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

LITHIUM AFTER ECT

LITHIUM AUGMENTATION PREVENTS RELAPSE AFTER ECT WITH A NNT OF 7

Lithium after ECT	
Design	Meta-analysis
Size	14 trials (N=9,748) 3 RCT (all positive, compared to maintenance ECT
Subjects	Adults with depression after a course of ECT Lithium usually as augmentation 7 trials included bipolar depression
Duration	4-14 months (median 6)
Primary outcome	Relapse rate
Result	Lithium prevented relapse into depression (NNT = 7)
Weaknesses	Only 1 RCT tested the hypothesis directly 4 trials were retrospective
Risks	Renal, thyroid, toxicity
Dose	Unknown (but level recommended for depression is 0.6-0.8 though could go up to 30% lower in elderly)
FDA Approval	Off-label
Funding	Research grant
Monthly cost	$10

Lambrichts S, Detraux J, Vansteelandt K, et al. Does lithium prevent relapse following successful electroconvulsive therapy for major depression? A systematic review and meta-analysis. Acta Psychiatr Scand. 2021;143(4):294-306. doi:10.1111/acps.13277

2

MINOCYCLINE FOR DEPRESSION

Worked in patients with high inflammation (CRP ≥3 mg/L) in this small RCT

Minocycline Augmentation	
Design	Randomized controlled trial
Size	Small (44)
Subjects	Major depression, non-response to current antidepressant At least mild inflammation (hs-CRP ≥ 1 mg/L)
Treatment	Minocycline 200mg/d
Duration	4 week
Primary outcome	HAM-D-17 change from baseline in subjects with high (hs-CRP ≥ 3 mg/L) vs. low (hs-CRP 1-3 mg/L) inflammation
Intent to treat?	Yes (drop out 11%)
Result	Large effect in high inflammation group (d=1.9) No effect in low inflammation group
Weaknesses	Small size, short duration
Risks	Well tolerated (photosensitivity, dizziness, nausea, allergic rash) Microbiome changes (C. difficile diarrhea possible)
Mechanism	Anti-inflammatory, neuroprotective, glutamate antagonism
FDA Approval	Off-label
Funding	NIH
Monthly cost	$30

Nettis MA, Lombardo G, Hastings C, et al. Augmentation therapy with minocycline in treatment-resistant depression patients with low-grade peripheral inflammation: results from a double-blind randomised clinical trial. Neuropsychopharmacology. 2021;46(5):939-948.

3

QUETIAPINE IN BIPOLAR WITH OCD

Adds to list of non-antidepressant options (topiramate, memantine, ondansetron, CBT, TMS)

Quetiapine in Bipolar with OCD	
Design	Randomized double-blind, placebo controlled trial
Size	Small (47)
Subjects	Euthymic bipolar I with OCD
Treatment	Quetiapine titrated to response (mean 325 mg/d) Start 25 mg/d x 1 wk, raise by 50mg/week
Duration	8 week
Primary outcome	Response on Yale–Brown Obsessive–Compulsive Scale (YBOCS)
Intent to treat?	No (drop out 15% equal in both groups)
Result	Positive (response 50% vs. 5%)
Weaknesses	Small size, drop outs not handled
Risks	Metabolic, tardive dyskinesia, sedation, EPS Antipsychotics are also known to worsen OCD
FDA Approval	Off-label
Funding	University grant
Monthly cost	$30

Sahraian A, Ghahremanpouri B, Mowla A. Is quetiapine effective for obsessive and compulsive symptoms in patients with bipolar disorder? A randomized, double-blind, placebo-controlled clinical trial, CNS Spectr. 2021;1-5.

4

NALTREXONE-BUPROPION IN METHAMPHETAMINE USE DISORDER

MODEST EFFECTS IN A LARGE TRIAL. JOINS MIRTAZAPINE, ATOMOXETINE, TOPIRAMATE, AND CITICOLINE FOR METH.

Naltrexone-bupropion in Methamphetamine Use Disorder	
Design	Randomized double-blind, placebo controlled trial (2-stage)
Stages	1: Randomize 24% to treatment, 76% to placebo 2: Non-responders to placebo re-randomized 1:1 to treatment
Size	Large (403)
Subjects	Adults with mod-severe methamphetamine use disorder
Treatment	Naltrexone XR inj (380 mg q3wk) with bupropion XL (450 mg qd)
Duration	6 weeks each stage
Primary outcome	Response (≥ 3/4 negative urine samples)
Intent to treat?	Yes (drop out 7-18%)
Result	Positive (weighted avg response 13.6% vs. 2.5%, NNT 9)
Weaknesses	Second phase was enriched by removing placebo non-responders (but similar results in both phases)
Risks	GI distress, tremor, malaise, sweating, low appetite
FDA Approval	Off-label
Funding	NIH
Monthly cost	$55 oral, $1600 inj

Trivedi MH, Walker R, Ling W, et al. Bupropion and Naltrexone in Methamphetamine Use Disorder. N Engl J Med. 2021;384(2):140-153.

5

DEPRESCRIBING PSYCH MEDS IN NURSING HOMES

NO WORSE AFTER THOUGHTFUL REMOVAL OF >1 MED, POSSIBLY BETTER

Deprescribing Psych Meds in Nursing Homes	
Design	Randomized, single-blinded controlled trial
Size	Large (723 patients in 33 nursing homes in Norway)
Subjects	Average age 86 (not schizophrenia, not end-of-life)
Intervention	COSMOS: Review meds experts using standardized assessments, evidence-based guidelines; Nurses increase patient activities. Control = Treatment as usual
Duration	4 months
Primary outcome	Number of psych meds (including anti-dementia)
Secondary outcomes	Neuropsychiatric Inventory Nursing Home Version (NPI-NH) Cornell Scale of Depression in Dementia (CSDD) Lawton and Brody's Physical Self Maintenance Scale (PSMS)
Intent to treat?	No (drop out 40%, death rate 9% in each group, others moved)
Result	Positive (≥ 1 psychotropic stopped in 34% vs 14% of patients) ADLs and self-care improved with deprescribing, other scales unchanged
Weaknesses	Multiple comparisons, high drop-out, nurses who helped increase ADLs were the ones that rated them, some MDs in intervention group were also in control group
Risks	None in study (possible worsening of psychiatric syndromes, withdrawal effects)
Funding	The Research Council of Norway and Rebekka Ege Hegermann's Foundation

Gedde MH, Husebo BS, Mannseth J, Kjome RLS, Naik M, Berge LI. Less is more: The impact of deprescribing psychotropic drugs on behavioral and psychological symptoms and daily functioning in nursing home patients. Results from the cluster-randomized controlled COSMOS trial. Am J Geriatr Psychiatry. 2021;29(3):304-315.

COSMOS Program

Standardized assessments
Behavioral symptoms of dementia (BPSD), ADLs, pain scores, cognitive status and ability, well-being and quality of life, BP/pulse, BMI

Medication reviews
With help of a nurse who took input on patient and family preferences and 2 academic physicians

Organization of patient's activities
Nurses adjust this to patient's needs and preferences

Deprescribing Guides

Deprescribing guides for antipsychotics, benzos, and anti-dementia meds
www.deprescribing.org

Beers criteria of risky meds in elderly
Google “American Geriatrics Society 2019 Updated AGS Beers Criteria for Potentially Inappropriate Medication Use in Older Adults” .pdf

All-in-one page from New Zealand
www.hqsc.govt.nz/our-programmes/medication-safety/projects/appropriate-prescribing-toolkit/tools-for-deprescribing/

Anticholinergic Burden Scale
www.acbcalc.com

Hypnotics Allowed by Beers

1. Doxepin (Silenor or liquid-generic 10mg/ml, 3-6 mg hs)
2. Ramelteon (Rozerem)
3. Melatonin (1-3 mg hs, moodtreatmentcenter.com/products)
4. Orexin antagonists
   Lemborexant (Dayvigo), suvorexant (Bellsomra)

and... CBT-insomnia!


IN NEED OF
REPLICATION

6

A DIET FOR ADHD

THE DASH DIET IMPROVED MULTIPLE SYMPTOMS IN CHILDREN

A Diet for ADHD	
Design	Randomized single-blind controlled trial
Size	Small (n=80)
Subjects	Children (6-12, only 1 girl) with ADHD in Iran (no meds/therapy)
Intervention	DASH Diet vs. Control diet
Duration	4 months
Outcomes (?primary)	Parent, child, and teacher rated ADHD symptoms (abbreviated 10-item Conner's scale, 18-item Swanson, Nolan and Pelham (SNAP-IV) scale, Strengths and Difficulties Questionnaire (SDQ))
Intent to treat?	No (drop out 7%, equal in both groups)
Result	Most measures positive (Parent/teacher Conner's, SNAP hyperactivity but not attention; Emotional symptoms, conduct, pro-social behaviors)
Weaknesses	Small size, primary outcome not specified Only teachers were blinded (but their ratings were most positive) Control diet was somewhat healthy
Risks	None (similar diet worked in 3 RCT of depression)
Funding	University

Khoshbakht Y, Moghtaderi F, Bidaki R, Hosseinzadeh M, Salehi-Abargouei A. The effect of dietary approaches to stop hypertension (DASH) diet on attention-deficit hyperactivity disorder (ADHD) symptoms: a randomized controlled clinical trial. Eur J Nutr. 2021;10.1007

DASH DIET

6-8
servings per day
of whole grains

4-5
servings per day
of vegetables

4-5
servings per day
of fruits

2-3
servings per day of
fat-free or low-fat dairy

4-5
servings per week of
nuts, seeds, legumes

Less than **6**
servings per day of
lean meat, poultry, fish

Less than **5**
servings per week
of sweets

2-3
servings per day
of fats and oils

Purchasing tips

Choose packaged foods with

- Fewer chemical ingredients
- Lower salt
- Lower added sugars

Ultra processed foods:

Packaged meals, hotdogs, cold cuts, bacon, sausage, soda, chips, microwave popcorn, candy, frozen desserts, sugary breakfast cereals, energy bars, bottled drinks, Frappuccinos, pre-mixed baking items, margarine, and premade sauces.

Nova Classification

1 - Unprocessed or minimally processed foods
2 - Processed culinary ingredients (oils, butter, sugar, salt... used for cooking)
3 - Processed foods (bottled/canned vegetables or fish; cheese, fresh bread)
4 - Ultra-processed food and drink products

Ultra processed foods:

“industrial formulations made entirely or mostly from substances extracted from foods (oils, fats, sugar, starch, and proteins), derived from food constituents (hydrogenated fats and modified starch), or synthesized in laboratories from food substrates or other organic sources (flavor enhancers, colors, and several food additives used to make the product hyper palatable).

Manufacturing techniques include extrusion, moulding and preprocessing by frying. Beverages may be ultra processed.”

A Scanning App

Psych Diet Guide
moodtreatmentcenter.com/lifestyle

Nutri-Score

Fruits, vegetables, fibers, and protein raise the score (“A”).

Sugars, salt, saturated fats, and high caloric density lower the score (“E”).

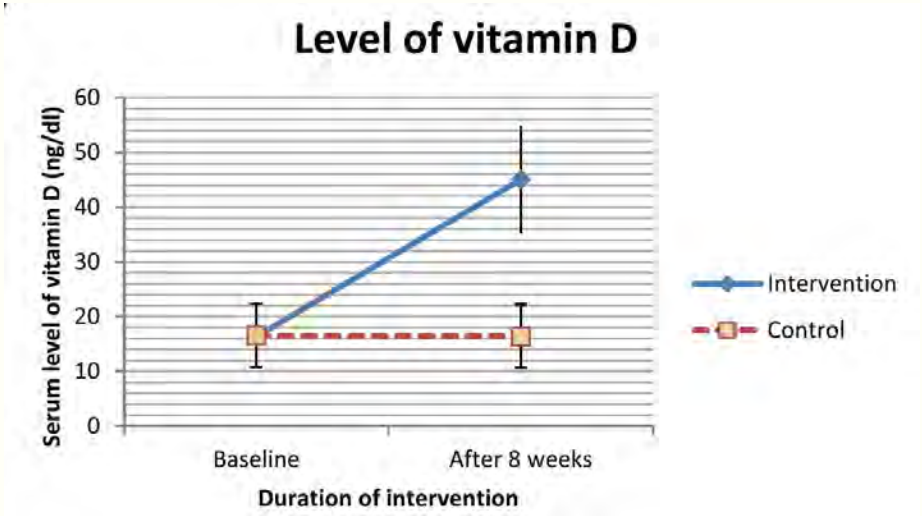
7

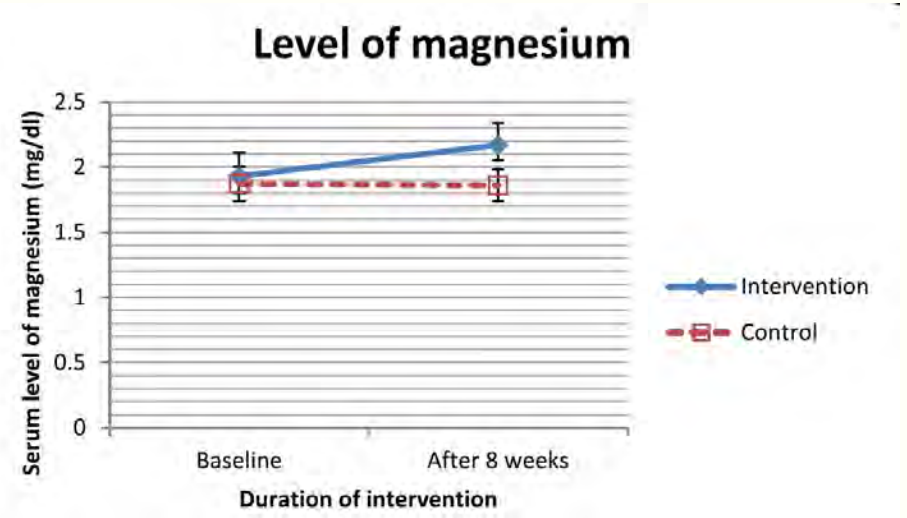
MAGNESIUM AND VITAMIN D IN ADHD

SUPPLEMENTATION HELPED NON-SPECIFIC SYMPTOMS

Mg and Vitamin D in ADHD	
Design	Randomized, double blind, placebo-controlled trial
Size	Small (n=66)
Subjects	Children (6-12) with DSM-IV ADHD in Iran, on methylphenidate 25-hydroxyvitamin D3 < 30 ng/dL (normal 30-40) Mg < 2.3 mg/dL (normal 1.7-2.2)
Intervention	Vitamin D (50,000 IU/week) plus magnesium (6 mg/kg/day)
Duration	8 weeks
Primary outcome	Strengths and difficulties questionnaire
Intent to treat?	N/A (no drop outs)
Result	Positive, effect size moderate to large (emotions, conduct, peer relations, prosocial behaviors, externalizing, internalizing)
Weaknesses	Small size. ADHD-specific scales not assessed.
Risks	Possible with elevated mg or vitamin D levels
Funding	University

Hemamy M, Pahlavani N, Amanollahi A, et al. The effect of vitamin D and magnesium supplementation on the mental health status of attention-deficit hyperactive children: a randomized controlled trial, BMC Pediatr. 2021;21(1):178.





Upper Limits?

Mg ≥ 2.6 mg/dl, Vitamin D ≥ 40 or 60 ng/dl

8

LIGHT THERAPY IN COMBAT-PTSD

PTSD SYMPTOMS IMPROVED INDEPENDENT OF SLEEP AND SEASONALITY

Light Therapy in PTSD	
Design	Randomized, single blind, placebo-controlled trial
Size	Small (n=69)
Subjects	69 veterans with combat related PTSD (Afghanistan/Iraq) History of winter depression excluded 2/3 were receiving other treatments for PTSD
Intervention	Lightbox: 30 min, 10,000 lux UV-filtered white light, within one hour of awakening Control: Low intensity negative air ion generator
Duration	8 weeks
Primary outcome	Clinician Assessed PTSD Scale (CAPS) and Clinician Global Impression Scale (CGI). Self-reported measures of depression, anxiety, side effects, and sleep. Wrist actigraphy
Intent to treat?	No (4% drop out rate)
Result	Positive only for PTSD (CAPS, CGI) Improvement correlated with phase-advance on wrist actigraphy No change in depression, anxiety, and sleep
Weaknesses	Small size
Risks	None in study (caution in eye diseases)
Funding	VA
Cost	$100-130

Youngstedt SD, Kline CE, Reynolds AM, et al. Bright light treatment of combat-related PTSD: A randomized controlled trial. Mil Med. 2021;usab014.

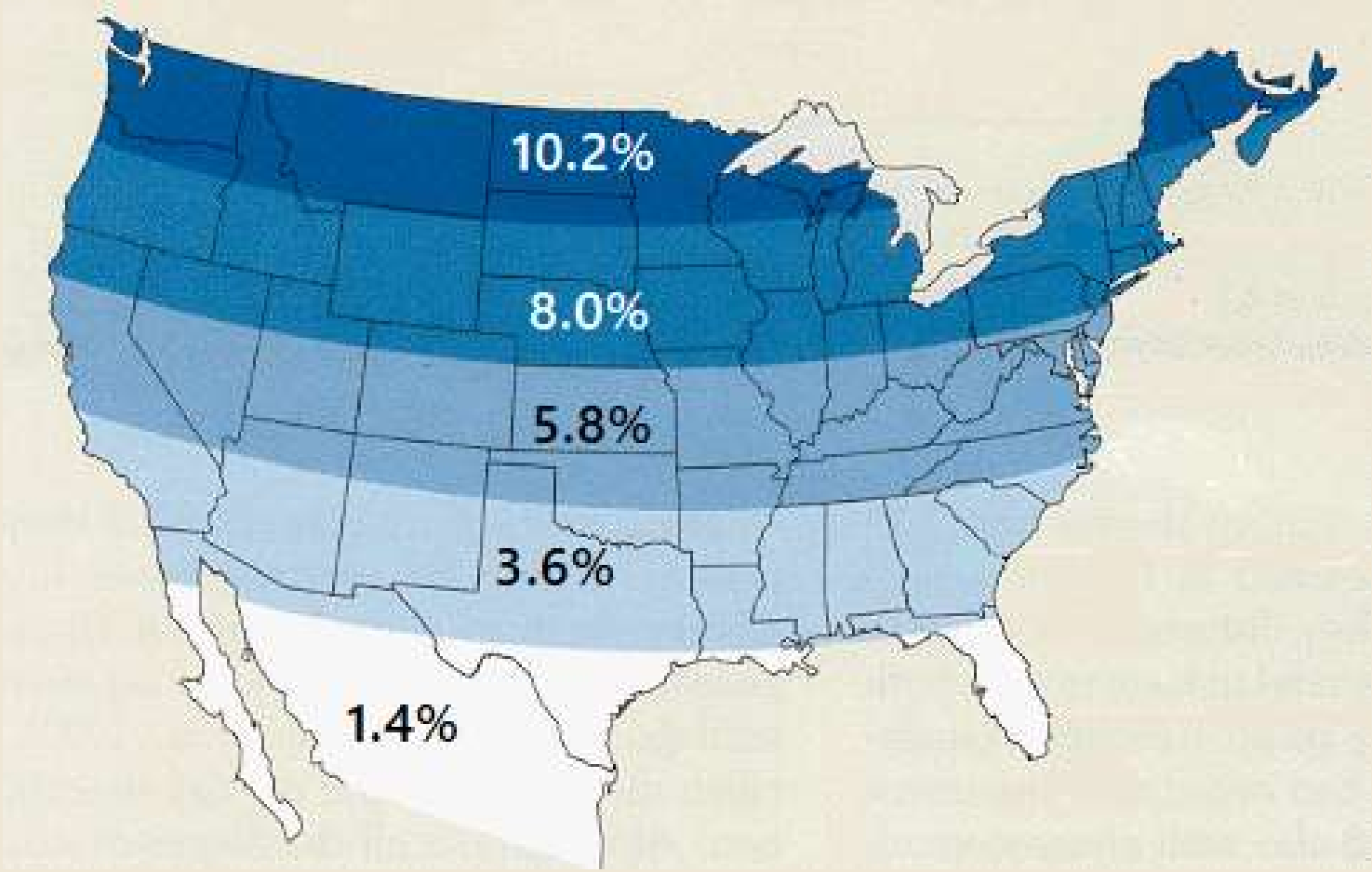
Daylight Plus or Classic

30 minutes in morning, within 1 hour of waking.

“Sit within 18 inches of box with light in field of vision but avoid looking directly into it. Engage in usual activities while under it.”

More at www.cet.org

Winter depression drops off below Charlotte, NC



William Jennings Bryan Dorn VA
Columbia, SC

Dr. Shannon Crowley
NC Wesleyan College

THE FUTURE

10

MDMA ASSISTED THERAPY IN PTSD

ROBUST EFFECTS HELP FAST-TRACK THIS PSCHEDELIC THERAPY

MDMA Assisted Psychotherapy for PTSD	
Design	Randomized, double blind, placebo-controlled phase III trial
Size	Small (n = 90)
Subjects	Severe PTSD (84% developmental trauma, 20% dissociative type) Past substance use disorders allowed Most had tried SSRIs and psychotherapy
Intervention	3 monthly 90-min sessions with MDMA (2 person team) Each followed by 3 weekly sessions to integrate experience
Duration	4 months
Primary outcome	Clinician rated CAPS-5 for PTSD
Secondary outcomes	Sheehan Disability Scale, scales for depression (BDI-II), alcohol and substance use (AUDIT, DUDIT), suicidality, and childhood adverse experiences (ACE)
Intent to treat?	Yes (12% drop out rate)
Result	Robust reduction in PTSD (effect size 0.9) Depression and functioning improved
Risks	Transient increase in BP, pulse, temperature Potential abuse liability, arrhythmias, and neuropsychiatric effects (psychosis, panic, dissociation)
Weaknesses	Small size. Difficult to blind the treatment (30% had tried MDMA).
Funding	Manufacturer (MAPS)

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.

FAILURES

ANTIDEPRESSANTS IN BIPOLAR DEPRESSION

THEY WORSEN RAPID CYCLING, AND DON'T DO MUCH ELSE

Citalopram in Bipolar Depression	
Design	Randomized, double blind, placebo-controlled trial
Size	Medium (n = 119)
Subjects	Bipolar I (63%) or bipolar II (37%) depression
Intervention	Citalopram mean 27 mg/day (start 10 mg/day as needed by 10 mg/week, max 60 mg/day) All on a "traditional mood stabilizer" (lithium, valproate, carbamazepine, or lamotrigine)
Duration	6 week and 1 year
Primary outcome	Rating scales for depression (MADRS) and mania (MRS-SAD) at 6 weeks (primary outcome) and 1 year (seconder outcome)
Intent to treat?	Yes (drop outs 30% short-term, 69% long-term)
Result	No difference in mania or depression after 6 weeks or 1 year History of rapid cycling had more manic symptoms on citalopram
Weaknesses	Secondary outcomes, high drop out
Funding	NIMH

Ghaemi SN, Whitham EA, Vohringer PA, et al. Citalopram for acute and preventive efficacy in bipolar depression (CAPE-BD): A randomized, double-blind, placebo-controlled trial. *J Clin Psychiatry*. 2021;82(1):19m13136.

Treatment	Where it Failed (in RCT)
Psilocybin	Depression, *not* treatment resistant type (did not surpass escitalopram in small, industry sponsored RCT)
Brexpiprazole	Acute mania (in 2 industry sponsored RCTs)
Antipsychotics	Delirium treatment and prevention Quetiapine failed to prevent delirium in a RCT. Earlier, meta-analysis found no benefit with antipsychotics for treatment or prevention of delirium.
Combinatorial genetic panels	MDD outcomes after a 1-3 antidepressants (Genecept) MDD in adolescents
Mirtazapine	PTSD
Riluzole	PTSD
Eszopiclone	PTSD (including sleep and nightmares)
Celecoxib	Augmentation of vortioxetine in MDD
Triple chronotherapy	Major depression (wake therapy + sleep phase advance + light therapy)
Memantine	Cognition in bipolar disorder
Atorvastatin	Nephrogenic diabetes insipidus on lithium

Failures

- Carhart-Harris R, Giribaldi B, Watts R, et al. Trial of psilocybin versus escitalopram for depression. N Engl J Med. 2021;384(15):1402-1411.
- Vieta E, Sachs G, Chang D, et al. Two randomized, double-blind, placebo-controlled trials and one open-label, long-term trial of brexpiprazole for the acute treatment of bipolar mania. J Psychopharmacol. 2021;35(8):971-982.
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- Nikooie R, Neufeld KJ, Oh ES, et al. Antipsychotics for treating delirium in hospitalized adults: a systematic review. Ann Intern Med. 2019;171(7):485-495.
- Vande Voort JL, Orth SS, Shekunov J, et al. A randomized controlled trial of combinatorial pharmacogenetics testing in adolescent depression. J Am Acad Child Adolesc Psychiatry. 2021;S0890-8567(21)00220-3.
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- Pollack MH, Hoge EA, Worthington JJ, et al. Eszopiclone for the treatment of posttraumatic stress disorder and associated insomnia: a randomized, double-blind, placebo-controlled trial. J Clin Psychiatry. 2011;72(7):892-897.
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- Yuen LD, Chen Y, Stewart JW, Arden P, Hellerstein DJ. A randomized, controlled trial assessing the acute efficacy of triple chronotherapy in unipolar depression. J Affect Disord. 2021;282:1143-1152.
- Fotso Soh J, Beaulieu S, Trepiccione F, et al. A double-blind, randomized, placebo-controlled pilot trial of atorvastatin for nephrogenic diabetes insipidus in lithium users. Bipolar Disord. 2021;23(1):66-75.
- Lu RB, Wang TY, Lee SY, et al. Add-on memantine may improve cognitive functions and attenuate inflammation in middle- to old-aged bipolar II disorder patients. J Affect Disord. 2021;279:229-238.
- Fotso Soh J, Beaulieu S, Trepiccione F, et al. A double-blind, randomized, placebo-controlled pilot trial of atorvastatin for nephrogenic diabetes insipidus in lithium users. Bipolar Disord. 2021;23(1):66-75.

SUMMARY

Treatment	When to use
Lithium	To prevent depression after ECT in bipolar and unipolar
Minocycline	Treatment resistant depression with hs-CRP ≥ 3
Quetiapine	Bipolar with OCD
Naltrexone-Bupropion	Methamphetamine use disorders
Deprescribing	Nursing home residents
DASH Diet	ADHD
Mg + Vit D	ADHD
Lightbox	PTSD