TOP TEN TREATMENT UPDATES

FROM THE PAST YEAR

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pubmed.gov

bipolarnews.org

www.jwatch.org

No conflicts related to content

Placebo controlled?

Double blind?

Size (>100)?

Drop out rate (<20%)?

Primary outcome positive?

Effect size (d, SMD) **or NNT?** (NNT < 10 needed to pass FDA)

(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

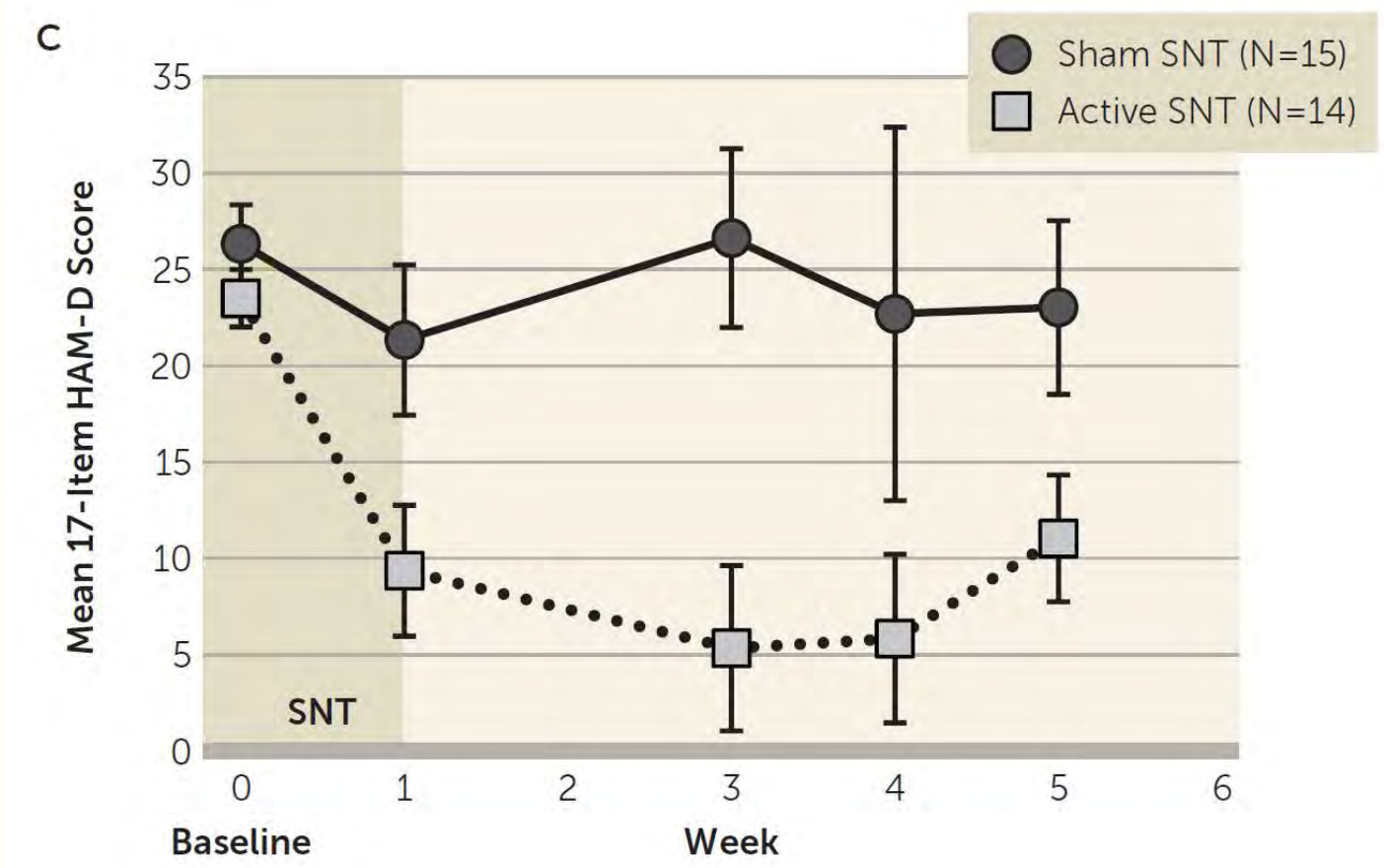
SAINT TMS

Unheard of recovery rates in treatment resistant depression

Stanford Neuromodulation Therapy	
Design	Randomized, double-blind, sham-controlled trial
Size	Small (n=29)
Subjects	Treatment resistant major depression, 5 past trials (mean)
Intervention	5 days of theta-burst TMS (iTBS), 3 min/hour for 10 hours a day
Duration	4 weeks
Primary outcome	Depression (MADRS)
Intent to treat?	N/A (no drop outs)
Result	Positive (79% vs 13% remission rates) True blind: Patients could not tell which treatment they received
Weaknesses	Small size
Funding	Independent

FDA approved, devices expected in 2023

Cole EJ et al. Stanford neuromodulation therapy (SNT): A double-blind randomized controlled trial. Am J Psychiatry. 2022 Feb;179(2):132-141.



Benefits wore off a little at 4 weeks post-treatment

The Stanford Approach

Theta-burst Stimulation (iTBS)

- Allows delivery of TMS in 3 min vs. 20-40 min
- The typical 6 wk protocol is just as effective as 6 wk of regular TMS, but a little less tolerable

MRI-Guided Coils

- Some evidence of advantage over anatomically guided

Stanford Neuromodulation Therapy

- Combines iTBS with MRI-guided coils
- But delivers the 3-min iTBS every hour for 10 hours a day instead of once-a-day on weekdays for 6 weeks
- Not FDA-approved, but devices available (eg Nexstim, Soterix)

2

BUPROPION WITH DEXTROMETHORPHAN

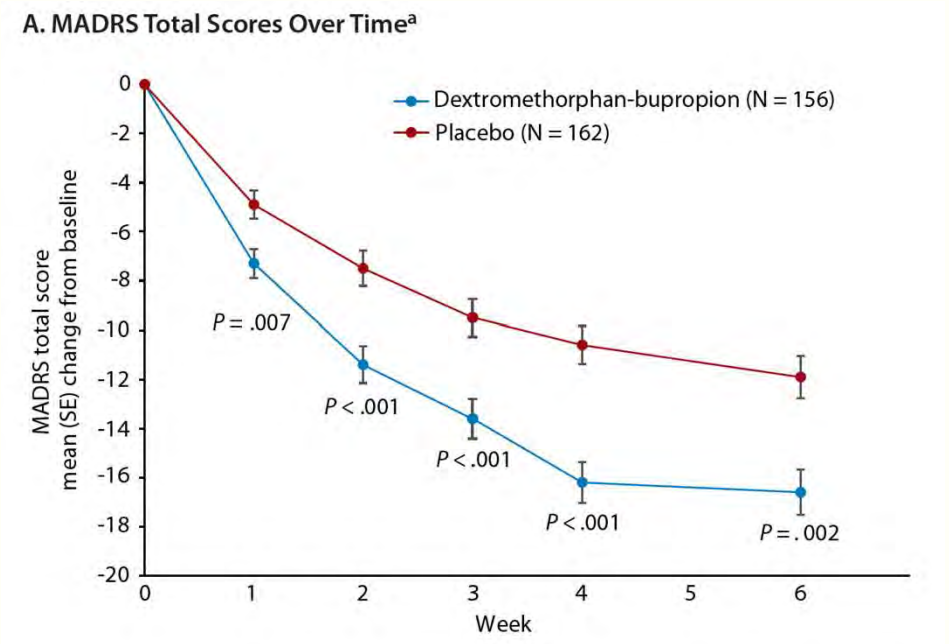
A combo pill brings faster onset and higher remission rates to MDD

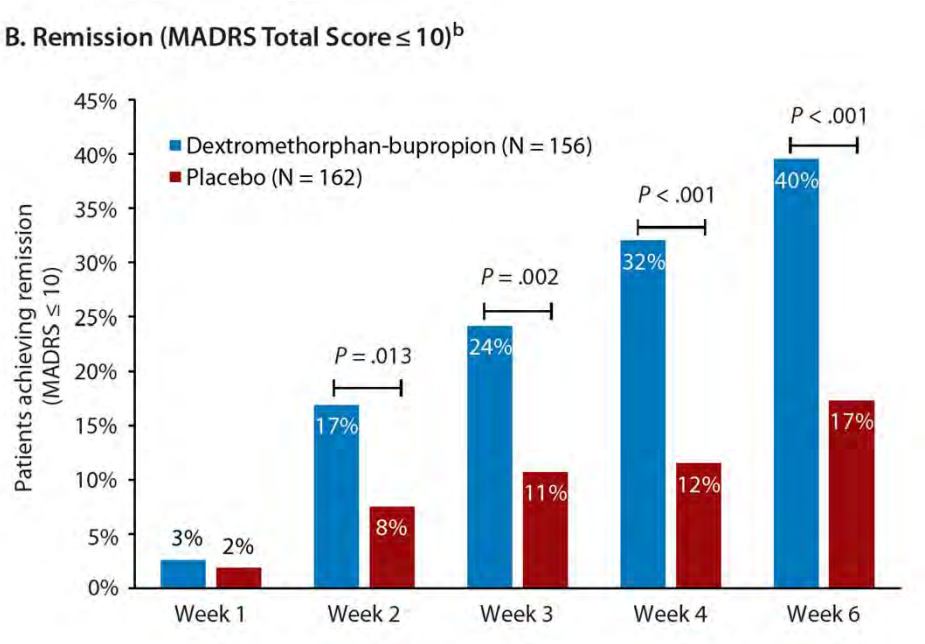
Bupropion-Dextromethorphan Combo in Major Depression	
Design	Two randomized, double-blind placebo-controlled trials 1. Compared combo to placebo alone 2. Compared combo to bupropion + placebo
Size	1. 80 2. 327
Subjects	Major depression, moderate-severe (*not* treatment resistant)
Duration	6 weeks
Primary outcome	Depression change on MADRS
Secondary outcome	Response, remission, quality of life, disability
Result	Greater MADRS reduction with combo (1. -14 vs -9; 2. -16 vs -12) Secondary outcomes favored combo
Weaknesses	High drop-out (18-30%) with more due to adverse events in combo (6.2%) than placebo (0.6%)
Risks	Dextromethorphan: Fatigue, nausea, dizziness Possible abuse, psychosis, dissociation, serotonin syndrome
Dose	Bupropion 105 mg bid, dextromethorphan 45 mg bid (both dosed qd for first 3 days)
FDA Approval	**Yes (Auvelity)**
Funding	Industry
Monthly cost	Dextromethorphan $20, bupropion $10

Tabuteau H, Jones A, Anderson A, et al. Effect of AXS-05 (dextromethorphan-bupropion) in major depressive disorder: a randomized double-blind controlled trial. Am J Psychiatry. 2022 May 18:appiajp21080800.

Iosifescu DV, Jones A, O'Gorman C, et al. Efficacy and Safety of AXS-05 (Dextromethorphan-Bupropion) in Patients With Major Depressive Disorder: A Phase 3 Randomized Clinical Trial (GEMINI). J Clin Psychiatry. 2022 May 30;83(4):21m14345.

Rapid action (2 weeks), high remission rates (40-47%)





Dextromethorphan

- FDA-approved as cough suppressant in 1958
- For pseudobulbar affect (with quinidine) in 2010
- Available as OTC liquid (7.5 ml = 45 mg)

- Metabolized by CYP2D6, which bupropion inhibits
- Nuedexta (dextromethorphan-quinidine) pairs it with an inert 2D6 inhibitor to extend its 2-4 hour half-life

- Increases glutamate (NMDA antagonism), norepinephrine and serotonin (reuptake inhibition)
- Anticonvulsant, neuroprotective
- Doses > 300mg are abused

3 NICOTINE CESSATION IN MDD: 3 THERAPIES COMPARED

Varenicline did not cause neuropsych side effects and outperformed bupropion and patch

What Works Best for Nicotine Cessation in Major Depression?	
Design	Randomized, placebo-controlled, secondary analysis of EAGLES trial
Size	6,653
Treatments	Nicotine counseling plus: Varenicline, bupropion, nicotine patch, or placebo
Subjects	MDD (40%) vs. no psych disorder (60%) Smoking at least ½ PPD
Duration	12 weeks
Primary outcome	1. Neuropsych adverse events 2. Continuous abstinence confirmed by CO testing at 8-12 weeks
Secondary outcome	Abstinence at 6 months
Result	1. No difference in neuropsych adverse effects by treatment or by underlying depression 2. Varenicline superior to bupropion and patch, which were equal to each other, in both those with and without depression (at both 12 weeks and 6 months)
Weaknesses	Secondary analysis
Risks	Nausea, vivid dreams
Dose	Varenicline 1mg bid, bupropion 150mg bid, nicotine patch (tapered from 21 mg/day)
FDA Approval	Yes
Funding	Makers of varenicline and bupropion
Monthly cost	Varenicline $200, bupropion $10, patch $20

Cinciripini PM, Kypriotakis G, Green C, et al. The effects of varenicline, bupropion, nicotine patch, and placebo on smoking cessation among smokers with major depression: A randomized clinical trial. *Depress Anxiety.* 2022;39(5):429-440.

A CARLAT PSYCHIATRY
REFERENCE TABLE

Varenicline (Chantix) Facts	
FDA indications	Nicotine cessation
Other uses	Alcohol use disorders (when comorbid with nicotine)
Dosage	Start 0.5 mg QAM for three days then 0.5 mg BID for four days, then 1 mg BID
Side effects	Nausea, insomnia, nightmares
Interactions	None (renally excreted)
Contraindications	None

4

MIRTAZAPINE IN OCD

Augmented sertraline in this small controlled trial

Mirtazapine Augmentation for OCD	
Design	Randomized, double-blind placebo-controlled trial
Size	61
Treatments	Mirtazapine
Subjects	OCD non-responsive to sertraline (avg 250 mg/day)
Duration	12 weeks
Primary outcome	YBOCS
Result	YBOCS lower with mirtazapine (11 vs 19)
Weaknesses	Small. Drop-outs 24% (more due to SE with mirtazapine)
Risks	Drowsiness
Dose	15-45 mg/night (avg 40 mg), start 7.5 raise by 7.5/week
FDA Approval	No
Funding	Independent grant
Monthly cost	$25

Mowla A, Baniasadipour H. Is mirtazapine augmentation effective for patients with obsessive-compulsive disorder who failed to respond to sertraline monotherapy? A placebo-controlled, double-blind, clinical trial. Int Clin Psychopharmacol. 2022 Jun 9.

5

CLONIDINE IN MANIA

An adjunctive option with secondary benefits

Clonidine in Mania	
Design	Randomized double-blind, placebo controlled trial
Size	70
Subjects	Inpatient mania
Treatment	Adjunctive clonidine 0.2-0.6 mg/night
Duration	24 days
Primary outcome	Young mania rating scale
Secondary outcomes	Sleep (subjective Pittsburgh SQI) Cognition (MMSE)
Intent to treat?	Yes (drop out 7-18%)
Result	Reduced mania (large effect size 0.90) Improved sleep (medium effect size 0.67) No effect on cognition
Weaknesses	Small, dropouts 17% (evenly distributed, not intent-to-treat) But is supported by earlier, smaller controlled trials
Risks	Hypotension, falls, sedation, rebound hypertension
FDA Approval	Off-label
Funding	University grant
Monthly cost	$12

Ahmadpanah M, Pezeshki R, Soltanian AR, et al. Influence of adjuvant clonidine on mania, sleep disturbances and cognitive performance - Results from a double-blind and placebo-controlled randomized study in individuals with bipolar I disorder during their manic phase. J Psychiatr Res. 2022 Feb;146:163-171.

Other Benefits of Clonidine

Confirmed (multiple RCTs)

- ADHD
- Opioid Use Disorder (WD and Prevention)
- Tics

Potential (small controlled trial)

- PTSD
- Insomnia
- Cognition in schizophrenia
- Self-harm in Borderline (as a PRN)
- Nicotine cessation
- Irritability in Autism
- Hot flashes

5

VITAMIN B6 FOR PROLACTINEMIA

Improved prolactin, psychosis, and cognition in schizophrenia

Vitamin B6 for Prolactinemia	
Design	Randomized, double-blind active-comparator trial
Size	Large (200), 97% retention
Subjects	Schizophrenia with hyperprolactinemia
Intervention	Vitamin B6 300 mg bid vs. Aripiprazole 5 mg bid
Duration	16 weeks
Primary outcome	Prolactin levels
Secondary outcomes	Psychotic symptoms (PANSS), cognition (MATRICS battery), side effect scales, labs
Result	Prolactin reduction B6 > aripiprazole (68% vs 37%) Psychotic symptoms B6 > aripiprazole (18% vs 12%) Cognition B6 > aripiprazole (10% vs -5.4%)
Weaknesses	Generalizability limited as most subjects male, Chinese, with treatment-resistant schizophrenia
Risks	Neuropathy and skin lesions at > 1000 mg daily
Funding	National Science Foundation of China

Zhuo C, Xu Y, Wang H, et al. Safety and efficacy of high-dose vitamin b6 as an adjunctive treatment for antipsychotic-induced hyperprolactinemia in male patients with treatment-resistant schizophrenia. Front Psychiatry. 2021;12:681418.

Other Benefits of B6

Potential (small controlled trials)

- Tremor
- Akathisia
- Tardive dyskinesia
- Dose 600-1200 mg/day

6

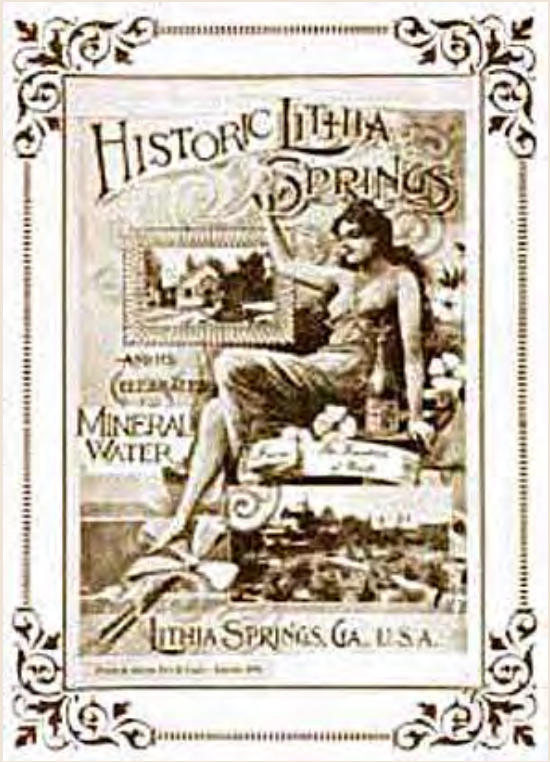
LITHIUM VS COVID

Lithium's anti-viral side proved true in this RCT of patients with COVID in ICU

Lithium vs COVID	
Design	Randomized placebo-controlled trial
Size	30
Subjects	COVID-19, hospitalized on dexamethasone
Duration	7-10 days
Primary outcome	Length of hospital stay & admission to ICU
Secondary outcome	Clinical symptoms and biomarkers
Result	Reduced hospital days (7 vs 12) Lower ICU admissions (0 vs 2) Lower rates of long-COVID neurologic symptoms (40% vs 73%) All inflammatory biomarkers lower with lithium
Weaknesses	Small
Risks	Few with short-term use of lithium
Dose	Lithium carbonate, level 0.6 and 1.2 mEq/L
Funding	Independent grant

Spuch C, López-García M, Rivera-Baltanás T, et al. Efficacy and Safety of Lithium Treatment in SARS-CoV-2 Infected Patients. Front Pharmacol. 2022 Apr 14;13:850583.

Lithium and Health



Confirmed

- Prevents suicide
- Lowers dementia risk (neuroprotective)
- Improves cardiac remodeling
- Antiviral effects, anti-COVID

Possible

- Lower cancer risk
- Anti-aging effects (protects telomeres)
- Lower risk of stroke and neurologic illness
- Lower risk of osteoporosis (2022)

7

SHIFT WORK AND SLEEP SCHEDULE

Better to wake before going to work than to go to sleep right after your shift

Sleep Schedule in Shift Work	
Design	Randomized, cross-over trial
Size	Small (n=60)
Subjects	Shift work disorder; mean age 30 years; 80% women; 66% night-shift nurses.
Intervention	Sleep in morning (9am–5pm) or evening (3pm–11pm) Then cross-over to opposite
Duration	2 weeks
Primary outcome	Sleepiness (Karolinska), Sleep quality (Pittsburgh SQI), Attention performance (psychomotor vigilance tests)
Intent to treat?	N/A (no drop outs)
Result	Evening sleep worked better 30-minute longer duration of sleep (5.3 vs. 4.8 hours) as well as improvements in sleep quality and daytime somnolence. Attention improved but not significantly.
Weaknesses	Small size, short duration
Funding	Taiwan Ministry of Science

Cheng WJ, Hang LW, Kubo T, et al. Impact of sleep timing on attention, sleepiness, and sleep quality among real-life night shift workers with shift work disorder: a cross-over clinical trial. Sleep. 2022;45(4):zsac034.

8 HYPNOTICS IN BENZO-RESISTANT INSOMNIA

Small study, but eszopiclone may improve insomnia when a benzo doesn't work

Eszopiclone vs. Suvorexant in Benzo-resistant Insomnia	
Design	Randomized open-label
Size	18
Subjects	Major depression and insomnia (mean age 58, Japanese) Non-responsive to 2 weeks of benzo-hypnotic
Duration	4 weeks
Primary outcome	Insomnia (self-reported ISI-J)
Secondary outcome	Pittsburgh Sleep Quality Index, Depression (BDI-II), Anxiety (GAD-7), Cognitive (digit span, digit symbol substitution)
Result	Eszopiclone improved insomnia severity and anxiety Suvorexant = non-significant improvements Depression and cognition unchanged
Weaknesses	Small (n=18, LOCF, 89% completion)
Risks	Although less effective here, suvorexant is safer in the elderly and has lower risk of tolerance/dependence
Dose	Age < 65: eszopiclone 3 mg, suvorexant 20 mg Age ≥ 65: eszopiclone 2 mg, suvorexant 15 mg
FDA Approval	Yes
Funding	Research grant
Monthly cost	Eszopiclone $10; Suvorexant $420

Shigetsura Y, Imai S, Endo H, et al. Assessment of suvorexant and eszopiclone as alternatives to benzodiazepines for treating insomnia in patients with major depressive disorder. *Clin Neuropharmacol* 2022, 45(3):52-60.

9

ANTIDEPRESSANT CONTINUATION

Long-term treatment reduced the relapse rate by 17 percentage points in this large trial of recurrent depression in primary care

Antidepressant Continuation	
Design	Randomized controlled trial
Size	Large (478); 81% completed
Subjects	Adults in primary care with at least 2 past depressions, currently in remission for at least 9 months (majority > 3 yr) Patients felt well enough to stop their antidepressant
Intervention	Slow cross taper to placebo over 1 month or remain on Citalopram, sertraline, fluoxetine, or mirtazapine
Duration	1 year
Primary Outcome	Relapse (by clinical interview with CIS-R q3mth)
Intent to treat?	No (drop out 7%, equal in both groups)
Result	Slightly higher relapse rates in placebo group (39% vs 56%) Anxiety and quality of life slightly lower in placebo group
Weaknesses	More WD symptoms in discontinuation group (3.1% vs 1.9%)
Funding	NIMH

Lewis G, Marston L, Duffy L, ET AL. Maintenance or Discontinuation of Antidepressants in Primary Care. N Engl J Med. 2021. 30;385(14):1257-1267.

10

“SKILLS FOR PILLS”

DBT Skills group fostered reduction in psych meds, particularly benzodiazepines, in borderline personality disorder

"Skills for Pills"	
Design	Retrospective, observational study
Size	Large (n=329)
Subjects	Borderline personality disorder All were invited to participate in a DBT skills group. Half took part; half did not, and the two were compared.
Selection Biases	Skills group started with greater severity and greater medication load. Those who declined it usually did so because of scheduling conflicts or preference for individual therapy.
Intervention	DBT Skills Group
Duration	6 months
Primary outcome	Number and type of psychotropics
Result	**Skills:** Reduction in number and dosage of meds **No Skills:** Slight increase in meds Largest drop was in benzodiazepines (Skills: 54% to 28%; No Skills: 40% to 41%); also drop in mood stabilizers and antipsychotics
Weaknesses	Retrospective, non-randomized, no symptom ratings.
Funding	Centro de Investigación Biomédica en Red de Salud Mental

Mitchell JM, Bogenschutz M, Lilienstein A, et al. MDMA-assisted therapy for severe PTSD: a randomized, double-blind, placebo-controlled phase 3 study. Nat Med. 2021;27(6):1025-1033.


RUNNER UPS

Runner Ups

Treatment	Finding
PEA	Effective as augmentation in mania in small RCT (600mg bid) Palmitoylethanolamide (PEA) is a fatty acid with possible benefits in depression
DBT	6 months was as effective as 12 months in large RCT (comparisons at 12 mth)
Mediterranean Diet	Treated depression in young men with only 3 sessions (4th RCT to test it) moodtreatmentcenter.com/lifestyle
SAGE test	A free cognitive test patients can administer at home Detected dementia 6 mth earlier than clinician-administered MMSE https://wexnermedical.osu.edu/brain-spine-neuro/memory disorders/sage#SAGETest

Runner Ups

- Abedini T, Hosseyni R, Ghannadi F, Sanjari Moghaddam H, Khodaei Ardakani MR, Talaei A, Akhondzadeh S. Efficacy and safety of palmitoylethanolamide as an adjunctive treatment for acute mania: a randomized, double-blind and placebo-controlled trial. Psychiatry Clin Neurosci. 2022 Jun 23.
- McMain SF, Chapman AL, Kuo JR, Dixon-Gordon KL, Guimond TH, Labrish C, Isaranuwatchai W, Streiner DL. The Effectiveness of 6 versus 12 Months of Dialectical Behavior Therapy for Borderline Personality Disorder: A Noninferiority Randomized Clinical Trial. Psychother Psychosom. 2022 Jun 23:1-16.
- Bayes J, Schloss J, Sibbritt D. A randomised controlled trial assessing the effect of a Mediterranean diet on the symptoms of depression in young men (the 'AMMEND' study): a study protocol. Br J Nutr. 2021 Sep 14;126(5):730-737.
- Scharre DW, Chang SI, Nagaraja HN, Wheeler NC, Kataki M. Self-Administered Gerocognitive Examination: longitudinal cohort testing for the early detection of dementia conversion. Alzheimers Res Ther. 2021 Dec 6;13(1):192.

SUMMARY

Treatment	When to use	Dose
Dextromethorphan	Augmentation of bupropion in depression	45 mg bid
Antidepressant Continuation	When used in recurrent depression (≥ 2), lowers relapse from 56% to 38%	
Mediterranean Diet	Depression	
Clonidine	Augmentation in bipolar mania	0.2-0.6 mg qhs
PEA	Augmentation in bipolar mania	600 mg bid
Mirtazapine	Augmentation of SSRI in OCD	30-45 mg qhs
Shift work	Advise to sleep in late afternoon	
Eszopiclone	May replace benzos for insomnia	2-3 mg qhs
Vitamin B6	Antipsychotic prolactinemia, akathisia Tremor on various meds	300 mg bid
DBT	Skills group cuts benzo use in half 6 month DBT may work as well as 12 mth	
Varenicline	First-line for nicotine cessation	1 mg bid
SAGE test	At-home screening for dementia	
SAINT TMS	Treatment-resistant depression	