TOP TEN TREATMENT UPDATES

FROM THE PAST YEAR

CHRIS AIKEN MD, NCPA 2023

Editor-in-chief, Carlat *Report* Director, Mood Treatment Center Instructor, WFU Dept Psychiatry

No conflicts related to content

pubmed.gov

bipolarnews.org

www.jwatch.org

Placebo controlled?

Double blind?

Size (>100)?

Drop out rate (<20%)?

Primary outcome positive?

Effect size (d, SMD) **or NNT?** (NNT < 10 is relevant)

(d: buspirone 0.2, SSRIs 0.3-0.4, benzos 0.5, amphetamine 0.9, average psych 0.5)

Replicated?

Backed by basic science?

PRACTICE CHANGING

1

Ketamine vs ECT

Ketamine was more effective in treatment resistant depression, but the population may explain why

Ketamine vs ECT in Non-Psychotic Depression	
Design	Randomized open-label
Size	365
Subjects	Treatment resistant non-psychotic depression, outpatients
Duration	3 weeks
Primary outcome	Response (>50% reduction on QIDS-SR-16)
Secondary outcome	Response and remission on QIDS, MADRS, CGI, PGI; Quality of life, subjective and objective memory tests
Result	Ketamine > ECT (55% vs 41% response)
Limitations	ECT only 3 weeks Non-psychotic population favors ketamine
Adverse effects	ECT: Musculoskeletal and memory Ketamine: Transient dissociation
Dose	ECT 3 times/week (start R unilateral, can change BL, did in 39%) Ketamine 2 times/week (0.5 mg/kg body weight IV)
FDA Approval	Yes
Funding	Independent (Patient-Centered Outcomes Research Institute)

Anand A, Mathew SJ, Sanacora G, et al. Ketamine versus ECT for Nonpsychotic Treatment-Resistant Major Depression. N Engl J Med. 2023;388(25):2315-2325.

2

Treatment Resistant Depression in Elderly

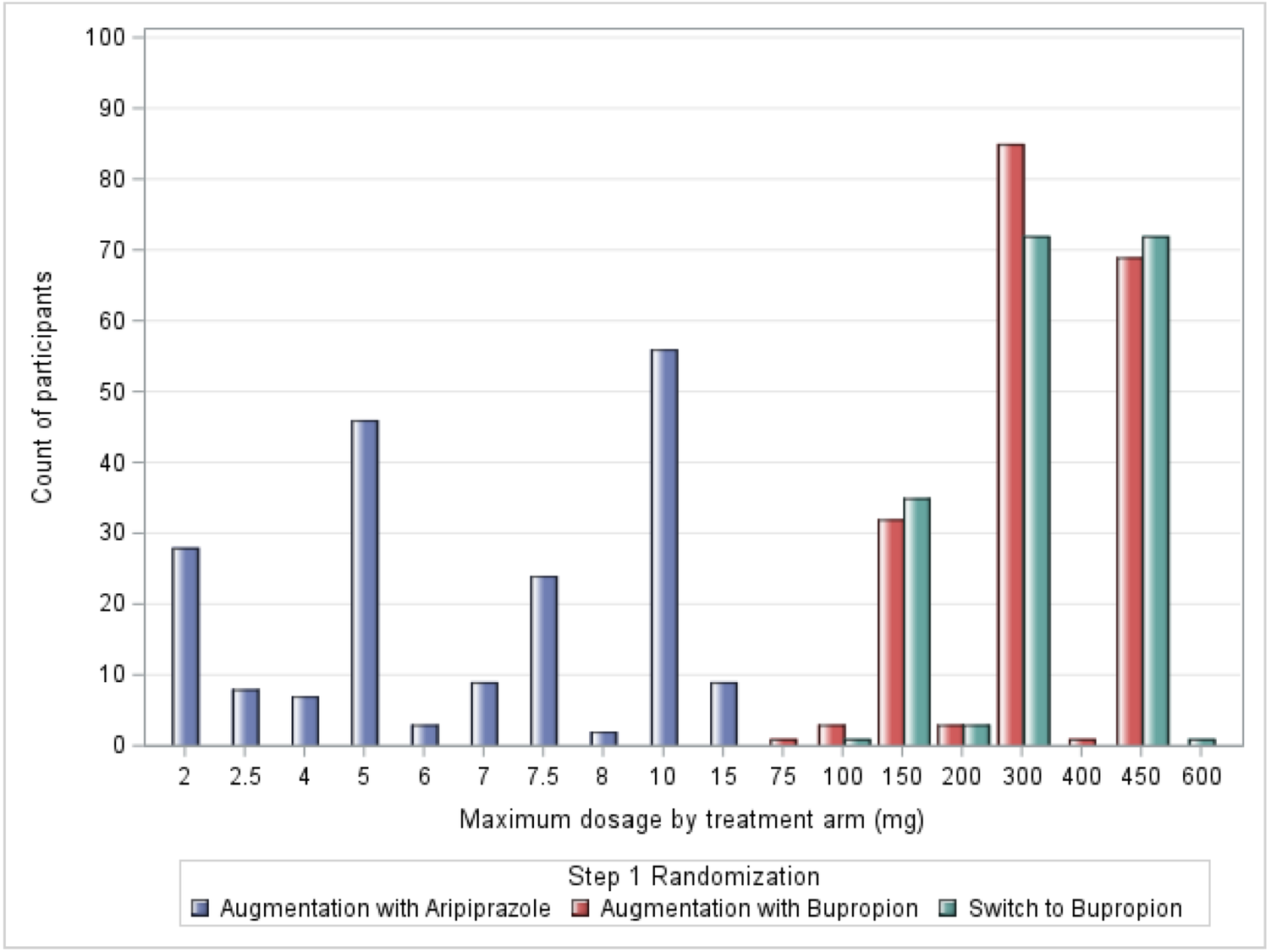
After two failures, move to augmentation, and aripiprazole augmented better than buproprion.

OPTIMUM: Treatment Resistant Depression in Elderly	
Design	Randomized, open-label, two-step trial
Treatment	Step 1: Augment with aripiprazole or bupropion; or switch to bupropion (n=619) Step 2: Augment with lithium or switch to nortriptyline (n=248)
Subjects	Treatment resistant major depression (≥ 2 trials, avg 2.3) Age over 60
Duration	10 weeks per step
Primary outcome	Change in psychological well-being (NIH Positive Affect and General Life Satisfaction scales)
Secondary outcomes	Remission (<10 on MADRS), change on MADRS, social and physical functioning scale
Result	Step 1: Favored aripiprazole (↑4.8 arip, 4.3 bup, 2.04 bup-switch) Step 2: Similar on both outcomes for lithium vs nortriptyline
Limitations	Open-label (rater blinded though), no placebo Taper rates not reported
Risks	Falls highest with bupropion augmentation
Doses	Aripiprazole 2.5-15 mg/d Bupropion XL 300-450 mg/d Nortriptyline level 80 to 120 ng/ml Lithium level 0.6 mmol/l
FDA Approval	Yes
Funding	Independent (Patient-Centered Outcomes Research Institute)

Lenze EJ, Mulsant BH, Roose SP, et al. Antidepressant Augmentation versus Switch in Treatment-Resistant Geriatric Depression. N Engl J Med. 2023;388(12):1067-1079.

Final doses of aripiprazole & bupropion

Figure S4a. Maximum Study Medication Dose Reached By Step 1 Participants



- Aripiprazole 2, 5, 10mg
- Bupropion 300-450mg

3

Haloperidol in Delirium

If you “have to do something,” try something else*

*Sleep regulation (melatonin, ramelteon, orexin antagonists), family support, regular orientation to a stable unchanging environment

Haloperidol in ICU Delirium	
Design	Randomized, placebo controlled
Size	963
Subjects	Adults admitted to ICU with delirium (avg age 70)
Duration	Follow up 90 days post treatment
Primary outcome	Days alive and out of the hospital
Secondary outcomes	Mortality, days without coma, delirium, or ventilator; serious adverse reactions, use of restraints or rescue meds for delirium (including other antipsychotics)
Result	No significant differences in any measures except more serious adverse reactions with haloperidol (11 vs 9) and need to stop due to QTc prolongation (2.4% vs 1.4%)
Limitations	Delirium not measured directly
Risks	QTc prolongation, akathisia and EPS, temperature dysregulation, falls, anticholinergic effects, NMS
Dose	2.5 mg IV tid plus 2.5 mg prn, max 20 mg/day, avg 8.3 mg/day Average treatment duration = 3.6 days
FDA Approval	No (and not recommended in practice guidelines)
Funding	Independent grants

Andersen-Ranberg NC, Poulsen LM, Perner A, et al. Haloperidol for the Treatment of Delirium in ICU Patients. N Engl J Med. 2022;387(26):2425-2435.

Non-pharm mgt of delirium

Grover S, Avasthi A. Clinical Practice Guidelines for Management of Delirium in Elderly. Indian J Psychiatry. 2018 Feb;60(Suppl 3):S329-S340.

Free online
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5840908/

Providing support and orientation

- Communication: use simple language, communicate in clear, simple, firm, slow-paced language and if require repeat the instruction
- Avoid abstract ideas/language
- Avoid discussion which cannot be appreciated by the patient
- Discuss topics which the person with delirium is interested in talking, is familiar with such as his hobbies and profession
- Reorientation: reorient the patient (repeated reminders for the day, time and location, and identity of key individuals including treating team members)
- Address the patient face-to-face, make proper eye contact, and give clear instructions when talking to patients
- Convey an attitude of warmth, calmness and kind firmness
- Understand the persons emotional state and encourage them to speak
- Do not try to provide too much of information at one go and when patient is not interested
- Clear markers/signs for patient's location
- Provision for calendar, clock, chart with the day's schedule in the patients room
- Avoid multitasking: provide one stimulus/task at a given time
- Bring familiar belonging from the home: personal/familiar objects (Photos, favorite blanket), night clothes, things kept at bedside in the home to enhance orientation and security
- If interested, patient may be encouraged to carry out cognitively stimulating activities: many times a day (puzzle books, Sudoku, magazines, or video games etc.)
- Minimize change of staff
- Use a television/radio/smartphones/listening to music etc. for relaxation can be allowed if the person wants the same, as these can help the patient maintain contact with the outside world; light music can prevent under stimulation and also provide a buffer against noise extremes
- Physical restraints to be kept away, if possible; when used should be for shortest possible duration and be removed in timely manner
- Encourage feelings of security and orientation by involving family members/caregivers
- Explain about each procedure or the act being done as part of treatment or general care (for example changing the bed sheet), to reduce the chances of misinterpretation
- Position your hands in the field of the vision and avoid rapid movements or gestures, which could be misinterpreted as signs to harm
- In case patient gets agitated, look for the triggers and use behavioural strategies (change in the environment, distraction) to reduce agitation
- Do not contradict the delusional beliefs- this can enhance the agitation and encourage disorientation
- Do not confront and disagree with the patient, even if the patient verbalizes inappropriate or inaccurate things
- Avoid having more than one patient with delirium in the same room, especially persons with agitated hyperactive delirium, as agitation of one patient reinforces/induces the agitation in the second patient

Providing an unambiguous environment

- Remove harmful and unfamiliar objects from the vicinity
- Avoid both sensory deprivation (provide glasses and hearing aids, if patient was using the same) and sensory overload (noise)
- Do away with unnecessary objects in the care area, maintain adequate space between beds
- If the provision exist or it is possible that, provide single room: will help in providing rest and lead to avoidance of extremes of sensory experience; this can also eliminate the disturbance caused by staff/family caregivers of other patients in the same room
- Frequent change of location of patient's bed should not be done
- Do not use medical jargon in front of the patient as this can enhance the feelings of paranoia
- Adequate lighting: appropriate lighting to the time of day and minimal lighting at night may reduce disorientation (40–60 W night light reduces misperceptions)
- Quiet environment, reduce noise (keep phones in the silent/vibrator mode, use vibrating beepers, reduce the noise from staff, equipment, visitors to the minimum with a aim of <45 decibels during the daytime and <20 decibels at night)
- Room temperature to be maintained between 21°C and 23.8°C
- Encourage family members to stay with the patient- can help in reorientation, provide a sense of safety, help in effective communication
- Educate the family about how to communicate

Maintaining competence

- Recognise and correct sensory impairments: make sure that patients have their glasses, hearing aids and dentures
- Check whether patient understands your language or an interpreter is required; if so use an interpreter
- Early mobilization: Ambulate at the earliest, if this is not possible than encourage whole range of movements for at least 15 minutes three times a day
- Encourage independence in self-care activities
- Encourage participation in treatment (for example, encourage the patient to give feedback about their pain)
- Ensure good uninterrupted sleep: schedule treatment/interventions/ Intravenous fluids in such a way that patient can have maximum periods of uninterrupted sleep (use a sleep protocol to promote quiet hours)
- Address the issues related to nutrition
- Do away with urinary catheter, central line, Intravenous fluid line etc at the earliest
- Adequate skin care and avoid development of bed sores
- Proper measures to be taken to prevent falls

Other supportive measures

- Maintain adequate oxygen saturation, correct electrolyte imbalance
- Adequate pain management: use non-pharmacological measures, local measures, in case of severe pain use appropriate analgesics (preferable non-narcotic agents) round the clock
- Unnecessary medications to be discontinued
- Treat infection: antibiotics
- Ensure regular bowel/bladder habits: avoid constipation
- Prevention, detection, management of major postoperative complications

Educate the Staff

- How to recognise and monitor the symptoms of delirium
- How to provide reorientation cues

4 Antipsychotics in Mood Disorders

4. Cariprazine advances by a small degree in MDD
5. Lumateperone shows strength for bipolar I and II depression and for mixed features
6. Iloperidone scores its first RCT in mania

Cariprazine (Vraylar) aug in MDD

Double-blind, placebo controlled RCTs 8 wk		
Sachs G et al 2023	1.5 vs 3 mg (n=751)	Small effect for 1.5mg, no benefit with 3mg
Durgam S et al 2016	1-2 vs 2-4.5 mg (n=819)	Small effect for 2-4.5mg, no benefit with 1-2mg
Earley WR et al 2018	1.5–4.5 mg (n=530)	No difference on primary measures

Bottom line

- **A well-tolerated antipsychotic with FDA approval in schizophrenia (1.5-6 mg), unipolar depression augmentation (1.5 mg), bipolar mania (3-6 mg), and bipolar depression (1.5 mg)**
- **However, the effect size is small in unipolar and bipolar depression**

Lumateperone (Caplyta) in Bipolar Dep/Mixed

Double-blind, placebo controlled RCTs 6 wk		
Calabrese JR et al 2021	42 mg (n=377) Monotherapy	Medium effect (0.56)
Suppes T et al 2023	28 vs 42 mg (n=529) Adj to Li or valproate	Small effect (0.27) for 42, no difference 28 mg
Study 403 (press 2023)	42 mg (n=383)	Positive (MDD and bipolar with mixed features)
Study 401	28 vs 42 mg (n=554) Monotherapy	Negative

Bottom line

- **A well-tolerated, sedating antipsychotic with low dopamine D2 blockade**
- **FDA approval in schizophrenia (42 mg) and bipolar depression (42 mg) with effect sizes that compare well to other agents, but unknown if anti-manic**
- **Joins lurasidone (Latuda) as a monotherapy option for unipolar mixed features**

Iloperidone (Fanapt) in Bipolar Mania

Double-blind, placebo controlled RCTs 4 wks		
NCT04819776	Dose unknown (n=400)	Positive with small p=0.000008

Bottom line

- **A branded option with no evidence in the depressed phase makes this a last resort**

Off-label Atypicals in Mania

	Effective?	Notes
Illoperidone (Fanapt)	Yes	Positive RCT in bipolar mania.
Paliperidone (Invega)	Possible	Failed FDA approval in mania (2/3 trials were negative). Approved in schizoaffective disorder.
Clozapine (Clozaril)	Possible	Positive controlled and open-label data in mania, but no placebo controlled trials.
Brexpiprazole (Rexulti)	No	Two large, failed RCTs in mania.
Lumateperone (Caplyta)	??	Unstudied in mania. FDA-approved in bipolar depression. Effective in depression with mixed features.
Lurasidone (Latuda)	??	Unstudied in mania. FDA-approved in bipolar depression. Effective in depression with mixed features.
Pimavanserin (Nuplazid)	??	Unstudied in mania. FDA approved only for psychosis during Parkinson's disease.

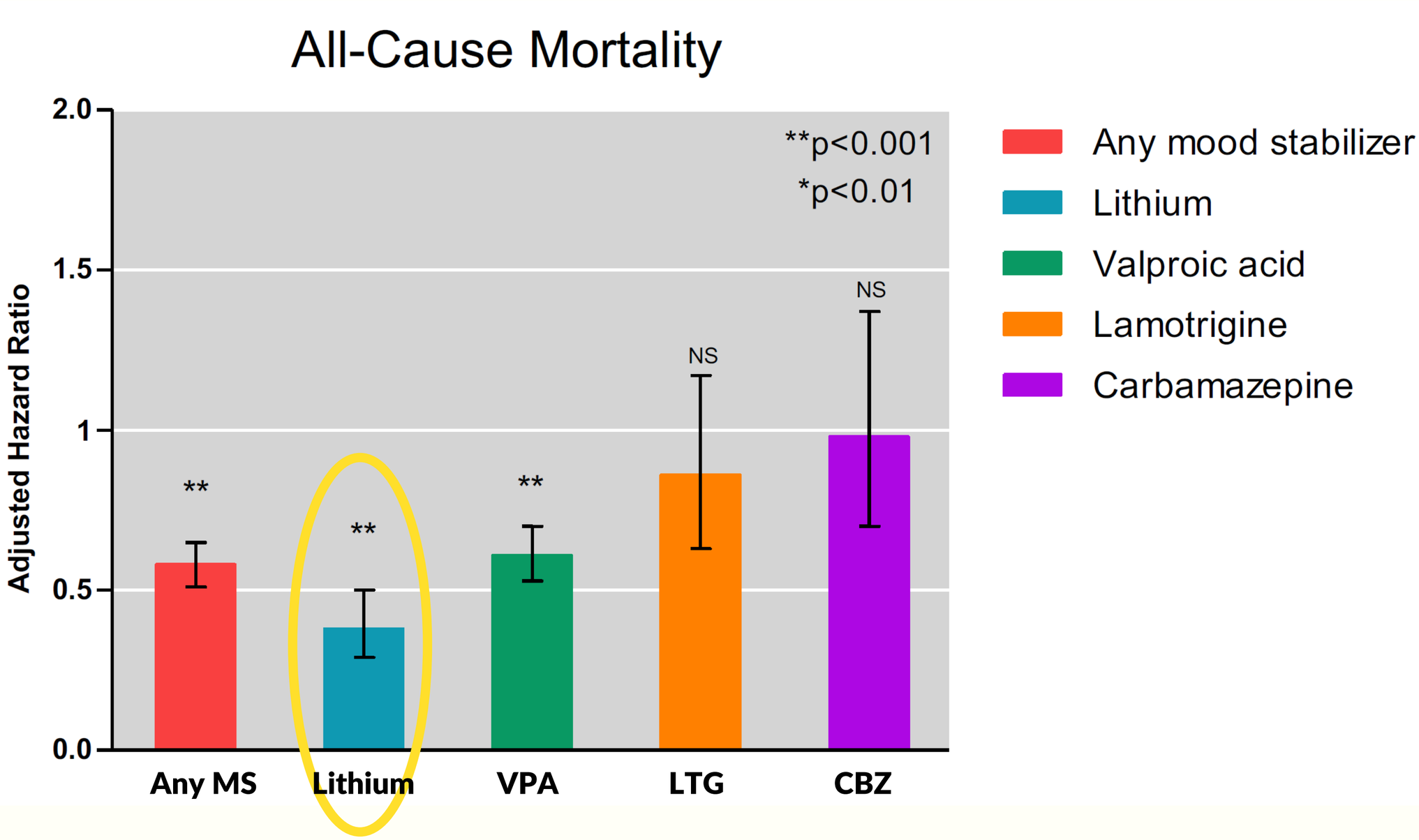
7

Lithium and Mortality

Lower risk of suicide and mortality with mood stabilizers in bipolar, particularly lithium (antipsychotics not examined)

Mortality with Mood Stabilizers	
Design	Cohort study
Size	25,787 subjects, 4,000 deaths, 760 were suicide
Subjects	Taiwan's National Health Insurance
Duration	5 years
Primary outcome	Standardized mortality ratio (likelihood of death compared to general population)
Result	Mortality lower with MS (adjusted hazard ratio 0.58 all-cause; 0.60 suicide; 0.55 other) Mortality lowest with lithium (adjusted hazard ratio 0.38 all-cause; 0.39 suicide; 0.37 other)
Limitations	Not adjusted for severity or healthy behaviors Adherence not known
Funding	Independent (Ministry of Science)

Chen PH, Tsai SY, Chen PY, et al. Mood stabilizers and risk of all-cause, natural, and suicide mortality in bipolar disorder: A nationwide cohort study. Acta Psychiatr Scand. 2023;147(3):234-247.


All-Cause Mortality
Adjusted Hazard Ratio
2.0
1.5
1
0.5
0.0
**p<0.001
*p<0.01
**
**
**
NS
NS
Any MS
Lithium
VPA
LTG
CBZ
Any mood stabilizer
Lithium
Valproic acid
Lamotrigine
Carbamazepine

8

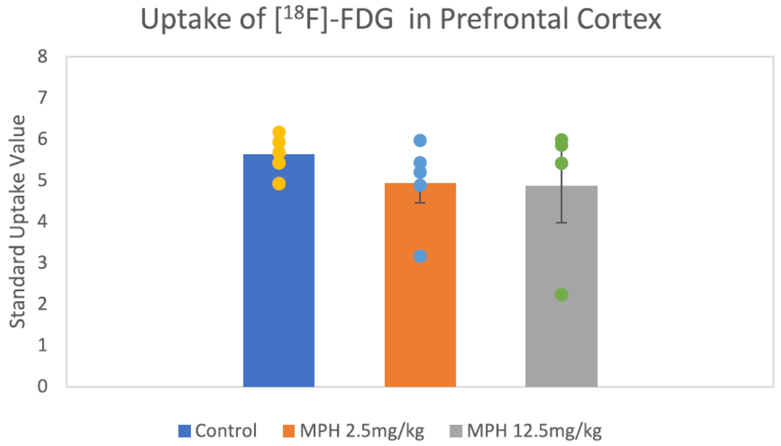
Long-term Methylphenidate

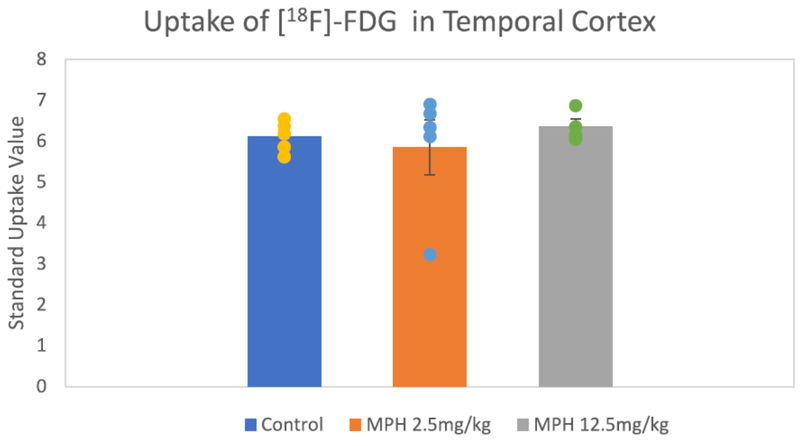
Reassuring results from a 2 year study in children, and a longer one in primates

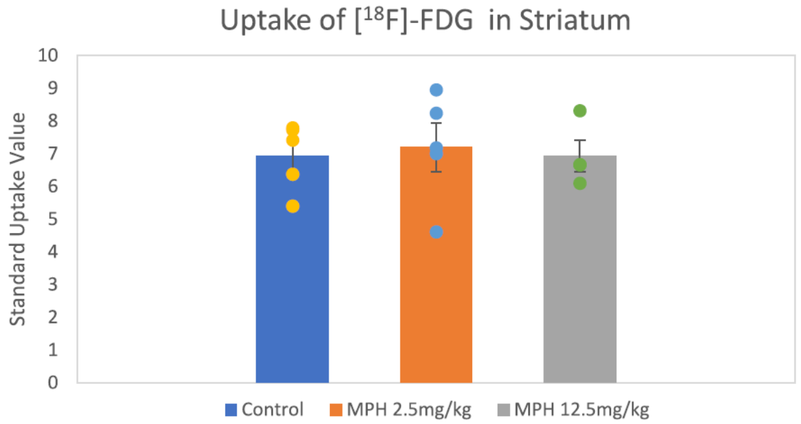
Long-term Effects of Methylphenidate in ADHD	
Design	Prospective non-randomized study comparing: 1. Children with ADHD intending to start methylphenidate 2. Children with ADHD who didn't intend to start med 3. Healthy controls
Size	1,410
Subjects	Stimulant-naive children and adolescents with ADHD European (93% White), age 6-17 (average 9), 76% male
Duration	2 years
Primary outcome	Rate of growth (normalized height velocity)
Secondary outcome	Cardiovascular, psychiatric, and neurological outcomes including psychosis, suicidality, tics, and substance use
Result	***With methylphenidate:*** Weight reduced at 6 months but weight/height normal by 2 years Mild increase in BP (108/65 to 113/67) and pulse (80 to 83) No differences in tics, psychosis, suicide, substance use Improvement in ADHD and mood
Limitations	Not randomized, and non-med group had lower ADHD severity High dropout rates (47-52%) No data on dose, formulation, adherence
Funding	Independent (EU Seventh Framework Programme)

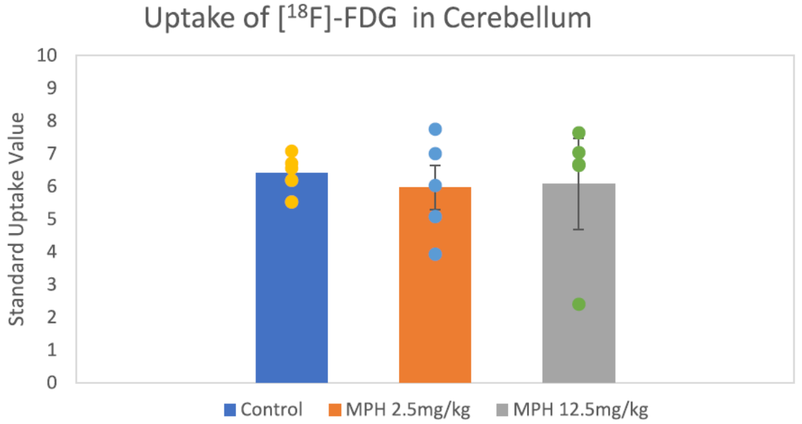
Man KKC, Häge A, Banaschewski T, et al. Long-term safety of methylphenidate in children and adolescents with ADHD: 2-year outcomes of the Attention Deficit Hyperactivity Disorder Drugs Use Chronic Effects (ADDUCE) study. Lancet Psychiatry. 2023;10(5):323-333.

No difference in primate brain after long-term methylphenidate high- and normal-dose









- 12 years (child to adolescence)
- High (5-10x) and normal dose groups
- Brain imaging (microPET/CT)

Zhang X, Berridge MS, Apana SM, Slikker W Jr, Paule MG, Talpos J. Discontinuation of methylphenidate after long-term exposure in nonhuman primates. Neurotoxicol Teratol. 2023;97:107173. doi:10.1016/j.ntt.2023.107173

9

Pro- and Pre-biotics for Antipsychotic Weight

Both helped, but the combination worked best:
11 lbs over 3 months

Pro- and Prebiotics for Metabolic Risks on Antipsychotics	
Design	Randomized placebo-controlled trial comparing probiotics, dietary fiber, and their combination
Size	131
Subjects	Schizophrenia or bipolar on antipsychotics
Duration	12 weeks
Primary outcome	BMI
Secondary outcome	Lipids, insulin resistance, microbiota flora
Result	BMI: Best results for combo, but all 3 treatment groups superior to placebo for BMI (for combo, 1.9 BMI diff, 11 lb wt difference) All groups superior to placebo on insulin resistance, insulin levels Combo superior to all others on cholesterol and greater microbiota flora
Limitations	Population (China). Did not look at differences in exercise levels.
Risks	Gas, bloating. Avoid probiotics in immunocompromised.
Dose	Probiotic: Lactobacillus, Bifidobacterium, and Enterococcus Fiber: 30 g/day fiber powder in liquid (eg, psyllium husk, Metamucil)
Funding	Research grant
Monthly cost	$10/month probiotics; $30/month fiber **Lab-approved probiotics at** https://psycheducation.org/blog/the-mind-gut-connection/

Huang J, Liu C, Yang Y, et al. The effects of probiotics plus dietary fiber on antipsychotic-induced weight gain: a randomized clinical trial. Transl Psychiatry. 2022;12(1):185.

10

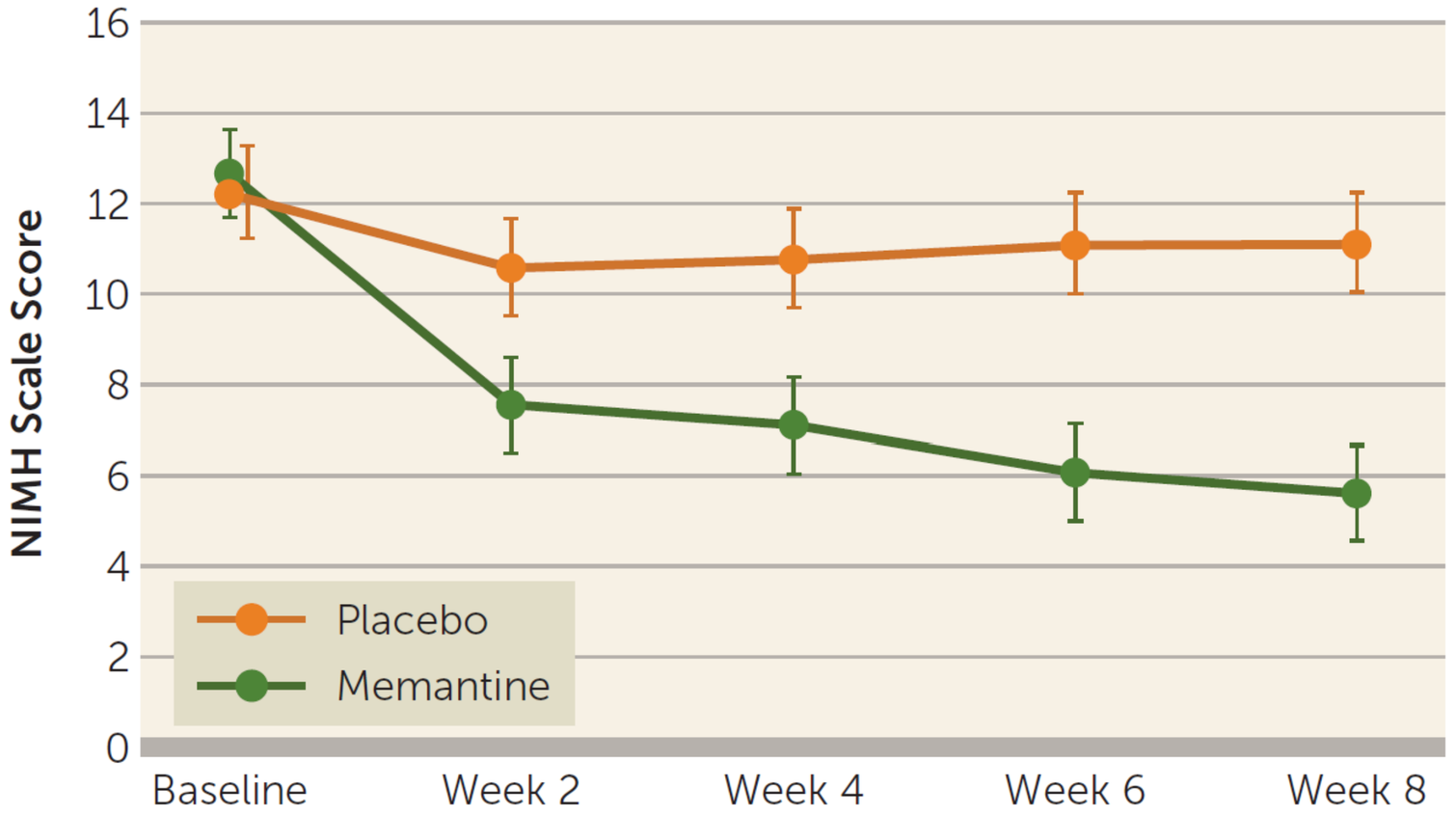
Memantine in Trichotillomania

Joins another glutamatergic (NAC) as an option for compulsive hair-pulling and skin-picking

Memantine in Trichotillomania	
Design	Randomized double-blind placebo-controlled trial
Size	100
Subjects	Adults with trichotillomania (53%), skin picking (43%), or both (4%) Average age 31, 86% women
Duration	8 weeks
Primary outcome	Change on NIMH Trichotillomania Symptom Severity Scale, modified to include skin picking
Secondary outcome	Sheehan Disability Scale, CGI
Result	Favored memantine (NNT 1.9, effect size 1.76) Similar for trichotillomania and skin picking
Limitations	All visits assessed virtually
Risks	Dizziness
Dose	20 mg/day (start 10 mg/day for 2 weeks)
Funding	University of Chicago
Monthly cost	$15

Grant JE, Chesivoir E, Valle S, Ehsan D, Chamberlain SR. Double-Blind Placebo-Controlled Study of Memantine in Trichotillomania and Skin-Picking Disorder. Am J Psychiatry. 2023;180(5):348-356.

FIGURE 2. Change in NIMH scale score over time with memantine and placebo[a]



[a] Statistically significant differences between groups emerged at week 4 and continued through week 8. NIMH scale=NIMH Trichotillomania Symptom Severity Scale, modified to include skin picking.

11

Driving on Cannabis

Impairments are just shy of a DUI, even though the driver feels safe

Driving on Cannabis	
Design	Randomized comparison of low (6%) THC, high (14%) TCH, placebo (0.02% THC) Double-blind
Size	191
Subjects	Cannabis users (≥4 uses in past month) did not smoke day before Age 21-55, 62% male, 43% white
Primary outcome	Composite driving score on simulation 30 min, 90 min, 3.5 hr, and 4.5 hr after smoking
Secondary outcome	Self-perception of driving, cannabis levels and use history
Result	Impaired driving at 30 and 90 min (medium effect size 0.6, comparable to blood alcohol 0.05-0.08%), small effect size at 3.5 (0.3), no difference at 4.5 hr Similar for low and high THC despite different serum levels 48-69% felt ready to drive when impaired
Limitations	92% correctly guessed placebo Healthy controls do not tell us about riskier populations
Funding	State of California

Marcotte TD, Umlauf A, Grelotti DJ, et al. Driving Performance and Cannabis Users' Perception of Safety: A Randomized Clinical Trial. JAMA Psychiatry. 2022;79(3):201-209.

SUMMARY

Treatment	When to use	Daily Dose
Memantine	Trichotillomania and skin picking	20 mg
Pre/Probiotics	Antipsychotic weight gain Depression, anxiety, cognition	Fiber 30 g/day
Lithium	Bipolar disorder Suicide risk Antidepressant augmentation	Levels 0.6-0.8 (depression), 0.8-1.0 (mania). 20-30% lower in elderly.
Aripiprazole	Antidepressant augmentation Bipolar mania, mixed Schizophrenia Severe irritability in autism	5-10 mg for depression
Cariprazine	Bipolar depression, mania, mixed Unipolar antidep augmentation Schizophrenia	1.5 mg for depression
Lumateperone	Bipolar depression, mixed Unipolar mixed (monotherapy) Schizophrenia	42 mg
Iloperidone	Bipolar mania	Unknown
Ketamine	Severe depression or suicidality needing rapid relief	

Uzedy
risperidone LAI
q1-2 mth

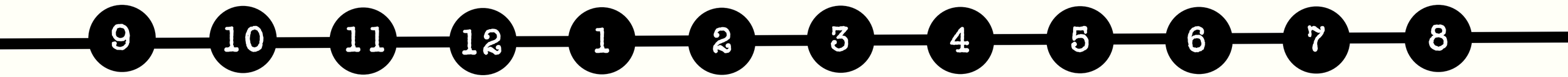
Vraylar
(cariprazine) for
antidepressant
augmentation

X-Waiver
removed for opioid
MAT therapy

Asimtufii
aripiprazole LAI
q2 mth

Stimulant
warnings updated
in PDR

Adderall Shortage



Auvelity
(dextro-
methorphan-
bupropion) for
MDD

SAINT TMS
for treatment
resistant MDD

Rebyota
first fecal
microbiota
approval, for *C*
difficile, opening
door for psychiatric
approvals

Warnings
1. CBD in food products
2. Xylazine (high potency opioid) contamination of illicit drugs

Rykindo
risperidone LAI

Leqembi
lecanemab for
Alzheimer's
dementia (IgG1
amyloid antibody)

Austedo XR
deutetrabenazine
for TD

ReVive OTC
naloxone opioid
antagonist

Opioid Warning
hyperalgesia added

Rexulti brexpiprazole)
for agitation in
Alzheimer's dementia

Escitalopram
GAD age lowered to 7

Opvee
nalmefene IN
opioid antagonist

Brixadi
buprenorphine XR INJ
for opioid MAT

Public Health Emerg Ends

FDA Updates Sept 2022 – Aug 2023