Godfrey, 1990	24 (patients with depression)	45.5, 54 %	Double-blinded, randomized controlled trial	L-methylfolate 15 mg + psychotropic medication	6 months	Placebo + psychotropic medication	HAM-D17	The treated group trended towards having a greater reduction in HAM-D versus the comparator
* Kakar, 2017	260	36.9, 53.5 %	Double-blinded, randomized controlled trial	L-methylfolate 15 mg + escitalopram	30 days	Placebo + escitalopram	HAM-D17	Response in the treated was better than the comparator
* Papakostas (Trial 1), 2012	148	47.9, 69.5 %	Double-blinded, randomized controlled trial	L-methylfolate 7.5/15 mg + SSRI	60 days	Placebo + SSRI	HAM-D17	No difference in response between treated and comparator groups
* Papakostas (Trial 2), 2012	75	48.4, 70.6 %	Double-blinded, randomized controlled trial	L-methylfolate 15 mg + SSRI	60 days	Placebo + SSRI	HAM-D17	The treated group had a greater response versus the comparator group

Results



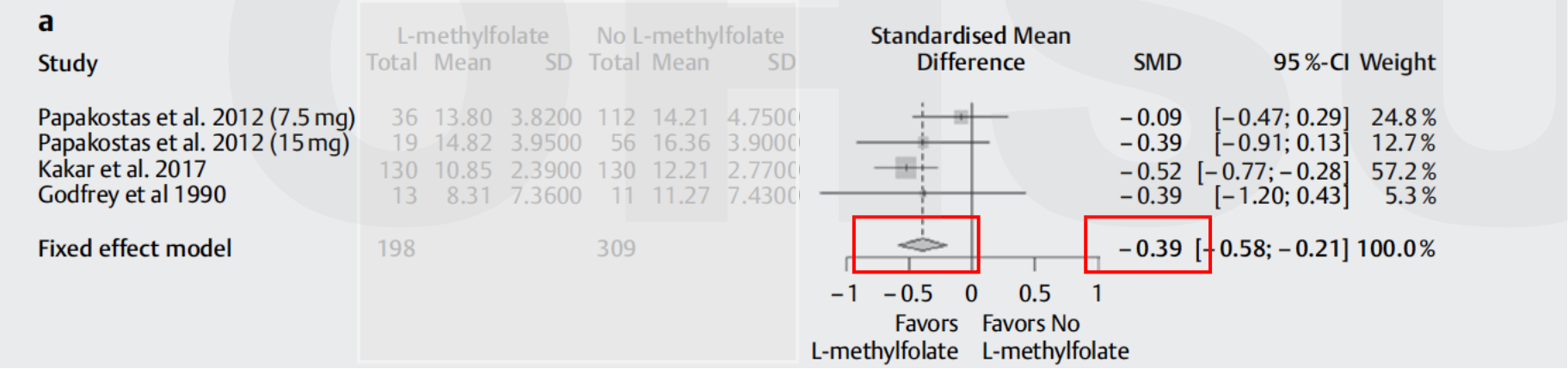
HAM-D17 scores at trial endpoint



Response versus no response (50% reduction)

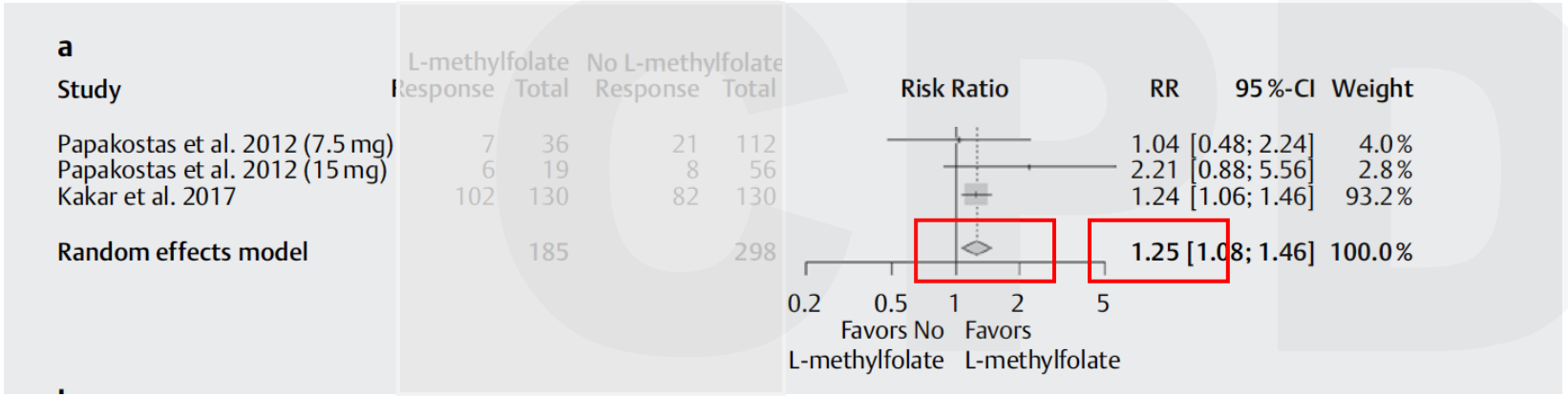
Results

the mean effect size of modern antidepressants in clinical trials is around 0.3, corresponding to approximately 10% reduction in symptoms



Relative size	Effect size
	0.0
Small	0.2
Medium	0.5
Large	0.8
	1.4

This diamond shows the combined average: effect size (magnitude of L-MTHF's effect)



25% greater likelihood of response in the treatment groups

This diamond shows the combined average: likelihood of response

Results

Favor the use of l-methylfolate as an adjunct to antidepressant therapy

Caveats

- One large study, 3 small studies
- Homogenous population
- Mild to moderate baseline depression symptoms
- No assessment of tolerability

My Take

It is reasonable to consider 15mg l-methylfolate for the treatment of *mild to moderate* depression in persons already taking an antidepressant if they are interested in *natural* treatment alternatives to psychotropic medications

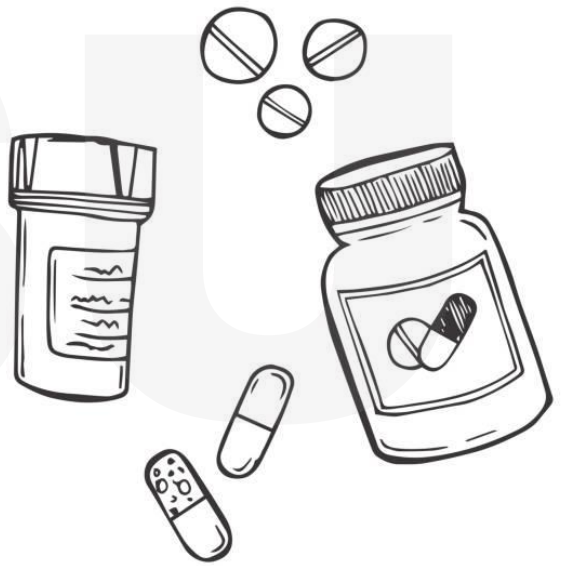
Case 2

- 84-year old patient with moderate stage Alzheimer's disease is seen in clinic for behavior change
- The caregiver says they have been "agitated" and is inquiring about a medication that might help
- She is not on any other medications for dementia related neuropsychiatric symptoms

- **<u>Question</u>: Should I prescribe brexpiprazole (Rexulti) because it was FDA approved for agitation in dementia last year?**

Brexpiprazole

- A newer atypical antipsychotic
- Partial agonist at 5HT1A and dopamine receptors (like aripiprazole), antagonist at 5HT2A and alpha-1b receptors
- FDA approved for schizophrenia, MDD (adjunct), *agitation associated with dementia due to Alzheimer's disease*
  - *First medication to receive FDA approval for behavioral symptoms in dementia*



FDA approved based on two 12-week DBRCT comparing brexpip to placebo[1,2]

1. Am J Geriatr Psychiatry. 2020;28(4):383-400
2. JAMA Neurol. 2023;80(12):1307-1316

Study

- Design: double blind, randomized placebo-controlled trial
- Patients: 345 people with Alzheimer's dementia with agitation in a care facility or community-based setting
  - Exclusion: history of a major mental disorder (MDD, bipolar illness, or psychosis unrelated to dementia) and those receiving treatment with antipsychotics, mood stabilizers, or anticonvulsants
- Intervention: placebo, brexpiprazole 2mg or brexpiprazole 3mg for 12 weeks
- Main outcome: change in Cohen-Mansfield Agitation Inventory (29-item behavior rating scale)

JAMA Neurol. 2023;80(12):1307-1316

Study

- Cohen Mansfield Agitation Inventory
  - 29 items, 4 domains: physical aggression, physical non-aggression, verbal aggression, verbal non-aggression
  - Score 1-7 based on frequency of symptoms
    - Never to several times per hour
  - 29-203 (higher scores suggest more severe symptoms)
  - Change of -17 is felt to be clinically meaningful[1]

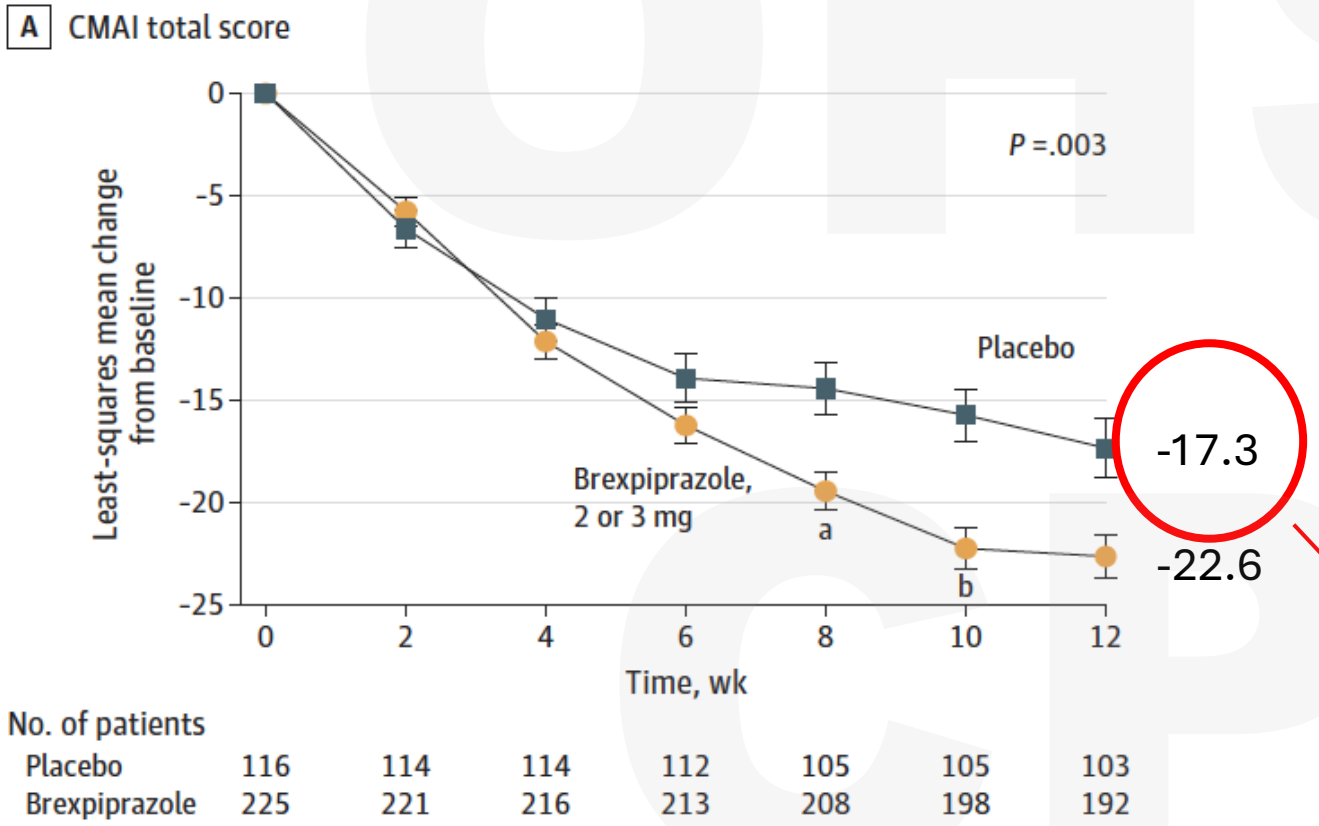
1. De Mauleon A, et al. Agitation in Alzheimer's disease: Novel outcome measures reflecting the International Psychogeriatric Association (IPA) agitation criteria. Alzheimers Dement 2021;17:-97.

Patient Characteristics

Table 1. Baseline Demographic and Clinical Characteristics (Randomized Sample)

Characteristic	Placebo (n = 117), No. (%)[a]	Brexpiprazole, No. (%)[a] 2 or 3 mg (n = 228)	2-mg Subgroup (n = 75)	3-mg Subgroup (n = 153)
Demographic				
Age, mean (SD), y	73.0 (7.0)	74.5 (7.7)	74.3 (7.3)	74.6 (8.0)
Sex				
Female	60 (51.3)	135 (59.2)	43 (57.3)	92 (60.1)
Male	57 (48.7)	93 (40.8)	32 (42.7)	61 (39.9)
Race				
Asian	1 (0.9)	3 (1.3)	0	3 (2.0)
Black or African American	1 (0.9)	11 (4.8)	5 (6.7)	6 (3.9)
White	115 (98.3)	214 (93.9)	70 (93.3)	144 (94.1)
MMSE score, mean (SD)	15.5 (3.9)	15.6 (3.7)	15.8 (3.2)	15.5 (3.9)
Psychosis (≥4 NPI delusion/hallucination symptoms)	21 (17.9)	44 (19.3)	14 (18.7)	30 (19.6)
CMAI total score, mean (SD)	79.4 (17.6)	80.4 (16.7)	78.6 (15.5)	81.2 (17.2)
Living situation				
Care facility	54 (46.2)	96 (42.1)	32 (42.7)	64 (41.8)
Community-based setting	63 (53.8)	132 (57.9)	43 (57.3)	89 (58.2)

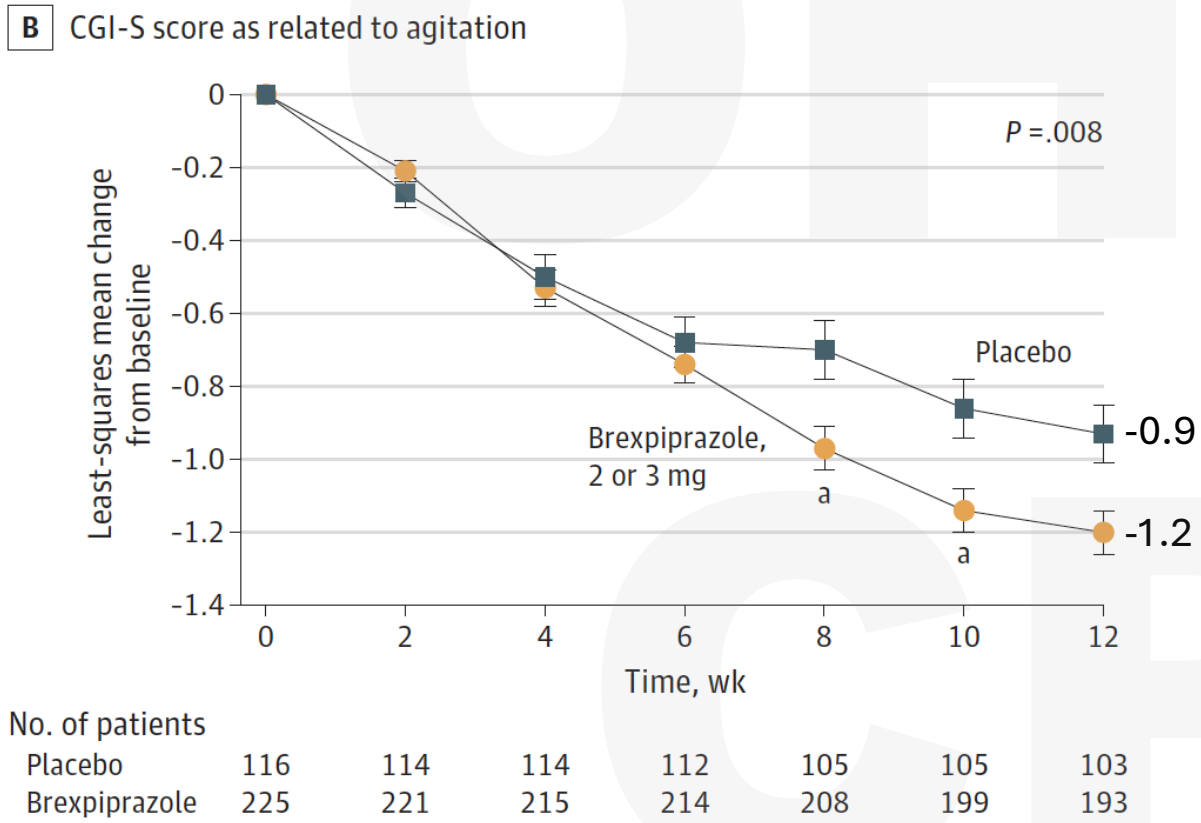
Results



- Treatment arm demonstrated a statistically significant improvement compared to placebo (difference of 5.32)
- Effect size 0.35, on par with other antipsychotics
- Improvement in physical aggression, and non-aggressive agitation

Placebo group improved too

Results



- Clinical Global Impression – Severity scale
  - 7-point scale that requires the clinician to rate the severity of the patient's illness at the time of assessment

    … change of one point is felt to be clinically meaningful
- Treatment showed a change from baseline greater than placebo
- Effect size = 0.31

Results

End point	Treatment group	No. of patients	Baseline, mean (SD)	At week 12, change from baseline, LS mean (SE), or No. (%) response rate	Treatment difference at week 12 vs placebo		
					LS mean difference or ratio of response rate (95% CI)	*P* value	Cohen *d* effect size
Primary end point							
CMAI total score[a]	Brexpiprazole 2 or 3 mg	225	80.6 (16.6)	−22.6 (1.1)	Difference, −5.32 (−8.77 to −1.87)	.003	0.35
	Placebo	116	79.2 (17.5)	−17.3 (1.4)			
Secondary end points: response rate and ratio[b]							
CMAI response rate[c]							
≥20% Improvement	Brexpiprazole 2 or 3 mg	225	NA	154 (68.4)	Ratio, 1.41 (1.15 to 1.72)[f]	<.001	NA
	Placebo	116	NA	55 (47.4)			
≥30% Improvement	Brexpiprazole 2 or 3 mg	225	NA	96 (42.7)	Ratio, 1.62 (1.18 to 2.23)[f]	.002	NA
	Placebo	116	NA	30 (25.9)			
≥40% Improvement	Brexpiprazole 2 or 3 mg	225	NA	52 (23.1)	Ratio, 1.62 (1.00 to 2.61)[f]	.03	NA
	Placebo	116	NA	17 (14.7)			

Tolerability

- High rate of completion
  - 86.8% of the brexpiprazole group
  - 88.9% of the placebo group
- Incidence of treatment related adverse events
  - 40.7% with brexpiprazole
  - 31.0% with placebo
- Rate of discontinuation due to adverse events
  - 5.3% with brexpiprazole
  - 4.3% with placebo

- The most common adverse events were somnolence, dizziness, asthenia, UTI

- 1 death in a patient with cachexia and pneumonia, thought to be unrelated to brexpiprazole

Tolerability

- All antipsychotics increase the risk of mortality in persons with dementia
- In 2005, FDA conducted a meta-analysis to systematically assess the available data to estimate the mortality risk
- Databased included 17 randomized, placebo-controlled trials evaluating six different antipsychotics in elderly subjects with dementia (5,377 patients; 3,611 drug, 1,766 placebo)
  - Over the course of a typical 10-week trial, the incidence of death was 4.5% in the antipsychotic arm vs. 2.6% in the placebo arm

- **Brexpiprazole follows a similar trend with the mortality risk estimated for other antipsychotics**

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS and SUICIDAL THOUGHTS AND BEHAVIORS

See full prescribing information for complete boxed warning.

- **Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at increased risk of death. REXULTI is not approved for the treatment of patients with dementia-related psychosis without agitation associated with dementia due to Alzheimer's disease. (5.1)**
- **Antidepressants increased the risk of suicidal thoughts and behaviors in patients aged 24 years and younger. Monitor for clinical worsening and emergence of suicidal thoughts and behaviors. Safety and effectiveness of REXULTI have not been established in pediatric patients with MDD. (5.2, 8.4)**

Results

Brexpiprazole (2 or 3mg) shows benefit over placebo for treatment of disruptive behavior due to Alzheimer's disease

The improvement is small (effect size 0.35) but both clinically and statistically significant

Brexpiprazole is generally well tolerated

Caveats

- Homogeneous patient population (mostly Caucasian)
- Most patients received one or more symptomatic treatments for AD (donepezil, rivastigmine, or memantine), suggesting brexpiprazole as adjunctive therapy (as opposed to monotherapy) for agitation
- Excluded persons with a h/o a major mental disorder
- Strong placebo effect (only a 5-point difference between placebo and treatment arms … clinically significant?)
- Industry sponsored

My Take

- The improvement with brexpiprazole is similar to clinical trials for other antipsychotic medications that were not FDA approved (suggesting a “class” effect)[1]
- Brexiprazole costs about $1,400 / month
- There are effective safer alternatives to antipsychotics for dementia related “agitation”

- Consider antidepressants (SRIs, trazodone, mirtazapine) for non-psychotic and non-aggressive behavior
- Consider less expensive antipsychotic for psychotic or aggressive behavior

1. Am J Geriatr Psychiatry2006;14:191-210

Case 3

- 32-year old presents to clinic with symptoms consistent with a depressive episode
- They are interested in starting treatment with an antidepressant but are very concerned about gaining weight

- **Question: Which antidepressant(s) are associated with the lowest risk of weight gain?**

Weight gain

- 31% of US adults are overweight (NIH)
- People with MDD are more likely to be overweight than those without
- Weight gain is a common side effect of antidepressant medications
  - Metabolic health, compliance, self-esteem, etc.
- Antidepressants are commonly prescribed
  - Between 2015-2018, 13% of adults reported taking an antidepressant in the past 30 days[1]
- Most studies have looked at differences between antidepressant class rather than in-class differences

1. NCHS Data Brief, No. 377, September 2020

Study

Annals of Internal Medicine

ORIGINAL RESEARCH

Medication-Induced Weight Change Across Common Antidepressant Treatments

- Design: Observational cohort study over 24 months
- Setting: EMR data from 2010-2019 in the US
- Participants:183,118 patients, ages 20-80, starting treatment with sertraline, citalopram, escitalopram, fluoxetine, paroxetine, bupropion, duloxetine, or venlafaxine

- Outcome measurements:
  - The effects of initiating each antidepressant on mean weight change at 6, 12, and 24 months after treatment initiation

Ann Intern Med. 2024;177:993-1003.

Patient characteristics

Table 2. Baseline Characteristics of the Study Population

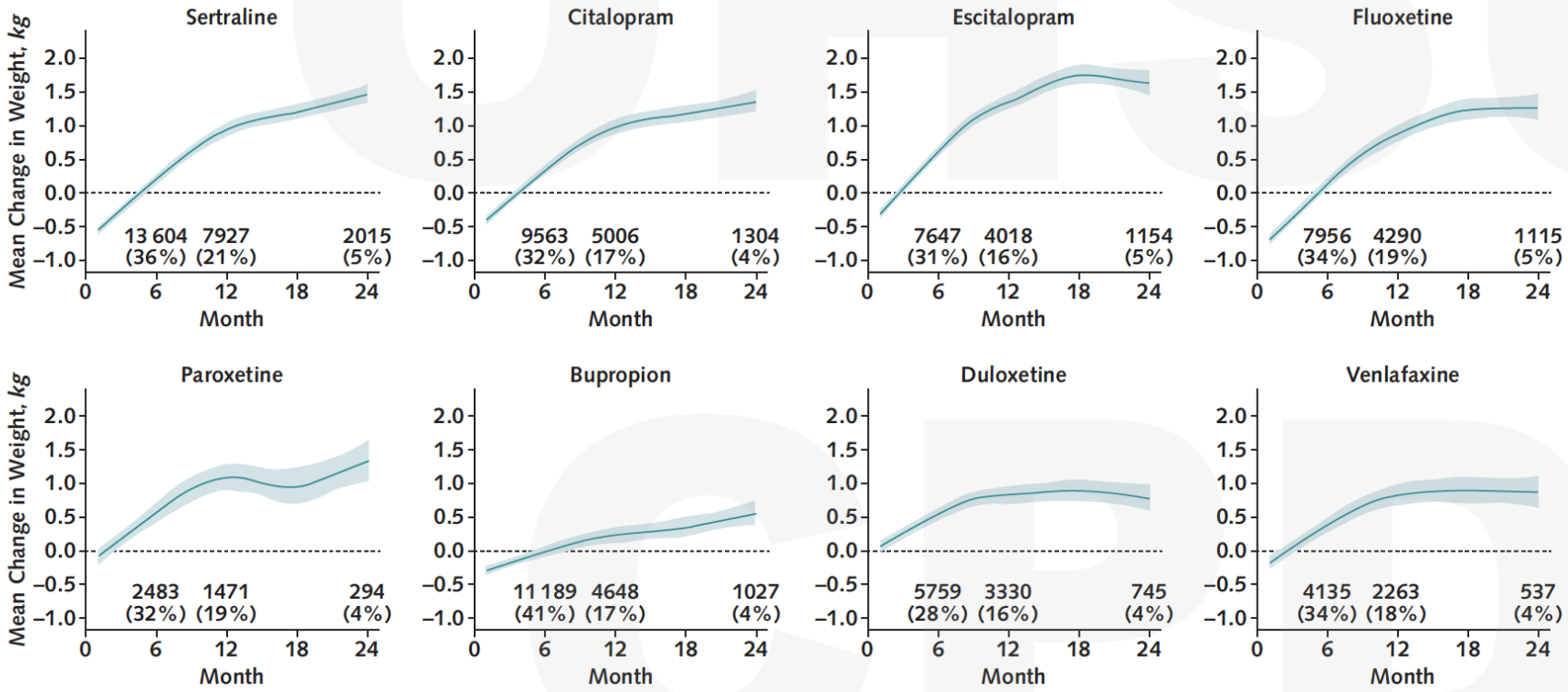
Characteristic	Overall (*n* = 183 118)	Sertraline (*n* = 37 351)	Citalopram (*n* = 30 184)	Escitalopram (*n* = 24 993)	Fluoxetine (*n* = 23 169)	Paroxetine (*n* = 7675)	Bupropion (*n* = 27 054)	Duloxetine (*n* = 20 435)	Venlafaxine (*n* = 12 257)
Mean age (SD), y	48.2 (15.7)	46.8 (16.7)	48.0 (16.1)	46.2 (16.1)	46.0 (15.9)	50.9 (14.8)	47.6 (14.1)	54.3 (14.1)	50.2 (14.1)
Sex, %									
Male	35	36	35	33	32	34	42	34	24
Female	65	64	65	67	68	66	58	66	76
Race, %									
Asian American/ Pacific Islander	2	2	2	2	2	1	2	1	1
Black/African American	15	16	12	14	12	17	14	19	13
White	79	77	80	81	80	77	80	76	81
Other or >1 race	5	5	5	4	6	5	4	4	5
Overweight/obesity status, %									
Overweight	30	30	30	29	29	31	30	28	30
Obesity	40	37	36	37	38	39	43	49	42
Diagnoses, %									
Depression	36	39	43	33	47	28	32	23	32
Anxiety	39	47	47	48	41	41	22	22	33
Neuropathic pain	16	12	13	11	12	14	13	40	19
Mental health disorder	2	3	2	2	3	2	2	2	2
Obsessive compulsive disorder	1	1	<1	<1	1	1	<1	<1	<1

Results

- Very low adherence: 1 in 3 still taking initially prescribed medication at 6 months
  - The percentage of patients who remained adherent:
    - 28% to 41% at 6 months
    - 16% to 21% at 12 months
    - 4% to 5% at 24 months

Results – Absolute Weight Change

Figure. Associations of antidepressant treatment initiation with weight change over 24 mo.



The figure shows adjusted population-level estimates of average weight change (*dark green line*) and 95% CIs from 1000 bootstrapped samples (*light green bands*) for initiating each of the 8 antidepressant treatments over 24 mo from initiation. The null (0 kg mean weight change) is depicted with a dashed horizontal line. The curves begin at month 1 because the model estimates effects on weight change only after baseline. Numbers (percentages) within each graph at the 6-, 12-, and 24-month marks are numbers of adherent participants (percentage of total) at each time point.

Treatment	6 months
Sertraline	0.21 (0.14, 0.28)
Citalopram	0.33 (0.27, 0.41)
Escitalopram	0.63 (0.55, 0.71)
Fluoxetine	0.14 (0.06, 0.23)
Paroxetine	0.58 (0.43, 0.73)
Bupropion	-0.01 (-0.09, 0.07)
Duloxetine	0.55 (0.45, 0.64)
Venlafaxine	0.34 (0.28, 0.50)

(x 2.2 to convert to lb)

- Absolute weight change
- Weight increased in all 8 treatment groups

Results – Mean Weight Change

Table 4. Weight Change Difference and Relative Risk for Gaining ≥5% of Baseline Weight at 6, 12, and 24 Months After Initiating Antidepressant Treatment Compared With Sertraline: Intention-to-Treat Analysis*

Treatment	6 Months	12 Months	24 Months
Mean weight change (95% CI), kg			
Sertraline	0.00 (Reference)	0.00 (Reference)	0.00 (Reference)
Citalopram	0.12 (0.02 to 0.23)	0.03 (−0.12 to 0.19)	−0.11 (−0.33 to 0.11)
Escitalopram	0.41 (0.31 to 0.52)	0.41 (0.25 to 0.56)	0.16 (−0.08 to 0.40)
Fluoxetine	−0.07 (−0.19 to 0.04)	−0.06 (−0.22 to 0.10)	−0.20 (−0.45 to 0.05)
Paroxetine	0.37 (0.20 to 0.54)	0.15 (−0.08 to 0.37)	−0.14 (−0.46 to 0.21)
Bupropion	−0.22 (−0.33 to −0.12)	−0.71 (−0.87 to −0.55)	−0.91 (−1.14 to −0.66)
Duloxetine	0.34 (0.22 to 0.44)	−0.11 (−0.29 to 0.04)	−0.69 (−0.93 to −0.43)
Venlafaxine	0.17 (0.03 to 0.31)	−0.12 (−0.30 to 0.08)	−0.59 (−0.87 to −0.32)
Risk ratio for gaining ≥5% of baseline weight (95% CI)			
Sertraline	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Citalopram	1.01 (0.97 to 1.06)	1.02 (0.98 to 1.06)	1.00 (0.96 to 1.05)
Escitalopram	1.15 (1.10 to 1.20)	1.10 (1.06 to 1.15)	1.01 (0.96 to 1.06)
Fluoxetine	0.98 (0.93 to 1.03)	0.96 (0.92 to 1.01)	0.96 (0.92 to 1.01)
Paroxetine	1.14 (1.06 to 1.22)	1.03 (0.95 to 1.09)	0.96 (0.90 to 1.03)
Bupropion	0.85 (0.81 to 0.89)	0.78 (0.75 to 0.82)	0.86 (0.81 to 0.90)
Duloxetine	1.10 (1.04 to 1.15)	1.00 (0.95 to 1.04)	0.92 (0.87 to 0.97)
Venlafaxine	1.02 (0.96 to 1.08)	0.95 (0.89 to 1.00)	0.90 (0.85 to 0.96)

- Compared to sertraline, 6-month weight gain was higher for escitalopram, paroxetine, duloxetine, venlafaxine, and citalopram
- Fluoxetine showed a similar weight change to sertraline
- Bupropion was associated with weight loss

Results – Risk of Gaining > 5%

Table 4. Weight Change Difference and Relative Risk for Gaining ≥5% of Baseline Weight at 6, 12, and 24 Months After Initiating Antidepressant Treatment Compared With Sertraline: Intention-to-Treat Analysis*

Treatment	6 Months	12 Months	24 Months
Mean weight change (95% CI), *kg*			
Sertraline	0.00 (Reference)	0.00 (Reference)	0.00 (Reference)
Citalopram	0.12 (0.02 to 0.23)	0.03 (−0.12 to 0.19)	−0.11 (−0.33 to 0.11)
Escitalopram	0.41 (0.31 to 0.52)	0.41 (0.25 to 0.56)	0.16 (−0.08 to 0.40)
Fluoxetine	−0.07 (−0.19 to 0.04)	−0.06 (−0.22 to 0.10)	−0.20 (−0.45 to 0.05)
Paroxetine	0.37 (0.20 to 0.54)	0.15 (−0.08 to 0.37)	−0.14 (−0.46 to 0.21)
Bupropion	−0.22 (−0.33 to −0.12)	−0.71 (−0.87 to −0.55)	−0.91 (−1.14 to −0.66)
Duloxetine	0.34 (0.22 to 0.44)	−0.11 (−0.29 to 0.04)	−0.69 (−0.93 to −0.43)
Venlafaxine	0.17 (0.03 to 0.31)	−0.12 (−0.30 to 0.08)	−0.59 (−0.87 to −0.32)
Risk ratio for gaining ≥5% of baseline weight (95% CI)			
Sertraline	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Citalopram	1.01 (0.97 to 1.06)	1.02 (0.98 to 1.06)	1.00 (0.96 to 1.05)
Escitalopram	1.15 (1.10 to 1.20)	1.10 (1.06 to 1.15)	1.01 (0.96 to 1.06)
Fluoxetine	0.98 (0.93 to 1.03)	0.96 (0.92 to 1.01)	0.96 (0.92 to 1.01)
Paroxetine	1.14 (1.06 to 1.22)	1.03 (0.95 to 1.09)	0.96 (0.90 to 1.03)
Bupropion	0.85 (0.81 to 0.89)	0.78 (0.75 to 0.82)	0.86 (0.81 to 0.90)
Duloxetine	1.10 (1.04 to 1.15)	1.00 (0.95 to 1.04)	0.92 (0.87 to 0.97)
Venlafaxine	1.02 (0.96 to 1.08)	0.95 (0.89 to 1.00)	0.90 (0.85 to 0.96)

- Escitalopram, paroxetine, and duloxetine were associated with a 10-15% higher risk of gaining at least 5% of baseline weight
- Bupropion was associated with a 15% reduced risk

Results

Despite several study limitations (most notably low adherence, particularly at 12 and 24 months) the study found differences in weight change between the different antidepressants

Weight gain is more significant with escitalopram, duloxetine, and paroxetine than with sertraline, fluoxetine, citalopram, and venlafaxine

Bupropion is the least likely to cause weight gain

My Take

- Small differences in mean weight change were found between eight first-line antidepressants, with bupropion consistently showing the least weight gain

- Weight gain is important to consider
- For a patient with MDD who is concerned about weight gain, bupropion would be a reasonable first line choice
- For a person with a primary anxiety disorder, or depression with anxiety, bupropion may worsen anxiety
    - Would consider fluoxetine or sertraline first OR provide psychoeducation about weight gain before starting other SSRIs or SNRIs

Case 4

- You look ahead at your schedule and see your first patient of the afternoon is requesting to be evaluated and treated for ADHD
- They are a 24-year old college graduate
- They also have a history of problematic alcohol use, so you are reluctant to prescribe a stimulant without some type of diagnostic workup
- You think about using an ADHD rating scale but ask yourself,

- **Question: Can I rely on scales alone to diagnose ADHD?**

ADHD

- ADHD is common among school-aged children, with a prevalence of 11.3%[1]
- About 50% of people no longer meet criteria for ADHD as adults[2]
  - Prevalence of about 6% in adults[3]
- We are seeing increasing numbers of adults seeking out (and being given) first time ADHD diagnoses

1. NCHS Data Brief No. 499, March 2024
2. Caye, A., et al Current Psychiatry Reports, 2016, 18(12)
3. MMWR Morbidity and Mortality Weekly Report 73, no. 40 (October 10, 2024): 890-895.

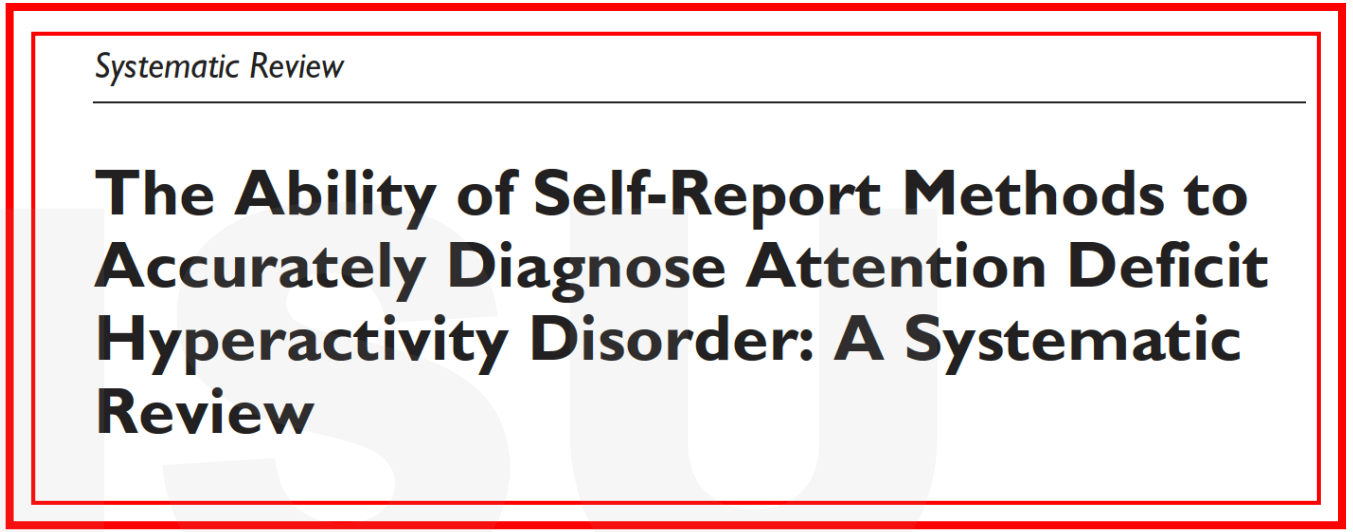
ADHD

- More challenging to diagnose ADHD in adults
- Limited access to academic records, parents, teachers, etc.
- Adult recall of childhood symptoms is unreliable[1]
- Adults often experience symptom that overlap with ADHD that are due to normal fluctuations in cognitive abilities, comorbid disorders, or the cognitive effects of substance use

- Lots of clinicians rely mainly on self-reported symptoms (often gathered via self-report questionnaires) when diagnosing adults with ADHD

1. Psychological Medicine, 50(5), 857–866.

Study



- Design: Systematic review

- Objective: To identify and analyze all studies of screening instruments commonly used to evaluate ADHD in adults from 1998-2022 (20 in total)
  - Studies that provided diagnostic accuracy statistics, specifically sensitivity and specificity and predictive values

Journal of Attention Disorders 2023, Vol. 27(12) 1343–1359

Study

- Method: A systematic literature search using the MEDLINE, PsycARTICLES, and PsycINFO databases

- Method: Analyzed the data to assess the diagnostic accuracy of various screening measures
  - … their ability to classify individuals correctly as having or not having ADHD via sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV)

Results

Predictive Values at Two Base Rates of ADHD comparing individual with ADHD and *normal controls*

Test	Reference	Sample	# Scale items used	Cut score used	Sensitivity	Specificity	Estimated rate of ADHD 5% PPV	5% NPV	10% PPV	10% NPV
ASRS	Brevik et al. 2020	646 ADHD (34y) vs. 908 controls (28y)	18 (A+B)	Total >= 16	98	22	6	100	12	99
BAARS-IV	Dvorsky et al. 2016	59 ADHD diagnosed using CAADID interview (20y) 27 without ADHD (21y)	9 items	3+ symptoms endorsed as often or very often on current Inattentive Subscale	89	30	6	98	12	96
BADDS	Brown 1996	143 controls, 142 High IQ ADHD adults (18-44y)	40	T>=50 on Total score	96	89	31	100	49	100
WURS-25	McCann et al. 2000	68 ADHD (34y) and 73 non ADHD (38y)	25	>=46	72	58	8	98	16	95

Predictive Values at Two Base Rates of ADHD comparing individual with ADHD and *Treatment seeking*/*Clinical samples*

13 total studies

Test	Reference	Sample	# Scale items used	Cut score used	Sensitivity	Specificity	Estimated rate of ADHD 5% PPV	5% NPV	10% PPV	10% NPV
ASRS	Pettersson et al. 2018	60 ADHD patients (28y), 48 Tx seeking controls (33y)	6 (Part A)	Total score >=14	92	27	6	98	12	97
CAARS-S:L	Luty et al. 2009	37 ADHD, 59 Non ADHD (38y) getting Tx for substance abuse	66	Cut score 91+ out of maximum of 198	97	83	60	41	57	44
CAARS-S:L	VanVoorhees et al. 2011	184 ADHD, 85 other or no dx	66	ADHD Index >=65 DSM-IV ADHD Symptom >= 65	91	27	6	98	12	96
WURS-25	Ward et al. 1993	81 ADHD, 70 patients with depression	25/61	>=46	86	81	19	99	33	98

Results

Predictive Values at Two Base Rates of ADHD comparing individual with ADHD and *normal controls*

Test	Reference	Sample	# Scale items used	Cut score used	Sensitivity	Specificity	Estimated rate of ADHD 5% PPV	5% NPV	10% PPV	10% NPV
ASRS	Brevik et al. 2020	646 ADHD (34y) vs. 908 controls (28y)	18 (A+B)	Total >= 16	98	22	6	100	12	99
BAARS-IV	Dvorsky et al. 2016	59 ADHD diagnosed using CAADID interview (20y) 27 without ADHD (21y)	9 items	3+ symptoms endorsed as often or very often on current Inattentive Subscale	89	30	6	98	12	96
BADDS	Brown 1996	143 controls, 142 High IQ ADHD adults (18-44y)	40	T>=50 on Total score	96	89	31	100	49	100
WURS-25	McCann et al. 2000	68 ADHD (34y) and 73 non ADHD (38y)	25	>=46	72	58	8	98	16	95

Predictive Values at Two Base Rates of ADHD comparing individual with ADHD and *Treatment seeking/Clinical samples*

Test	Reference	Sample	# Scale items used	Cut score used	Sensitivity	Specificity	Estimated rate of ADHD 5% PPV	5% NPV	10% PPV	10% NPV
ASRS	Pettersson et al. 2018	60 ADHD patients (28y), 48 Tx seeking controls (33y)	6 (Part A)	Total score >=14	92	27	6	98	12	97
CAARS-S:L	Luty et al. 2009	37 ADHD, 59 Non ADHD (38y) getting Tx for substance abuse	66	Cut score 91+ out of maximum of 198	97	83	60	41	57	44
CAARS-S:L	VanVoorhees et al. 2011	184 ADHD, 85 other or no dx	66	ADHD Index >=65 DSM-IV ADHD Symptom >= 65	91	27	6	98	12	96
WURS-25	Ward et al. 1993	81 ADHD, 70 patients with depression	25/61	>=46	86	81	19	99	33	98

Average: 79%

Results

Predictive Values at Two Base Rates of ADHD comparing individual with ADHD and *normal controls*

Test	Reference	Sample	# Scale items used	Cut score used	Sensitivity	Specificity	Estimated rate of ADHD 5% PPV	5% NPV	10% PPV	10% NPV
ASRS	Brevik et al. 2020	646 ADHD (34y) vs. 908 controls (28y)	18 (A+B)	Total >= 16	98	22	6	100	12	99
BAARS-IV	Dvorsky et al. 2016	59 ADHD diagnosed using CAADID interview (20y) 27 without ADHD (21y)	9 items	3+ symptoms endorsed as often or very often on current Inattentive Subscale	89	30	6	98	12	96
BADDS	Brown 1996	143 controls, 142 High IQ ADHD adults (18-44y)	40	T>=50 on Total score	96	89	31	100	49	100
WURS-25	McCann et al. 2000	68 ADHD (34y) and 73 non ADHD (38y)	25	>=46	72	58	8	98	16	95

Predictive Values at Two Base Rates of ADHD comparing individual with ADHD and *Treatment seeking/Clinical samples*

Test	Reference	Sample	# Scale items used	Cut score used	Sensitivity	Specificity	Estimated rate of ADHD 5% PPV	5% NPV	10% PPV	10% NPV
ASRS	Pettersson et al. 2018	60 ADHD patients (28y), 48 Tx seeking controls (33y)	6 (Part A)	Total score >=14	92	27	6	98	12	97
CAARS-S:L	Luty et al. 2009	37 ADHD, 59 Non ADHD (38y) getting Tx for substance abuse	66	Cut score 91+ out of maximum of 198	97	83	60	41	57	44
CAARS-S:L	VanVoorhees et al. 2011	184 ADHD, 85 other or no dx	66	ADHD Index >=65 DSM-IV ADHD Symptom >= 65	91	27	6	98	12	96
WURS-25	Ward et al. 1993	81 ADHD, 70 patients with depression	25/61	>=46	86	81	19	99	33	98

Average: 61%

Results

Predictive Values at Two Base Rates of ADHD comparing individual with ADHD and *normal controls*

Test	Reference	Sample	# Scale items used	Cut score used	Sensitivity	Specificity	Estimated rate of ADHD 5% PPV	5% NPV	10% PPV	10% NPV
ASRS	Brevik et al. 2020	646 ADHD (34y) vs. 908 controls (28y)	18 (A+B)	Total >= 16	98	22	6	100	12	99
BAARS-IV	Dvorsky et al. 2016	59 ADHD diagnosed using CAADID interview (20y) 27 without ADHD (21y)	9 items	3+ symptoms endorsed as often or very often on current Inattentive Subscale	89	30	6	98	12	96
BADDS	Brown 1996	143 controls, 142 High IQ ADHD adults (18-44y)	40	T>=50 on Total score	96	89	31	100	49	100
WURS-25	McCann et al. 2000	68 ADHD (34y) and 73 non ADHD (38y)	25	>=46	72	58	8	98	16	95

Predictive Values at Two Base Rates of ADHD comparing individual with ADHD and *Treatment seeking/Clinical samples*

Test	Reference	Sample	# Scale items used	Cut score used	Sensitivity	Specificity	Estimated rate of ADHD 5% PPV	5% NPV	10% PPV	10% NPV
ASRS	Pettersson et al. 2018	60 ADHD patients (28y), 48 Tx seeking controls (33y)	6 (Part A)	Total score >=14	92	27	6	98	12	97
CAARS-S:L	Luty et al. 2009	37 ADHD, 59 Non ADHD (38y) getting Tx for substance abuse	66	Cut score 91+ out of maximum of 198	97	83	60	41	57	44
CAARS-S:L	VanVoorhees et al. 2011	184 ADHD, 85 other or no dx	66	ADHD Index >=65 DSM-IV ADHD Symptom >= 65	91	27	6	98	12	96
WURS-25	Ward et al. 1993	81 ADHD, 70 patients with depression	25/61	>=46	86	81	19	99	33	98

Average: 25%

Results

Predictive Values at Two Base Rates of ADHD comparing individual with ADHD and *normal controls*

Test	Reference	Sample	# Scale items used	Cut score used	Sensitivity	Specificity	Estimated rate of ADHD 5% PPV	5% NPV	10% PPV	10% NPV
ASRS	Brevik et al. 2020	646 ADHD (34y) vs. 908 controls (28y)	18 (A+B)	Total >= 16	98	22	6	100	12	99
BAARS-IV	Dvorsky et al. 2016	59 ADHD diagnosed using CAADID interview (20y) 27 without ADHD (21y)	9 items	3+ symptoms endorsed as often or very often on current Inattentive Subscale	89	30	6	98	12	96
BADDS	Brown 1996	143 controls, 142 High IQ ADHD adults (18-44y)	40	T>=50 on Total score	96	89	31	100	49	100
WURS-25	McCann et al. 2000	68 ADHD (34y) and 73 non ADHD (38y)	25	>=46	72	58	8	98	16	95

Predictive Values at Two Base Rates of ADHD comparing individual with ADHD and *Treatment seeking/Clinical samples*

Test	Reference	Sample	# Scale items used	Cut score used	Sensitivity	Specificity	Estimated rate of ADHD 5% PPV	5% NPV	10% PPV	10% NPV
ASRS	Pettersson et al. 2018	60 ADHD patients (28y), 48 Tx seeking controls (33y)	6 (Part A)	Total score >=14	92	27	6	98	12	97
CAARS-S:L	Luty et al. 2009	37 ADHD, 59 Non ADHD (38y) getting Tx for substance abuse	66	Cut score 91+ out of maximum of 198	97	83	60	41	57	44
CAARS-S:L	VanVoorhees et al. 2011	184 ADHD, 85 other or no dx	66	ADHD Index >=65 DSM-IV ADHD Symptom >= 65	91	27	6	98	12	96
WURS-25	Ward et al. 1993	81 ADHD, 70 patients with depression	25/61	>=46	86	81	19	99	33	98

Average: 89%

Results

Sensitive but not specific: Low false negative rates, but high false positive rates. Correctly identify people with ADHD, but also produce many false positives

Low Positive Predictive Values: Many people who screen positive for ADHD may not actually have the disorder.

High Negative Predictive Values: Screening measures have an excellent ability to correctly classify people who do not have ADHD. These methods are very reliable in *ruling out* ADHD when the test result is negative

My Take

- Don’t rely on rating scales for diagnosing ADHD
  - Patients seeking care often test positive
- Rating scales are screening instruments and need to be paired with a full clinical evaluation that considers childhood history and ruling out other causes of ADHD symptoms (including substance use)
- It can help to refer patients to psychologists or psychiatrists for assistance with diagnosis

Case 5

- Your last patient of the afternoon is a 45-year old with ADHD who is requesting a dose increase in methylphenidate
- He is currently on the maximum dose: 60mg divided TID

- **Question: Do the benefits of prescribing higher-than FDA recommended doses of stimulants outweigh the risks?**

ADHD

- There is variability in how individuals respond to stimulants
- We can’t predict the ideal max dose for our patients
  - So, we often start low and titrate slowly, trying to find the optimal dose
- There is no universal consensus on the maximum dose at which point the titration should stop

- Whether stimulant doses exceeding the FDA maximum limit is associated with positive risk benefit is unclear

ADHD

- Three classes of stimulants
  - Methylphenidate (Ritalin): dose max 60mg
  - Mixed amphetamine salts (Adderall): dose max 40mg
  - Dextroamphetamine (Dexedrine): dose max 40mg

amphetamines

Study

JAMA Psychiatry | Original Investigation

Treatment Outcomes With Licensed and Unlicensed Stimulant Doses for Adults With Attention-Deficit/Hyperactivity Disorder

A Systematic Review and Meta-Analysis

Luis C. Farhat, MD; José M. Flores, MD, PhD; Victor J. Avila-Quintero, MD; Guilherme V. Polanczyk, MD, PhD; Andrea Cipriani, MD, PhD; Toshi A. Furukawa, MD, PhD; Michael H. Bloch, MD, MS; Samuele Cortese, MD, PhD

- Design: Systematic review and meta-analysis of double-blinded randomized clinical trials of stimulants against placebo in adults with ADHD

- Objective: To investigate the impact of stimulant doses on treatment outcomes in adults with ADHD and to determine whether unlicensed doses are associated with positive risk benefits compared with FDA recommended doses

JAMA Psychiatry. 2024;81(2):157-166.

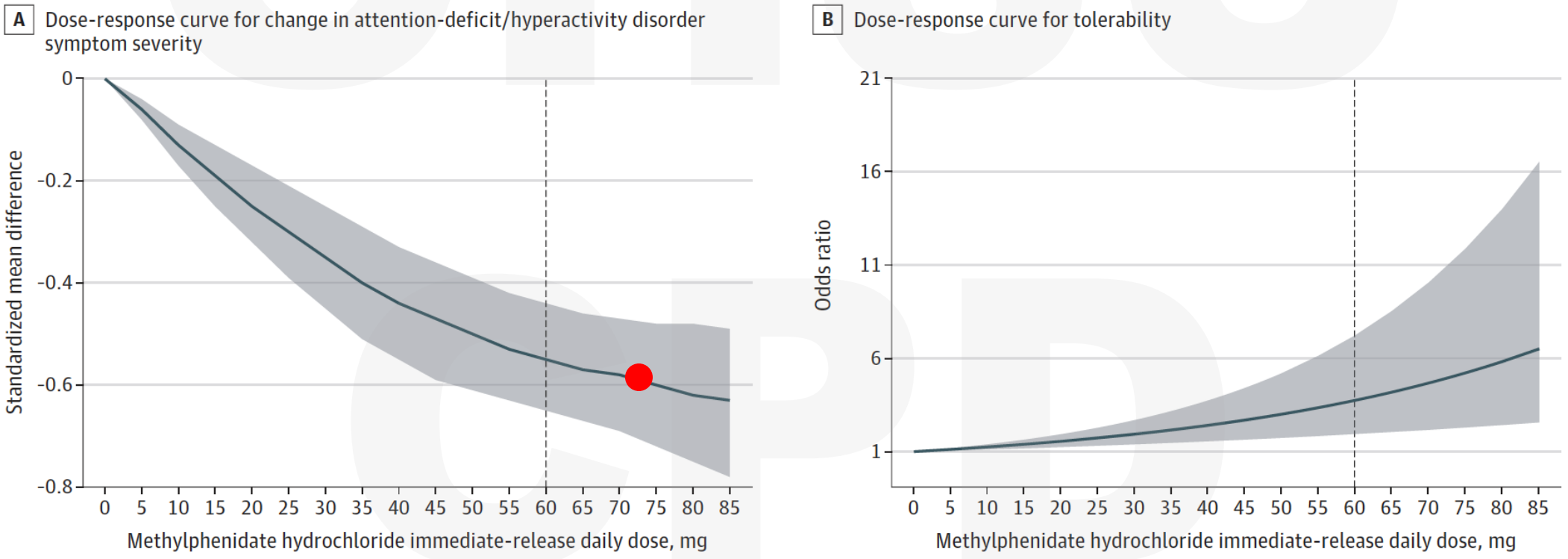
Study

- Method: 47 RCT (7,714 patients) were included in the study, and data were extracted and synthesized in a dose-response meta-analyses and network meta-analyses

- Outcome measures: change in ADHD symptoms and discontinuation due to adverse events (tolerability)
  - Methylphenidate
  - Amphetamines

Results

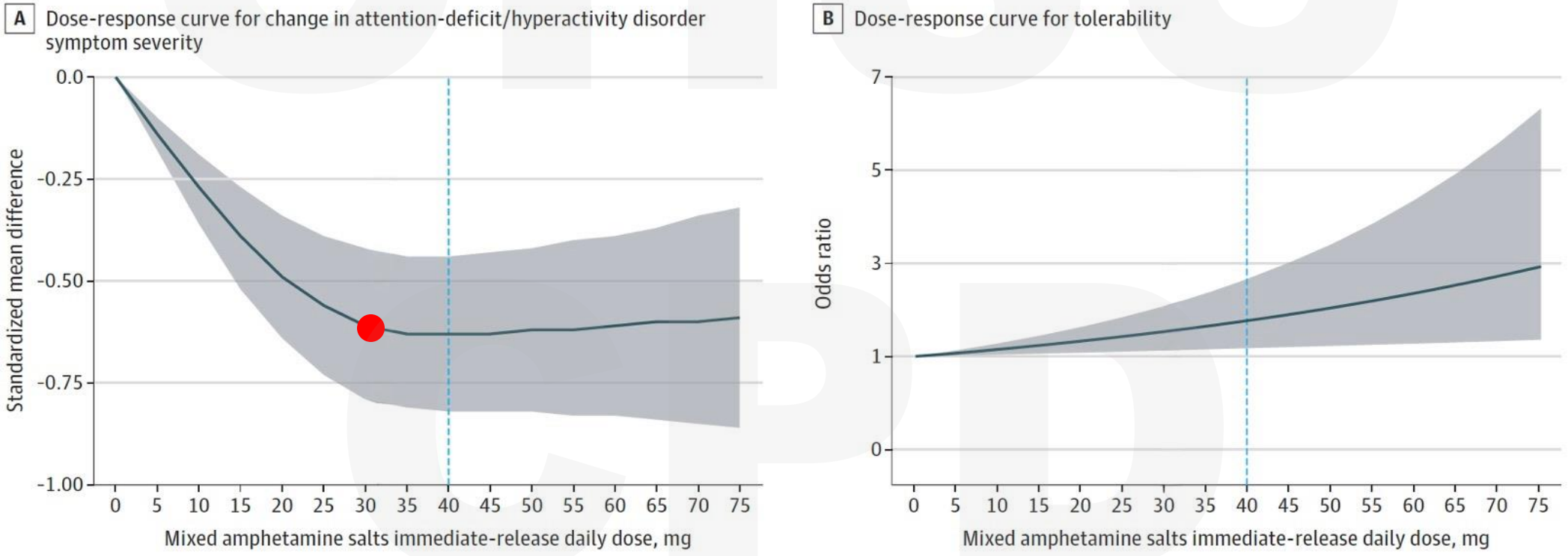
Figure 2. Dose-Response Curves for Methylphenidate



ED95 (mean dose associated with 95% symptom reduction): 72.5mg

Results

Figure 4. Dose-Response Curves for Amphetamine



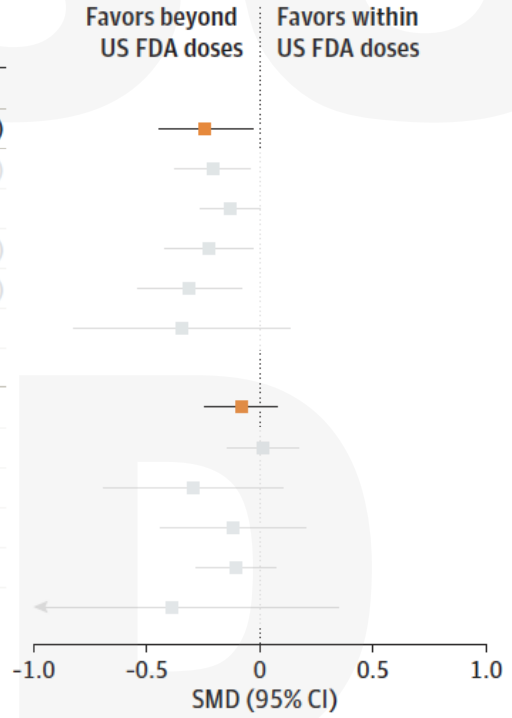
ED95 (mean dose associated with 95% symptom reduction): 30mg

Results – Efficacy Comparison

Figure 3. Network Estimates for Stimulant Doses Beyond US Food and Drug Administration (FDA) Recommendations Against Lower Doses Within FDA Recommendations

A Change in ADHD Symptoms

Source	SMD (95% CI)
Methylphenidate	
Main analysis	−0.23 (−0.44 to −0.02)
Excluding crossover RCTs	−0.21 (−0.37 to −0.04)
Excluding high risk of bias RCTs	−0.13 (−0.26 to 0.00)
Categorizing arms based on equivalent doses	−0.22 (−0.42 to −0.03)
Categorizing flexible-dose arms based on mean dose	−0.31 (−0.53 to −0.08)
Only flexible dose (beyond US FDA) vs fixed dose (within US FDA)	−0.34 (−0.82 to 0.13)
Amphetamine	
Main analysis	−0.08 (−0.24 to 0.08)
Excluding crossover RCTs	0.02 (−0.14 to 0.17)
Excluding high risk of bias RCTs	−0.29 (−0.69 to 0.10)
Categorizing arms based on equivalent doses	−0.11 (−0.44 to 0.21)
Categorizing flexible-dose arms based on mean dose	−0.10 (−0.27 to 0.07)
Only flexible dose (beyond US FDA) vs fixed dose (within US FDA)	−0.39 (−1.13 to 0.35)



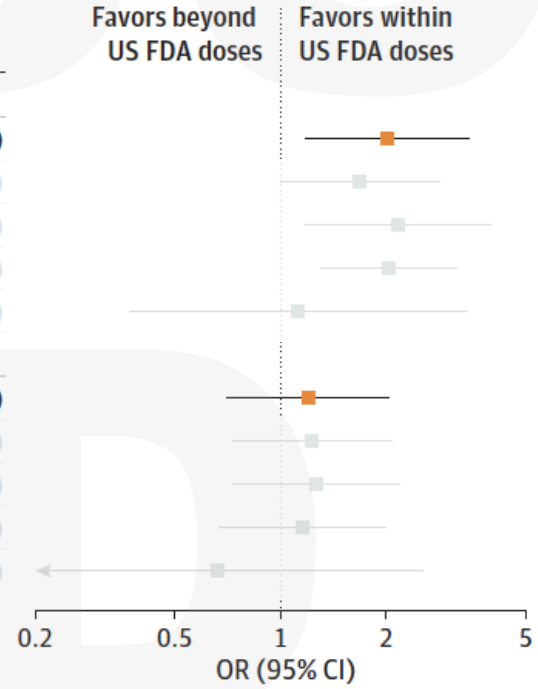
Standardized mean difference (SMD) for change in ADHD symptoms

Results – Tolerability Comparison

Figure 3. Network Estimates for Stimulant Doses Beyond US Food and Drug Administration (FDA) Recommendations Against Lower Doses Within FDA Recommendations

B Discontinuations due to adverse events

Source	OR (95% CI)
Methylphenidate	
Main analysis	2.02 (1.19-3.43)
Categorizing arms based on equivalent doses	1.68 (1.00-2.81)
Categorizing flexible-dose arms based on mean dose	2.16 (1.18-3.97)
Mantel-Haenszel fixed effects	2.03 (1.31-3.14)
Only flexible dose (beyond US FDA) vs fixed dose (within US FDA)	1.12 (0.37-3.38)
Amphetamine	
Main analysis	1.19 (0.71-2.02)
Categorizing arms based on equivalent doses	1.23 (0.73-2.06)
Categorizing flexible-dose arms based on mean dose	1.26 (0.73-2.17)
Mantel-Haenszel fixed effects	1.15 (0.67-1.97)
Only flexible dose (beyond US FDA) vs fixed dose (within US FDA)	0.66 (0.17-2.53)



Odds ratio for tolerability

Results

Higher doses of stimulants were generally associated with larger reductions of symptoms within the FDA approved range

For methylphenidate, higher than FDA approved doses were associated with greater reductions of symptoms in comparison with FDA approved doses…but the benefit was small and accompanied by increased risk of adverse effects

For amphetamines, higher than FDA approved doses were not associated with additional reductions of symptoms in comparison with FDA approved doses

My Take

- FDA approved doses are likely to be sufficient for most patients
- Tolerability of stimulants decreases with each dose increase

- Study results are based on averages, some adults may experience greater benefit and tolerability with higher than FDA approved doses than the average patient
  - It's reasonable to trial higher doses for *some* patients, but only cautiously, but this should not be a part of your routine practice

Case 6

- You are seeing a 21-year old in clinic who describes feeling depressed and anxious
- Their symptoms have been present for over a year
- You take a social history which includes inquiring about the number of hours spent on social media and they report on average 4 hours per day spent on Tik Tok, Facebook, and Instagram

- **Question: Can cutting back on social media help to improve mood and sense of wellbeing?**

Social Media and Mental Health

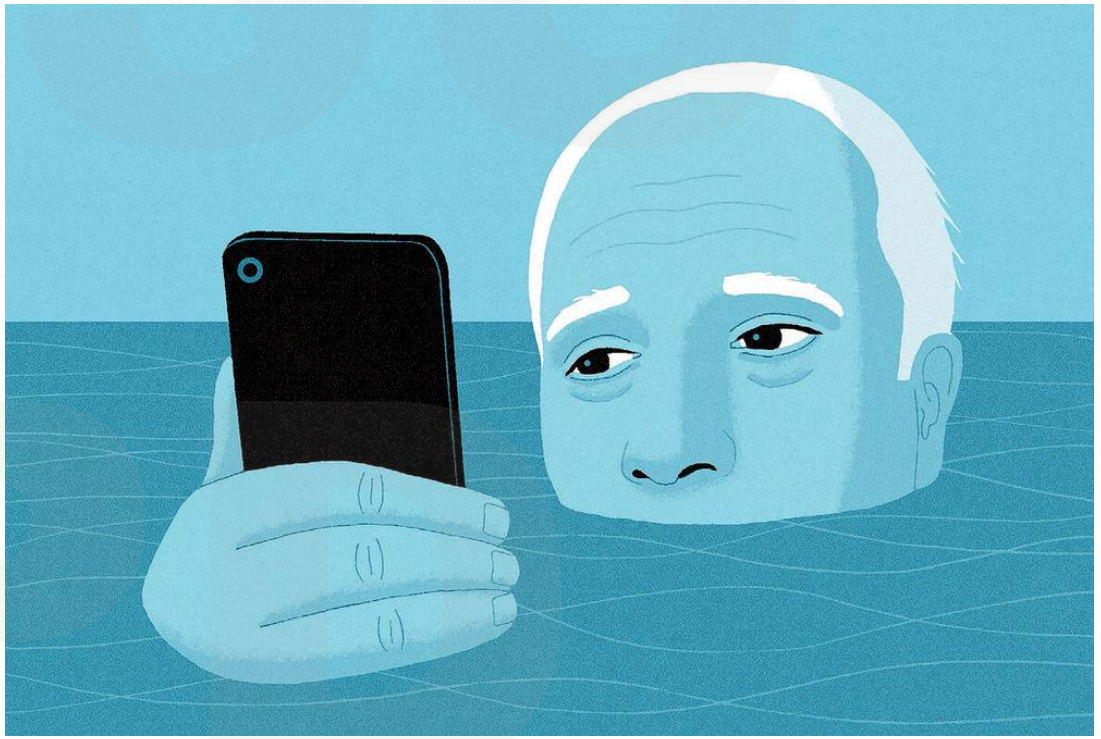
- In Jan 2024, 239 million people in the US were using social media (73% of the population)[1]
- Social media allows us to communicate and connect, raise awareness, find outlets for creative expression, acquire information and knowledge
- It has a reinforcing nature
  - Designed to encourage repeated engagement by providing us with positive feedback like likes, comments, and shares

1. Ani Petrosyan, Statista. Feb 27, 2024

Social Media and Mental Health

- Constant comparison can lead to low self-esteem
- FOMO can lead to anxiety
- Blue light can impact sleep
- Sedentary when using devices

A growing body of literature suggests that social media use correlates with depression and anxiety symptoms[1]



1. Bettmann, J.E., et al. Clin Soc Work J 49, 368–379 (2021).

Study

Taking a one-week break from social media improves wellbeing, depression, and anxiety – a randomised controlled trial.

- Design: 2-arm, randomized controlled trial
- Objective: to understand the impact of taking a one-week break from social media on wellbeing, depression and anxiety compared to using social media as normal
- Participants: 154 adult daily user of social media willing to stop for one-week
  - Mean age: 28.9
  - Sex: 62% female
  - Average time on SM: 484 minutes per week
- Method: randomized to 2 groups: off social media for a week vs social media as usual

Lambert, J, Barnstable, G, Minter, E, Cooper, J & McEwan, D 2022, Cyberpsychology, Behavior, and Social Networking, vol. 25, no. 5, pp. 287-293.

Study

- Outcome measures:
  - Wellbeing: Warwick-Edinburgh Mental Well-being Scale (WEMWBS, 14-item instrument that asks respondents to respond to statements about their feelings and thoughts that best describes their experience over the previous two weeks on a 5-point scale
    - 0-32: very low wellbeing, 32-40: low, 40-59: average, 59-70: above average
    - BASELINE MEAN: 45
  - Depression: PHQ-8, measures the frequency of depressive symptoms over the last two weeks on a 3-point scale
    - 0-4: No depression, 5-9: mild, 10-14: moderate, 15-19: moderately severe, 20-24: severe
    - BASELINE MEAN: 7.6
  - Anxiety: GAD-7, measures the frequency of anxiety symptoms over the last two weeks on a 3-point scale
    - 0-4: Minimal anxiety, 5-9: mild, 10-14: moderate, 15-21: severe
    - BASELINE MEAN: 6.4

Results

- Minutes of social media use
  - Intervention group: 509 minutes → 20.7 minutes
  - Control group: 484.5 minutes → 444.5 minutes
  - Screenshot statistics were provided to check adherence to the break

Results

	Intervention			Control			Adjusted Mean Difference (95% CI)
	N	Mean	SD	N	Mean	SD	
WELLBEING							
Baseline	81	46.00	7.78	73	43.92	8.33	
One week	74	55.93	7.65	66	45.05	8.06	4.90 (2.97, 6.83)***
PHQ-8							
Baseline	81	7.46	4.62	73	7.84	4.80	
One week	74	4.84	3.89	66	6.95	4.45	-2.17 (-3.28, -1.06)***
GAD-7							
Baseline	81	5.95	4.32	73	6.92	5.00	
One week	74	3.88	3.84	66	5.94	4.30	-1.68 (-2.79, -0.57)**

**P<.01. *** P < 0.001

Controlled for baseline scores, age, gender

Results

	Intervention			Control			Adjusted Mean Difference (95% CI)
	N	Mean	SD	N	Mean	SD	
WELLBEING							
Baseline	81	46.00	7.78	73	43.92	8.33	
One week	74	55.93	7.65	66	45.05	8.06	4.90 (2.97, 6.83)***
PHQ-8							
Baseline	81	7.46	4.62	73	7.84	4.80	
One week	74	4.84	3.89	66	6.95	4.45	-2.17 (-3.28, -1.06)***
GAD-7							
Baseline	81	5.95	4.32	73	6.92	5.00	
One week	74	3.88	3.84	66	5.94	4.30	-1.68 (-2.79, -0.57)**

**P<.01. *** P < 0.001

Controlled for baseline scores, age, gender

Results

	Intervention			Control			Adjusted Mean Difference (95% CI)
	N	Mean	SD	N	Mean	SD	
WELLBEING							
Baseline	81	46.00	7.78	73	43.92	8.33	
One week	74	55.93	7.65	66	45.05	8.06	4.90 (2.97, 6.83)***
PHQ-8							
Baseline	81	7.46	4.62	73	7.84	4.80	
One week	74	4.84	3.89	66	6.95	4.45	-2.17 (-3.28, -1.06)***
GAD-7							
Baseline	81	5.95	4.32	73	6.92	5.00	
One week	74	3.88	3.84	66	5.94	4.30	-1.68 (-2.79, -0.57)**

**P<.01. *** P < 0.001

Controlled for baseline scores, age, gender

Results

1-week break from social media was associated with a statistically significant improvement in measures of wellbeing, depression, and anxiety

((Changes were statistically significant but not necessarily clinically significant))

Adds to the growing body of evidence that short breaks in social media can positively affect mental health

My Take

- We routinely recommend lifestyle changes (eg, increasing exercise, socializing, getting adequate sleep, reducing alcohol intake) to our patients. It may be time to add reducing social media use to that list.

- Log off, cut down, be more mindful
- Turn of social media notifications, sign out of social media sites, delete apps, turn off their phones, and download app blockers

Summary

- L-methylfolate: reasonable as an adjunct for mild to moderate depression
- Brexpiprazole: helpful for agitation in dementia but expensive and probably not any better than current atypical antipsychotics
- Bupropion: the best antidepressant for patients concerned about weight gain

Summary

- ADHD rating scales are better for ruling out ADHD (when negative) than ruling it in (when positive)
- Avoid higher than FDA recommended doses of stimulants for patient being treated for ADHD
- Ask patients with depression and anxiety how much time they spend on social media and encourage a reduction in use to improve wellbeing

The End

Questions?