Beyond Neurotransmitters: How Metabolism is Foundational for Mental Health

An older idea, new science, and a wider horizon for psychiatry

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Grand Rounds · Silver Hill · June 24, 2026

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DISCLOSURES

Matthew Bernstein, MD

In compliance with the ACCME Standards for Commercial Support of CME, as the speaker I do not have any relevant financial relationships to disclose in relation to this presentation.

LEARNING OBJECTIVES

As a result of participating in this activity, you should be able to:

1. Describe the bidirectional relationship between metabolic health and brain health, focusing on the mechanisms by which metabolism affects mental health symptoms

2. Review the evidence for metabolic interventions, including ketogenic diets and exercise, in the management of serious mental illnesses

3. Discuss the interventions that clinicians can employ in their practices today that leverage these important insights to improve outcomes

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ONE PATIENT'S TRAJECTORY

The question this talk tries to answer

THEN
on admission to Accord, 12 months ago

- Years of intensive inpatient and residential psychiatric care
- Persistent auditory hallucinations; sedated (only awake about 10 hours per day) and unable to function socially or vocationally

MEDICATIONS · 8 daily

Clozapine ~500 mg	Cariprazine 1.5 mg
Lithium 600 mg	Lamotrigine 250 mg
Fluvoxamine 50 mg	+ 3 supportive meds
	for clozapine side effects

NOW
12 months later

- Working part-time; exercising regularly
- Re-engaged with family and creative pursuits. Per parents: “we got our son back!”

MEDICATIONS · 4 daily

Clozapine ~90 mg	↓ **~80%**
Lithium 450 mg	↓ **~25%**
Lamotrigine 250 mg	*unchanged*
Fluvoxamine 50 mg	*unchanged*

One patient. Illustrative, not evidence. Chosen because the conventional treatment was excellent — and he was still losing his life.

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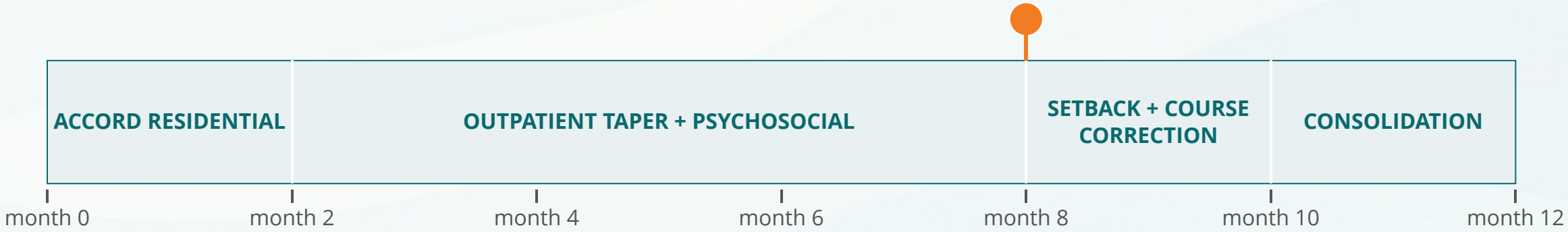
HOW WE GOT THERE: 12 MONTHS, NOT LINEAR

Discharged at 2 months; one symptom recurrence at month 8 required a course correction

Setback at month 8 (≈ 6 months post-discharge): *AH ↑, social withdrawal, missed a week of work.*



Immersive metabolic programming—KD, exercise, circadian rhythm, mind-body practices, etc.
Residential structure
Alliance building
Begin medication tapering

Gradual clozapine taper
Nutrition / lifestyle
Intensive psychosocial work
Functional gains compound

Clozapine briefly ↑ to ~100 mg
Diet/exercise tightened (ketones had drifted)
Social engagement rebuilt with support

Symptoms back to minimal
Full functional recovery
Clozapine re-lowered to ~90 mg

The work was the combination — metabolic + psychosocial + careful tapering.

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WHAT THIS CASE IS — AND ISN'T

- **This is N = 1.** It's not evidence — it poses a question.
- **Selection: conventional care was excellent, and he was still losing his life.** Most arcs are less dramatic.
- **He is not off medication.** He is on a fraction. Clozapine remains in his regimen.
- **The combination matters.** No single intervention did this.

What biological framework makes this possible?

That's the next 65 minutes.

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TODAY'S ROADMAP

Five sections, ~65 minutes

1. **The metabolic gap**
   The clinical gap our current model leaves behind
2. **Ketogenic metabolic therapy**
   Mechanism and a century of precedent
3. **Clinical evidence**
   What the trials actually show
4. **More mechanisms — why it works**
   How metabolic and brain systems converge
5. **Putting it into practice**
   Implementation, deprescribing, and synergistic care

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SECTION 1

The Metabolic Gap

The clinical gap our current model leaves behind

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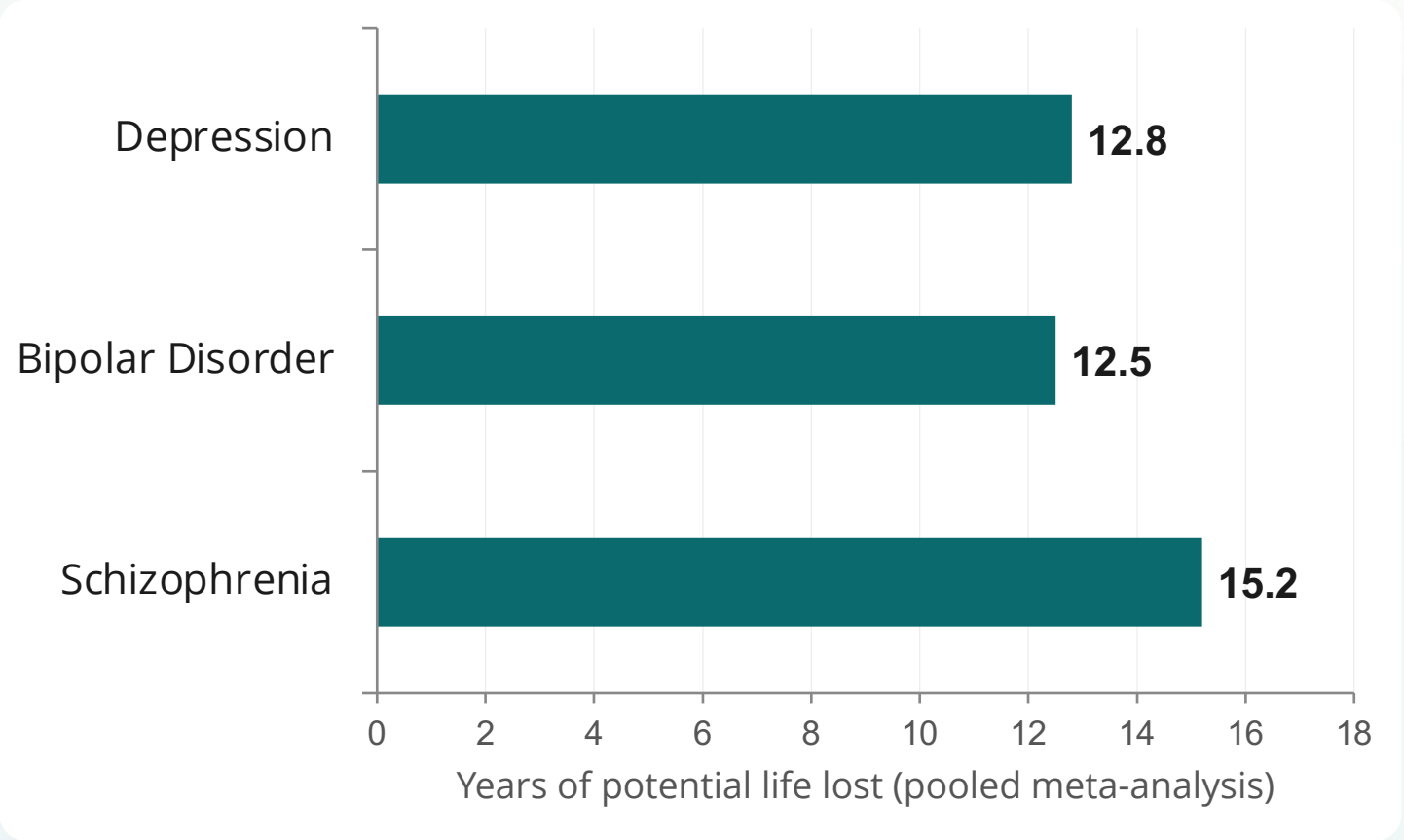
THE MORTALITY GAP

Excess mortality in serious mental illness — driven by cardiometabolic disease



Why?

Excess mortality is largely cardiometabolic — not suicide

Drivers include:

- Diabetes, cardiovascular disease, obesity
- Antipsychotic-induced metabolic burden
- Reduced access to somatic care
- Intrinsic disease-related metabolic dysregulation

Chan JKN, et al. eClinicalMedicine 2023;65:102294. Chesney E, Goodwin GM, Fazel S. World Psychiatry 2014;13(2):153–160.

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THE TREATMENT-RESISTANCE GAP

Symptom reduction ≠ functional recovery

30–50%

Treatment resistance

across psychiatric disorders despite multiple medication trials

10–20

Years of life lost

in serious mental illness vs. matched controls

Persistent

Functional impairment

in occupational, social, cognitive, and independent-living domains — even when symptoms are reduced

- **We don't achieve adequate functional recoveries because we treat the symptom, not the disease.**
- *A neurotransmitter-focused, symptom-oriented model leaves the underlying metabolic biology — cellular energy deficits, insulin signaling dysfunction, mitochondrial impairment — unaddressed.*

Penninx BWJH, Lange SMM. Dialogues Clin Neurosci 2018. Sethi et al. Nature Mental Health 2026.

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METABOLIC HEALTH ≠ WEIGHT

The clinical target is metabolic function, not BMI

Among OBESE adults (BMI ≥ 30): 31.7% are metabolically HEALTHY

Among NORMAL-WEIGHT adults (BMI < 25): 23.5% are metabolically UNHEALTHY ("skinny-fat")

Wildman 2008 (NHANES 1999–2004, US adults ≥20): *"metabolically unhealthy" = ≥2 of 6 cardiometabolic abnormalities (↑BP, ↑triglycerides, ↑glucose, ↑HOMA-IR, ↑CRP, ↓HDL).*

→ Screen for metabolic function, not just BMI.

Wildman RP, et al. Arch Intern Med 2008;168(15):1617–1624. Zembic A, et al. JAMA Netw Open 2021.

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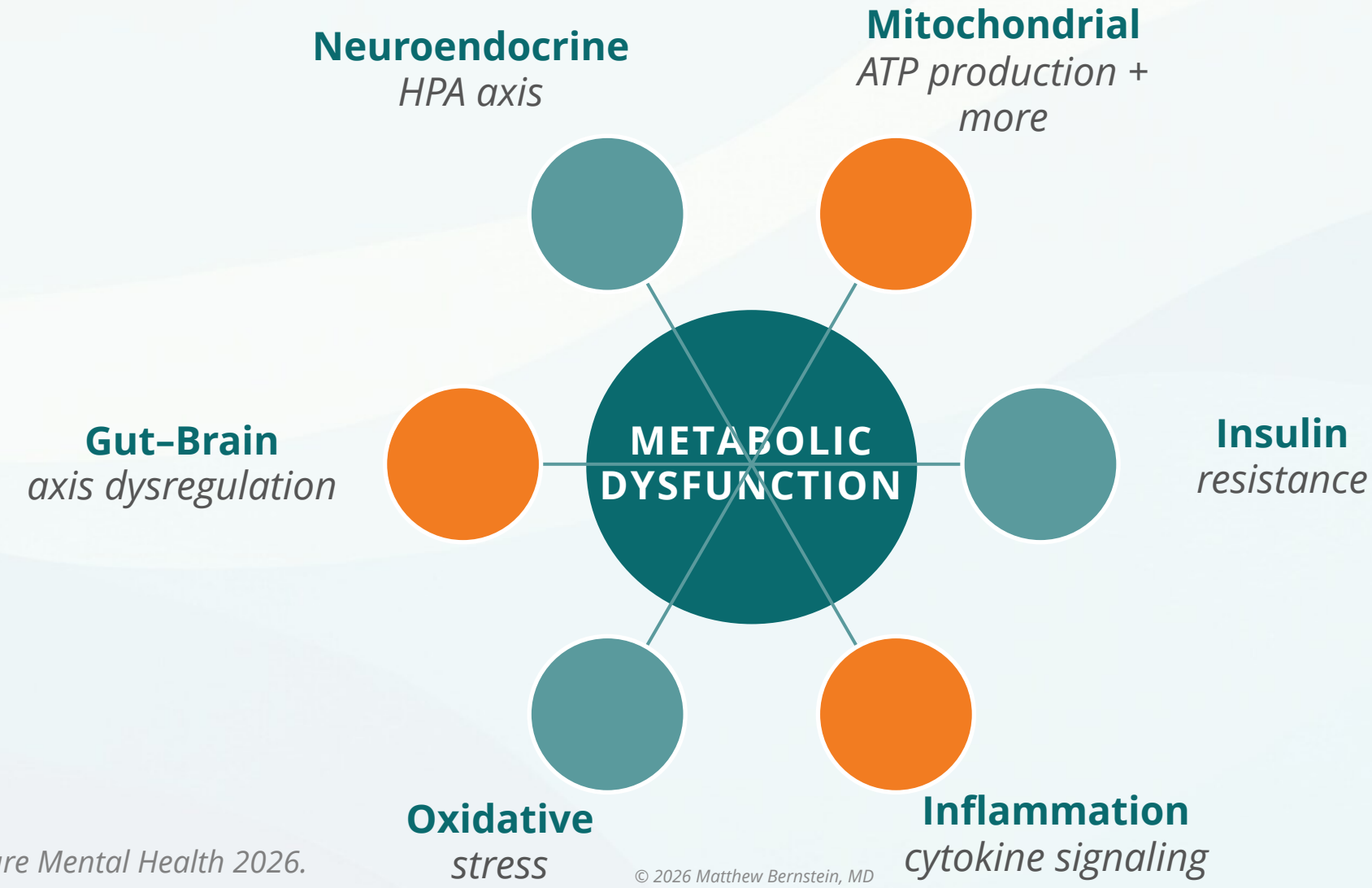
THE METABOLIC PSYCHIATRY FRAMEWORK

Five interdependent biological systems converge on brain function



Sethi et al. Nature Mental Health 2026.

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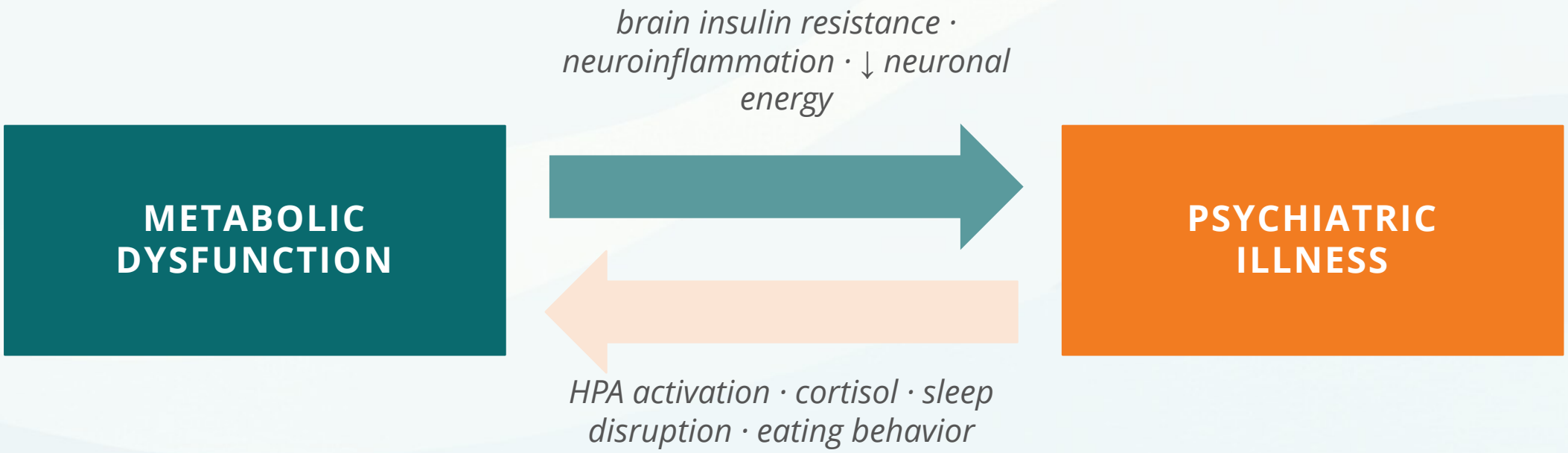
A BIDIRECTIONAL, SELF-REINFORCING SYSTEM

Metabolic and psychiatric dysfunction prime and amplify each other



Shared mechanisms: *insulin resistance · mitochondrial dysfunction · oxidative stress · inflammation*

Perry BI, et al. JAMA Psychiatry 2021;78(4):416–425. Sethi et al. Nature Mental Health 2026.

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THE BRAIN IS A HIGH-DEMAND, LOW-RESERVE ORGAN

Even mild metabolic disruption shifts neural energetics

2% of body weight — uses ~20% of the body's energy at rest

Minimal energy reserves *(limited glycogen, no fat storage)* → high vulnerability to metabolic disruption

WHAT METABOLIC DISRUPTION DOES TO BRAIN ENERGETICS

Drivers (multifactorial): *insulin resistance · inflammation · oxidative stress · medications · genetic vulnerability*

↓ Oxidative phosphorylation
Mitochondria can't meet neuronal demand

↑ Glycolytic compensation (lactate shift)
Yield drops to ~2 ATP / glucose vs ~30 from OXPHOS

↓ Net ATP availability
Energy supply mismatched to high-demand processes (Na^+/K^+ pump, synaptic vesicle cycling)

→ Network instability
Impaired synaptic transmission, slower processing, reduced stress resilience

Clinical correlates: *anhedonia · psychomotor slowing · cognitive fatigue · reduced executive function*

Attwell D, Laughlin SB. J Cereb Blood Flow Metab 2001;21:1133–1145. Sethi et al. Nature Mental Health 2026.

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SECTION 2

Ketogenic Metabolic Therapy

Mechanism and a century of precedent

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ESTABLISHED PRECEDENT: A METABOLIC THERAPY FOR A BRAIN DISORDER

The ketogenic diet has treated epilepsy for over 100 years, and ***works when medications fail***

THE EFFECT OF KETONEMIA ON THE COURSE OF EPILEPSY

Interest in the treatment of essential epilepsy has been again aroused by the favorable results of prolonged fasting reported from the Presbyterian Hospital in New York by Dr. H. R. Geyelin. A fairly large number of patients with severe cases of epilepsy were subjected by Dr. Geyelin to periods of absolute fasting and a good proportion of these patients remained free from epileptic seizures during the fasting period and for several months after their return to normal diets. It is necessary to maintain the utmost conservatism in drawing conclusions from the results of therapeutic measures in this disease, since the interval between attacks, even in the absence of therapy, may be very long, and also because so many procedures, which at one time or another had been thought curative, have failed in the end. Nevertheless, Dr. Geyelin's results are promising.

It has occurred to us that the benefit of Dr. Geyelin's procedure may be dependent on the ketonemia which must result from such fasts and that possibly equally good results could be obtained if a ketonemia were produced by some other means. The ketone bodies, acetoacetic acid and its derivatives, (b- oxybutyric acid and acetone) are formed from fat and protein whenever a disproportion exists between the amount of fatty acid and the amount of sugar actually burning in the tissues. The recent work of Shaffer makes it highly probable that the sugar enters into a definite chemical di-molecular reaction with acetoacetic acid. In any case, as has long been known, it is possible to provoke ketogenesis by feeding diets which are very rich in fat and very low in carbohydrate. It is proposed, therefore, to try the effect of such ketogenic diets on a series of epileptics.

In choosing cases for study we are anxious to take only patients with so-called essential epilepsy who are having attacks of grand mal or psychic equivalents at fairly frequent intervals, two or more a week. We desire to place such patients in the hospital where the food intake can be quantitatively controlled and where the effects produced may be followed by repeated analysis of blood and urine.

R. M. Wilder

The Clinic Bulletin · Mayo Clinic · July 27, 1921

> ***"It is possible to provoke ketogenesis by feeding diets which are very rich in fat and very low in carbohydrate. It is proposed, therefore, to try the effect of such ketogenic diets on a series of epileptics."***

— R.M. Wilder, The Clinic Bulletin, Mayo Clinic, 1921

the first proposal — and naming — of the ketogenic diet

13 **randomized controlled trials**
in ***drug-refractory*** *epilepsy*

2 **Cochrane reviews**
confirm efficacy ***when medications fail***

Wilder RM. The effect of ketonemia on the course of epilepsy. Mayo Clin Bull 1921;2:307. Anderson J, et al. Curr Treat Options Psychiatry 2025.

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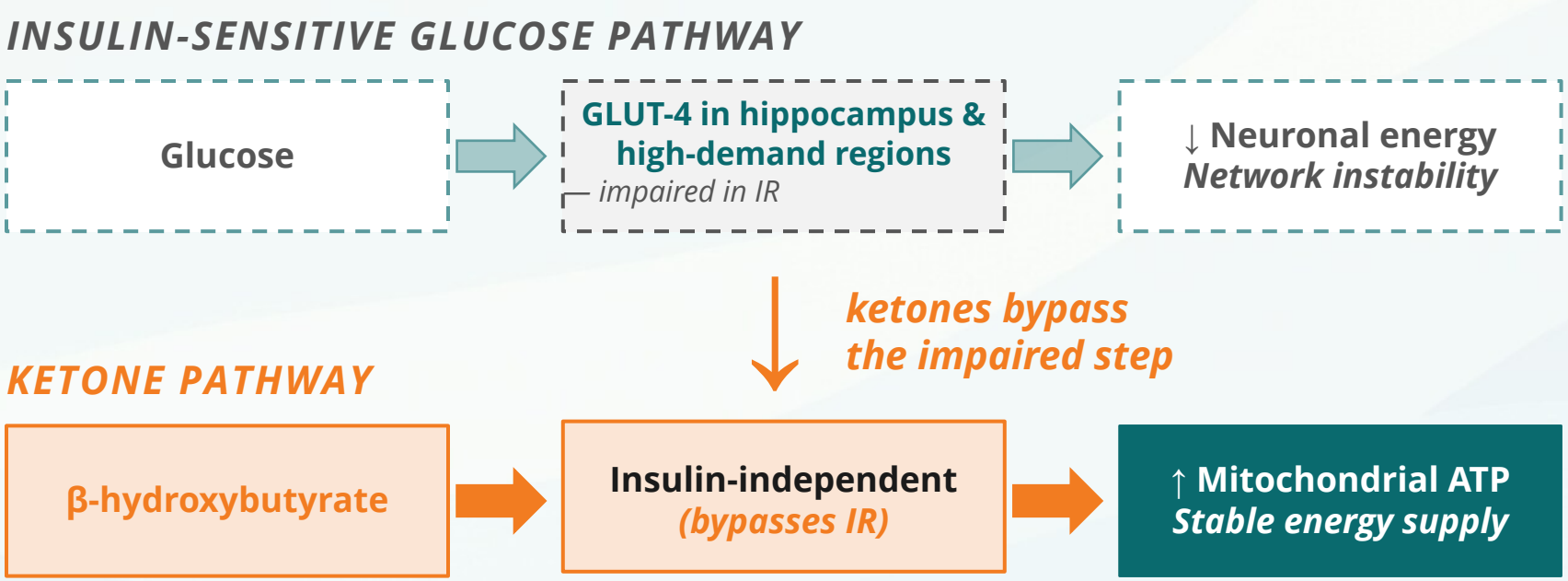
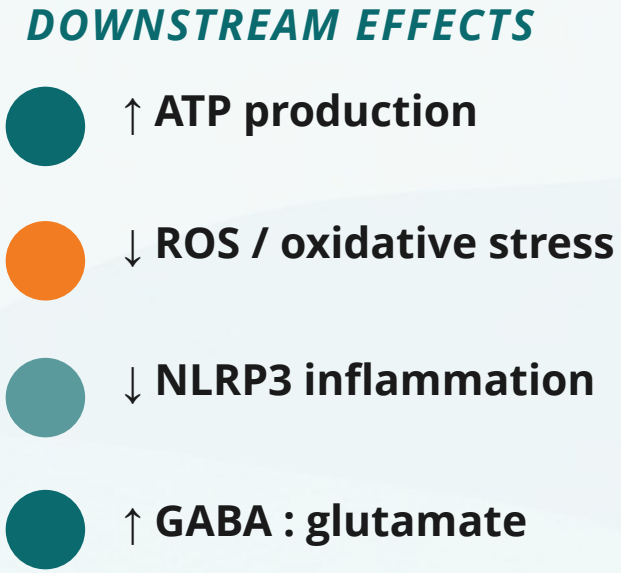
KETONES AS BRAIN FUEL

An insulin-independent energy source that bypasses impaired glucose uptake





Ketones function as both alternative fuel and metabolic signaling molecules.

Targeting shared core mechanisms: mitochondrial function · oxidative stress · inflammation · neuroplasticity.

McNay EC, Pearson-Leary J. Exp Neurol 2020;323:113076. Newman JC, Verdin E. Annu Rev Nutr 2017. Youm Y-H, et al. Nat Med 2015.

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CELLULAR EFFECTS OF KETOGENIC METABOLISM

Five intersecting biological systems

SYSTEM	MECHANISM	PSYCHIATRIC RELEVANCE
Mitochondria	BHB activates PGC-1α → biogenesis & mitophagy; ↑ ATP production	*Restores cellular energetics; addresses convergent vulnerability across MDD, BD, SCZ*
Inflammation	BHB inhibits NLRP3 inflammasome → ↓ IL-1β, IL-18	*Modulates immuno-metabolic depression subtype (~20–30% of cases)*
Oxidative stress	↑ NAD^+/NADH ratio; ↑ endogenous antioxidant systems	*Reduces cellular damage and supports neural resilience*
Neurotransmis-sion	↑ GABA : glutamate balance; ↓ excitotoxicity	*Stabilizes neural networks; explains seizure efficacy*
Insulin signaling	↓ hyperinsulinemia; restored peripheral & central insulin sensitivity	*Particularly relevant in treatment-resistant bipolar depression*

Newman JC, Verdin E. Annu Rev Nutr 2017. Youm Y-H, et al. Nat Med 2015. Calkin C, et al. J Clin Psychiatry 2022.

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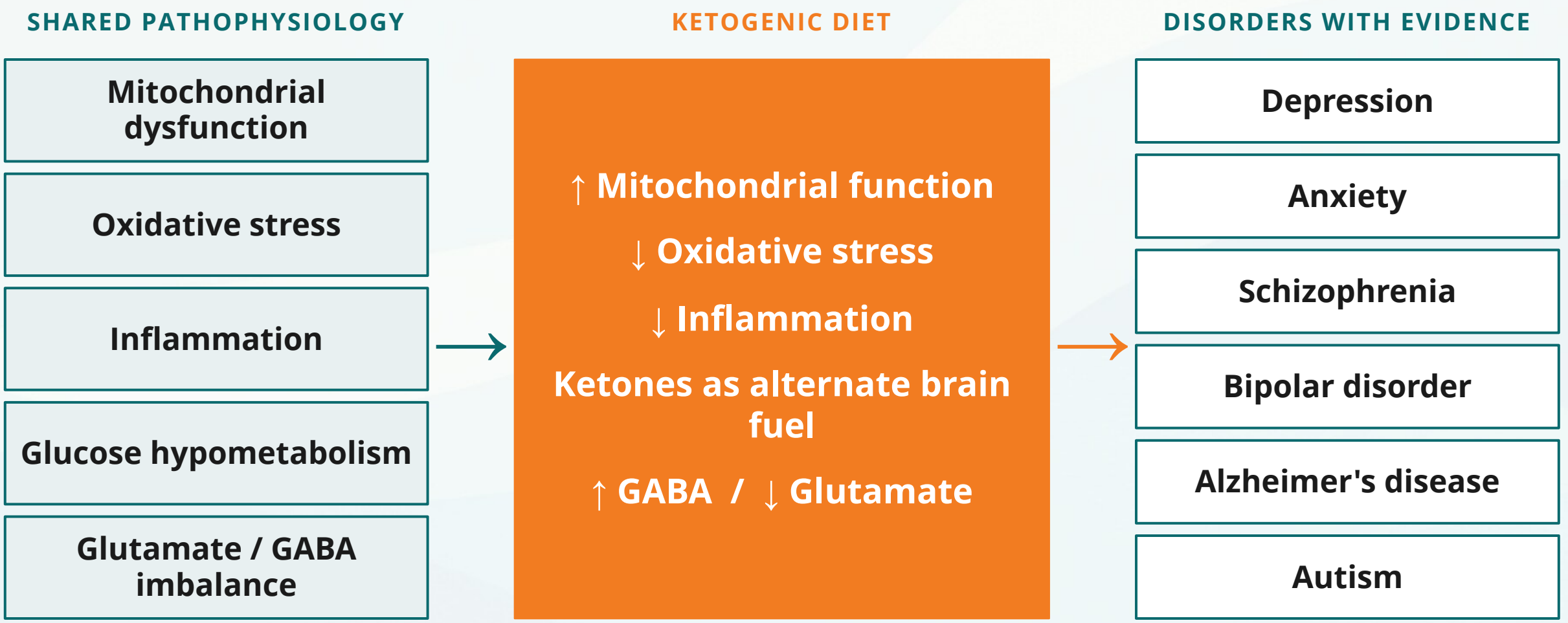
KETOGENIC DIET AS *TRANSDIAGNOSTIC* METABOLIC THERAPY



Evidence varies by disorder: RCT-level for depression (Gao 2026, n=88) and Alzheimer's/MCI; uncontrolled trials and pilots for SCZ and BD; one small randomized trial (El-Rashidy 2017, n=45) plus case series for autism.

Adapted from Anderson J, et al. Curr Treat Options Psychiatry 2025;12:1 (Fig. 1). El-Rashidy O, et al. Metab Brain Dis 2017;32(6):1935–1941.

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SECTION 3

Clinical Evidence

What the trials show in SMI

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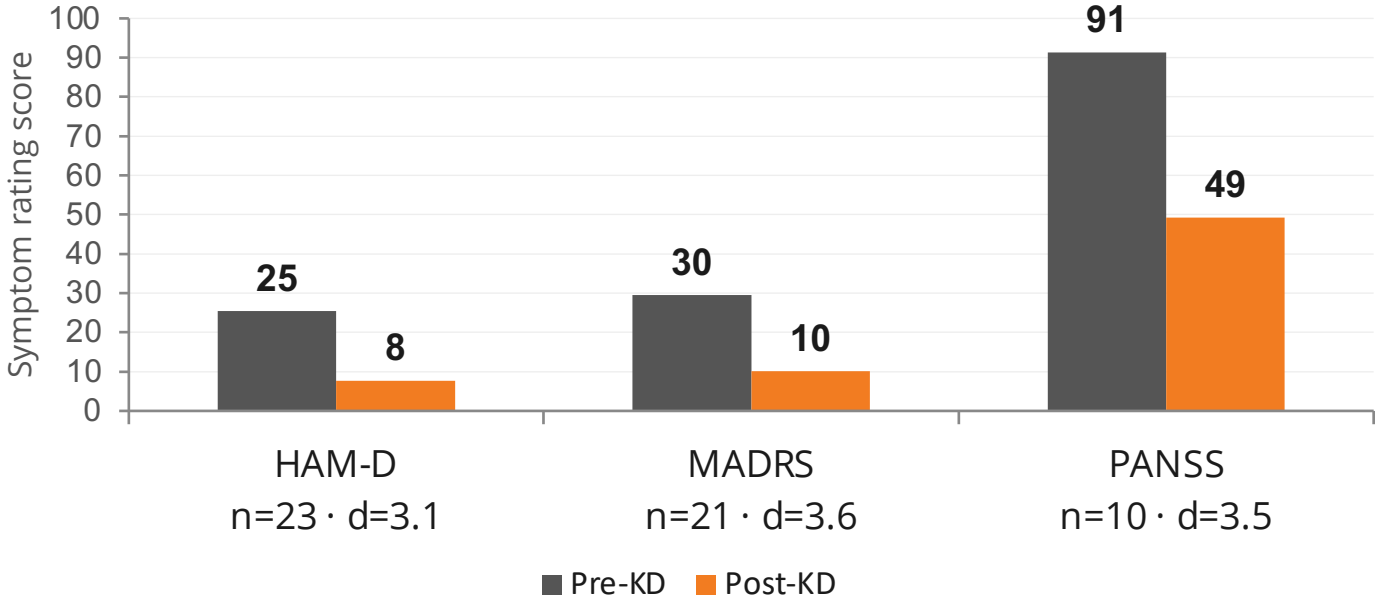
DANAN 2022: INPATIENT KD IN REFRACTORY MENTAL ILLNESS

Retrospective analysis — depression and psychosis symptoms

DESIGN
Retrospective cohort, single inpatient unit

SAMPLE
28 analyzed (of 31 admitted)

DURATION
Inpatient, mean 85-day stay



43% achieved clinical remission
12 of 28 patients

64% reduced or stopped medication
18 of 28 patients

d = 3.8 CGI-S illness severity
all improved ≥1 point

Limitations: retrospective, single-arm, no control, inpatient setting with concurrent care. All changes P < 0.001 (PANSS measured in the 10 schizoaffective patients).

Danan A, Westman EC, Saslow LR, Ede G. Frontiers in Psychiatry 2022;13:951376.

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SETHI 2024: KD PILOT IN SCHIZOPHRENIA + BIPOLAR DISORDER

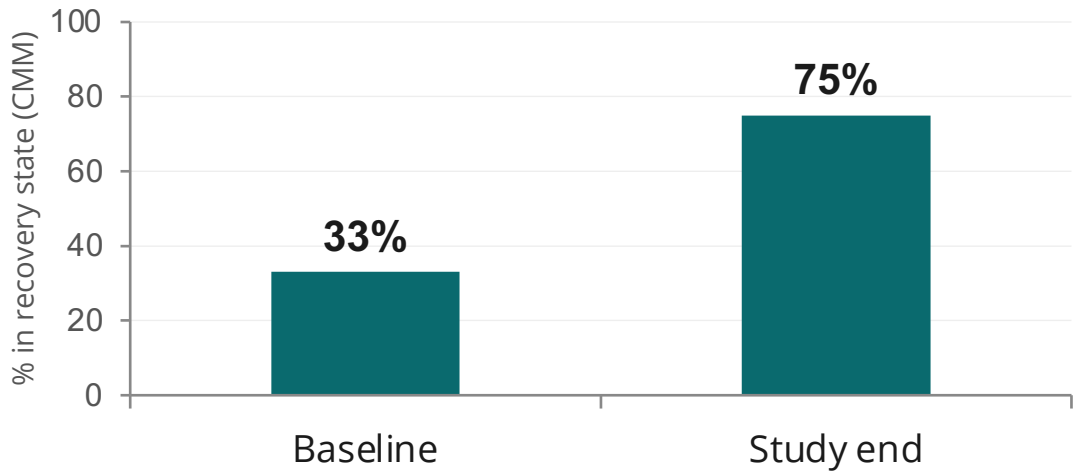
Stanford open-label trial with compliance tracking

DESIGN
Single-arm, open-label KD intervention

SAMPLE
23 enrolled / 21 completed (BD, SCZ)

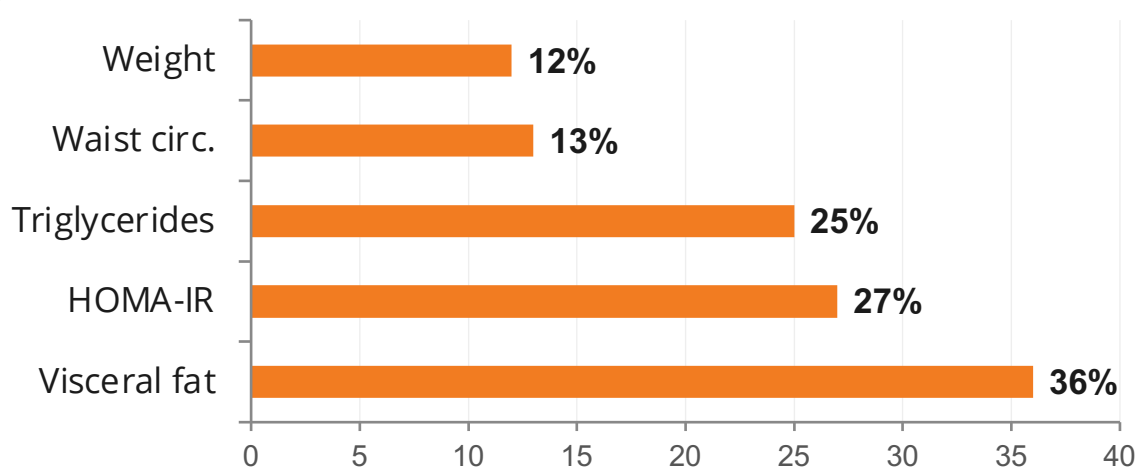
DURATION
4 months

PSYCHIATRIC RECOVERY STATE



100% *of fully adherent (n=14) reached recovery*

METABOLIC IMPROVEMENT (ADHERENT)



CGI severity −31% (p<0.001) · schizophrenia BPRS −32% · *0 participants met criteria for metabolic-syndrome at study end.*

Sethi S, Wakeham D, Ketter T, et al. Psychiatry Research 2024;335:115866.

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CAMPBELL 2025: KD IN EUTHYMIC BIPOLAR + BRAIN MRS

Clinical, metabolic, and MR-spectroscopy findings

DESIGN
Single-arm pilot, modified KD

SAMPLE
27 enrolled / 20 completed (euthymic BD)

DURATION
6–8 weeks

DAILY EMA vs KETONE LEVELS (n=14)

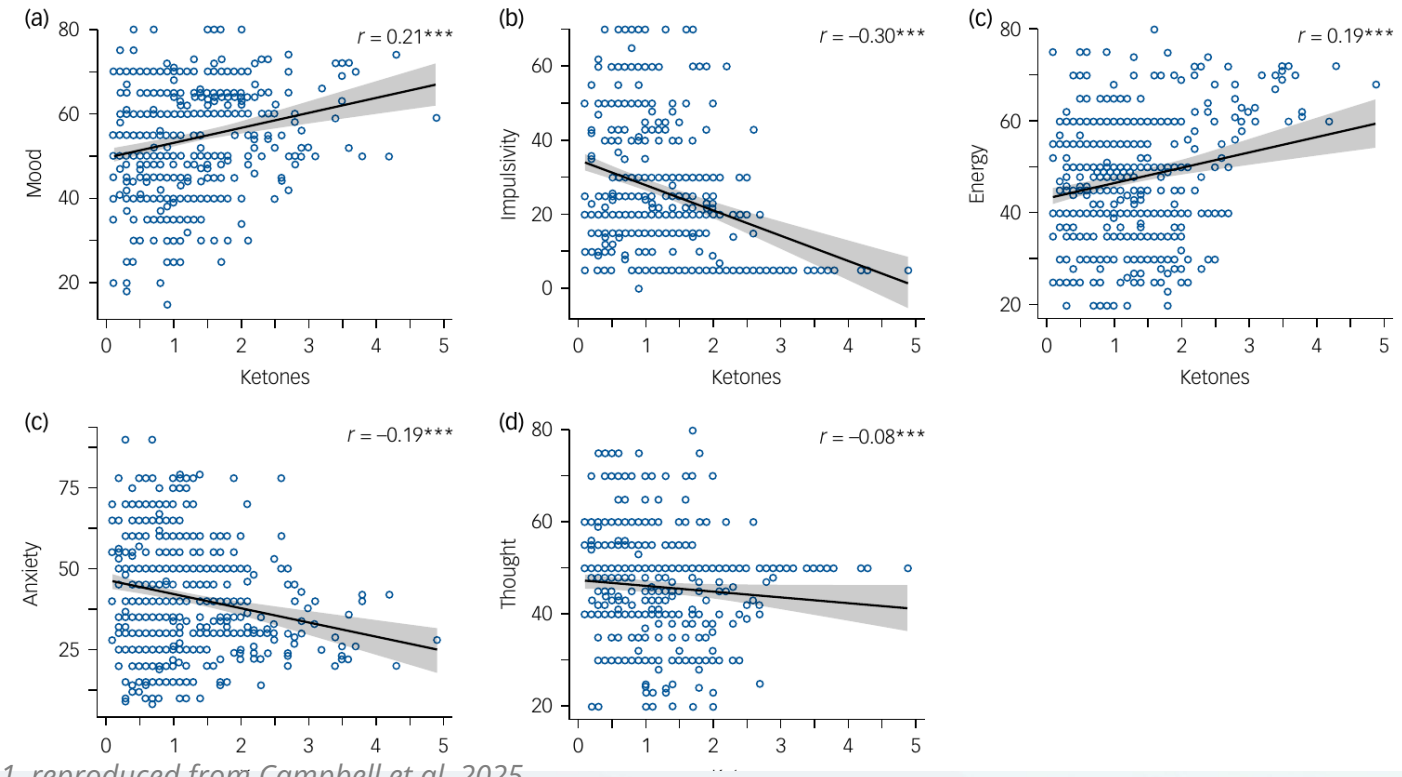

Fig. 1, reproduced from Campbell et al. 2025

BRAIN MRS & METABOLIC

↓13.6%
brain Glx, posterior cingulate (p<0.001)

First biological signal in BD on KD — lower excitatory tone

−4.2 kg weight

−7.4 mmHg systolic BP

(all p<0.05)

Campbell IH, Needham N, Grossi H, et al. BJPsych Open 2025;11(2):e34.

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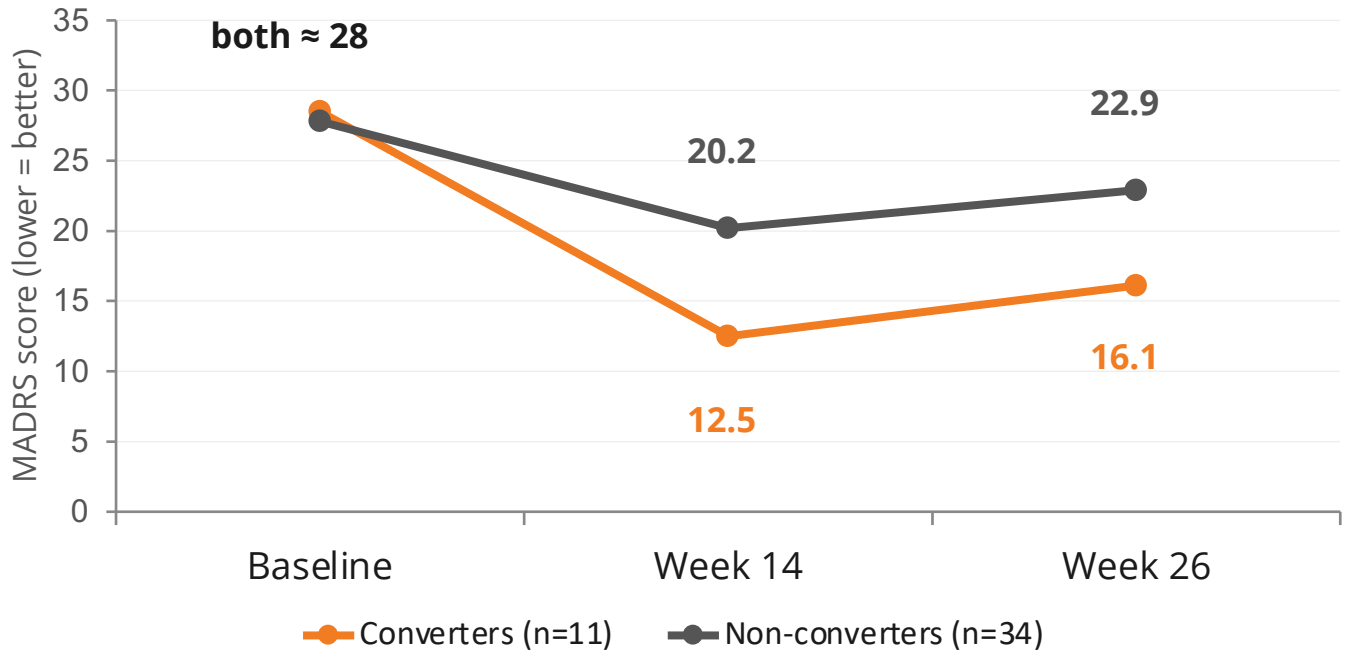
CALKIN 2022 (TRIO-BD): REVERSING INSULIN RESISTANCE IMPROVES TR BIPOLAR DEPRESSION

Patients whose insulin resistance reversed showed large, sustained MADRS improvement

DESIGN
Randomized, quadruple-masked, placebo-controlled

SAMPLE
45 patients: TR bipolar depression + insulin resistance

DURATION
26 weeks



EFFECT SIZES (CONVERTERS vs NON)

MADRS **Cohen d = 1.17** (wk 14)

GAF **d = 1.47** (wk 14)

Large effects, sustained to wk 26 (P = .031–.008)

81.8% vs **39.3%**

met ≥30% MADRS response (converters vs non; P=.031)

Headline: *Treatment resistant Bipolar depression improves from reversing insulin resistance with metformin*

Calkin CV, Chengappa KNR, Cairns K, et al. J Clin Psychiatry 2022;83(2):21m14022.

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KETOGENIC DIET IN DEPRESSION: CONVERGENT SIGNAL

One controlled trial, one systematic review, one pilot — all point the same way

RCT — treatment-resistant depression

Gao 2026, JAMA Psychiatry

n = 88 · 6-week diet · UK

- End of diet (wk 6): KD beat control, d=−0.68 (p=.05)
- Ketosis held with support: 64% ≥1.5 mmol/L, rising
- Support stopped at wk 6 → 48% quit, only 20% continued
- Wk-12 fade = adherence drop, not lost efficacy

Systematic review

Janssen-Aguilar 2026

≈ 50 studies · adults

- Consistent antidepressant signal
- Across heterogeneous designs
- Modest effect sizes
- High between-study heterogeneity

Pilot — young adults

Decker 2025

n = 24 · 12 weeks

- ~69–71% symptom reduction
- ↑ well-being and cognition
- ↑ body composition
- Single-arm (no control)

Convergent signal across RCT, review, and pilot — *in the controlled trial, benefit tracked diet adherence, which fell once support ended. Durable delivery, not efficacy, is the open question.*

Gao M, et al. JAMA Psychiatry 2026;83(4):331–340. Janssen-Aguilar R, et al. JAMA Psychiatry 2026;83(1):13–22. Decker DD, et al. Transl Psychiatry 2025;15:322.

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SECTION 4

More Mechanisms — Why It Works

How metabolic and brain systems converge

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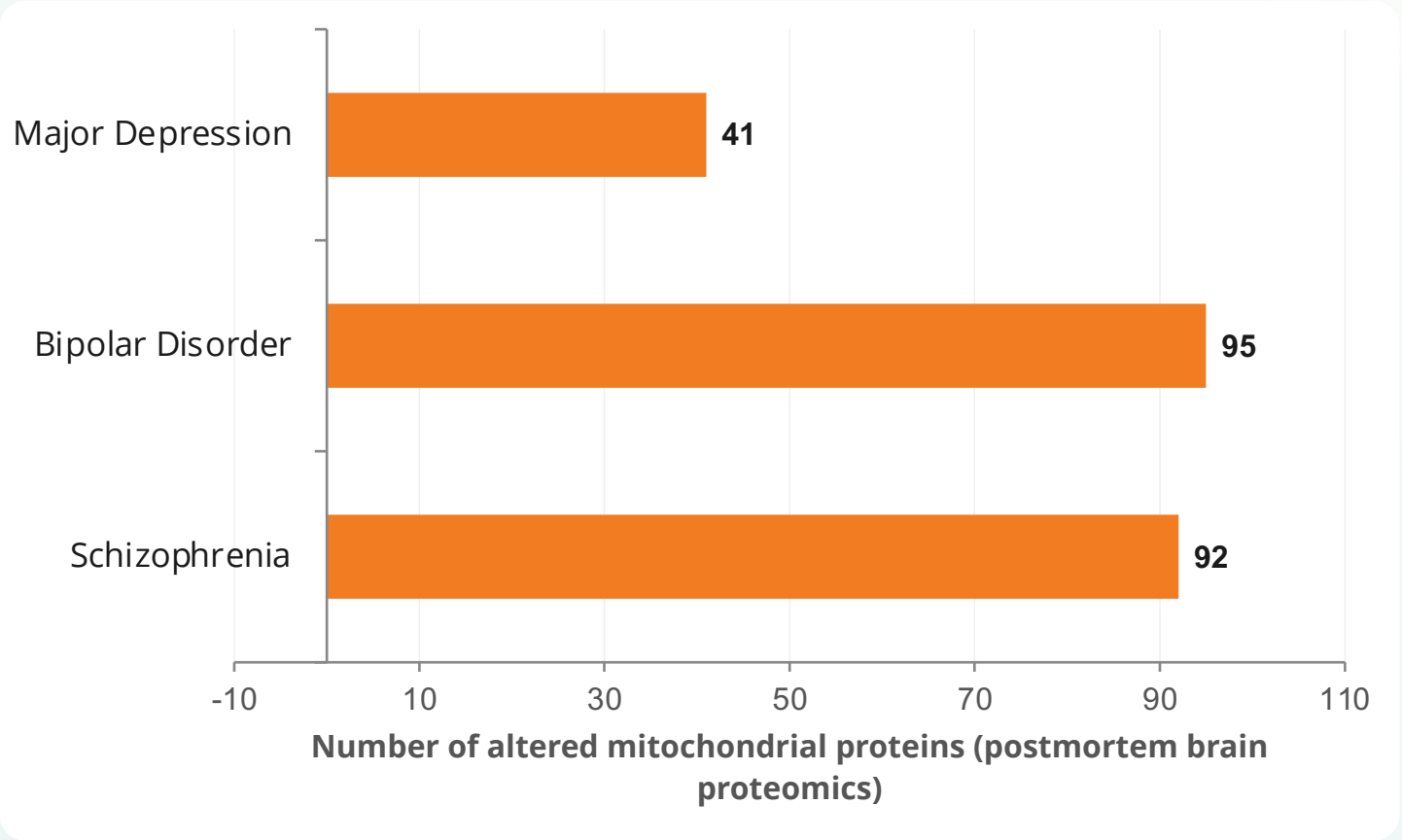
MITOCHONDRIAL DYSFUNCTION

Convergent evidence across major psychiatric disorders



CONVERGENT FINDINGS

- ↓ ATP production
- Energy demand–supply mismatch
- Compensatory reliance on less efficient pathways

Schizophrenia

post-mortem studies show region- and cell-type–specific mitochondrial vulnerability (complex I deficits)

Zuccoli GS, et al. Front Neurosci 2017;11:493. Whitehurst T, et al. Neurosci Biobehav Rev 2022;132:449–464. Sethi et al. Nature Mental Health 2026.

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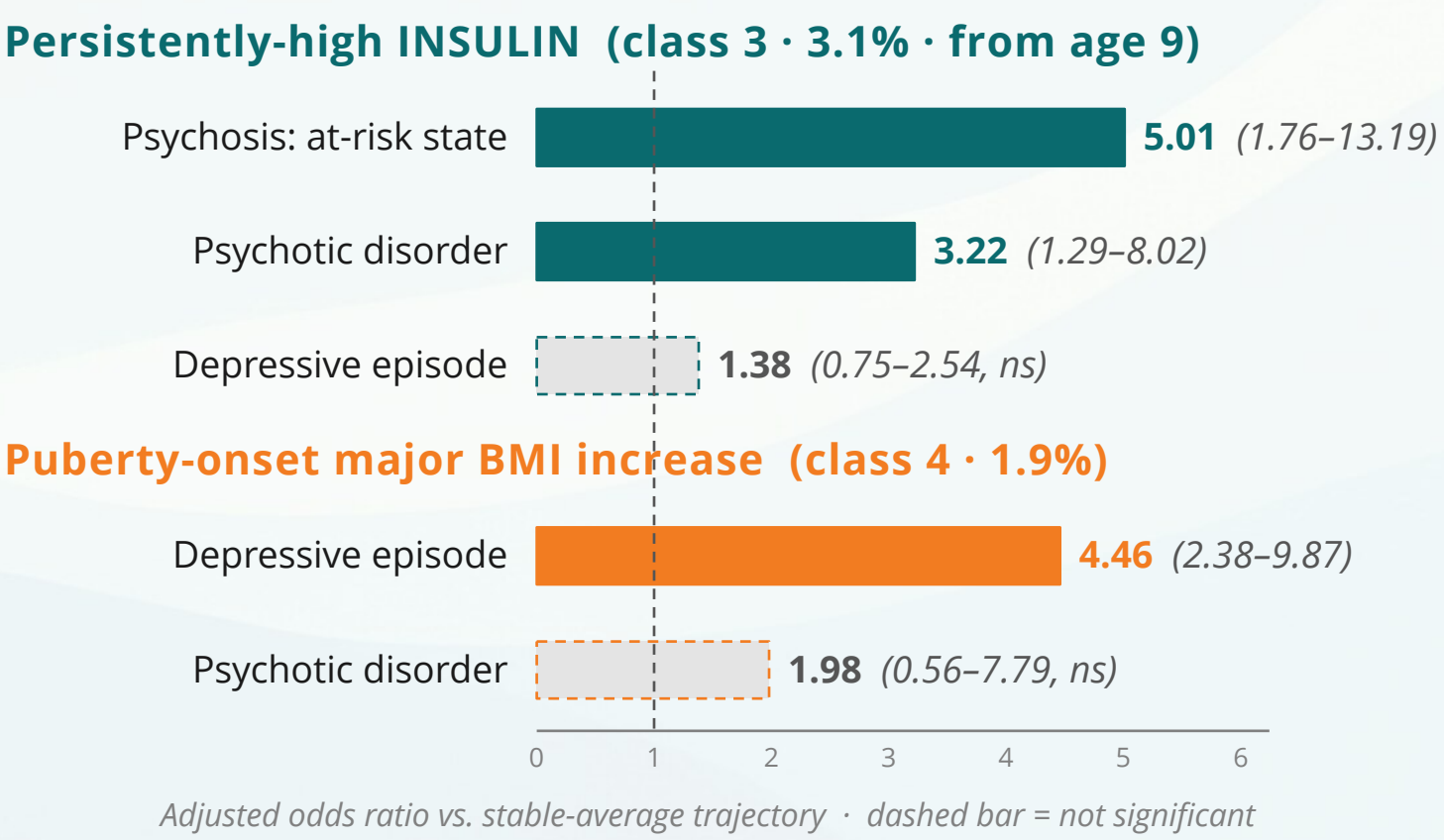
METABOLIC TRAJECTORIES PRECEDE PSYCHIATRIC ILLNESS

(ALSPAC general-population UK birth cohort) — childhood trajectories predict adult risk at age 24



DIRECTIONALITY: METABOLISM COMES FIRST

- Metabolic trajectories diverge by mid-childhood — years before psychiatric onset at 24.
- Temporal precedence is the strongest observational signal for direction.

Corroborated cross-sectionally:

- *insulin resistance ≈2× incident depression (Watson 2021)*
- *abnormal across 70 studies, n>240,000 (Fernandes 2022)*

Perry BI, et al. JAMA Psychiatry 2021;78(4):416–425. Watson K, et al. Am J Psychiatry 2021. Fernandes BS, et al. Neurosci Biobehav Rev 2022.

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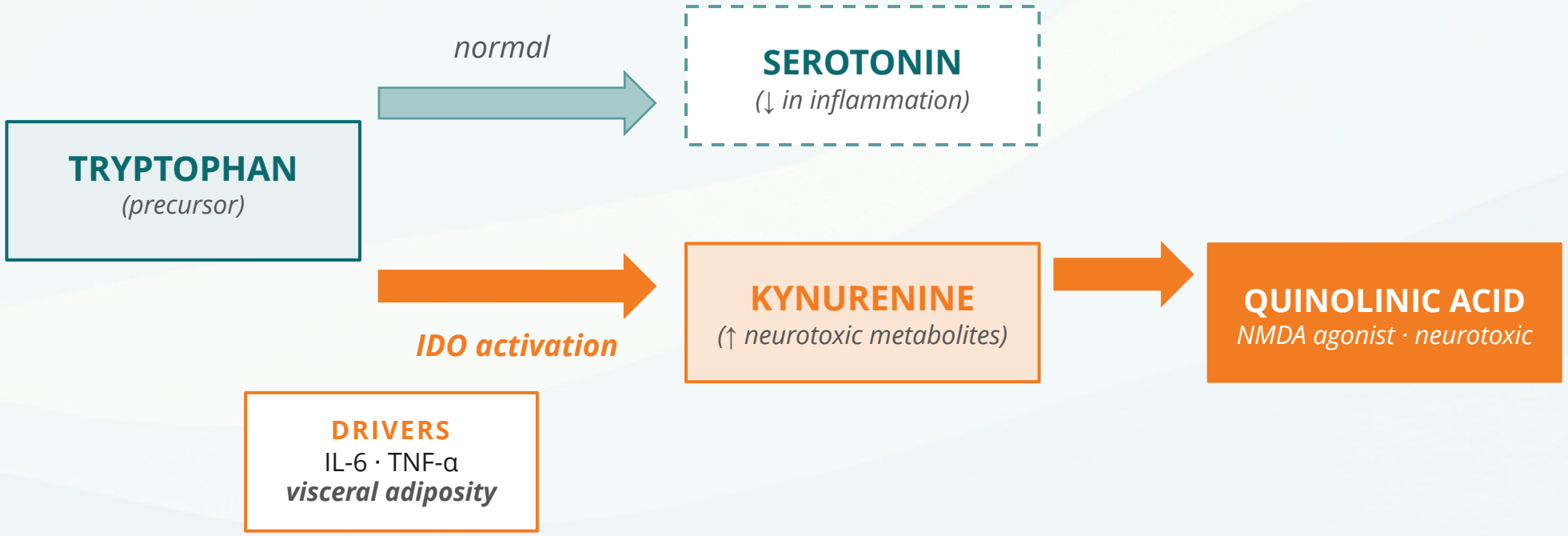
INFLAMMATION SHIFTS NEUROTRANSMITTER CHEMISTRY

Cytokines redirect tryptophan from serotonin toward neurotoxic metabolites



Clinical phenotype: *anhedonia · social withdrawal · fatigue · cognitive slowing*

Neurotransmitter alterations are downstream of integrated immune–metabolic–endocrine signaling

Penninx BWJH. Lancet Reg Health Eur 2024. Sethi et al. Nature Mental Health 2026.

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ENVIRONMENTAL & STRESS DRIVERS OF METABOLIC DYSREGULATION

Modifiable inputs that converge on shared physiology

DIET

Ultra-processed, high-glycemic intake

→ chronic hyperinsulinemia, nutrient insufficiency affecting cellular energy metabolism

STRESS / ACEs

Chronic psychological stress, adverse childhood experiences

→ persistent HPA activation, immune priming, cortisol dysregulation

SLEEP / CIRCADIAN

Disrupted timing, shift work, irregular eating

→ impaired hormonal rhythmicity, reduced metabolic flexibility

SEDENTARY BEHAVIOR

Reduced physical activity

→ ↓ mitochondrial efficiency, impaired glucose utilization

CONVERGE ON

Metabolic dysregulation

Inflammation
Insulin resistance
Mitochondrial strain
Allostatic load

These inputs are modifiable. *Interventions that improve metabolism — nutrition, exercise, sleep, mind-body practices and psychosocial support — also support brain function.*

Felitti VJ, et al. Am J Prev Med 1998. McEwen BS. Physiol Rev 2007;87(3):873–904.

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DYSGLYCEMIA IS INTRINSIC TO SCHIZOPHRENIA

A bioenergetic vulnerability that predates — and may drive — peripheral metabolic disease

1920s *Pre-antipsychotic era*	Glucose intolerance described in “dementia praecox” — before any drugs existed
First-episode & population *Antipsychotic-naïve*	↑ fasting insulin & IR at first episode; diabetes risk elevated before antipsychotics begin (Pillinger 2017; Perry 2016; Rajkumar 2017)
Genetic & sibling *Heritable component*	Shared genetic liability with type 2 diabetes; IR present in unaffected siblings (Chouinard 2019)
Drug-free cellular *Postmortem · iPSC models*	↓ DLPFC glycolytic enzymes & glucose transporters; iPSC organoids show ↓ ATP and oxphos deficits (Sullivan 2018; Henkel 2022; Hamel 2026)

WHAT THIS MEANS

Schizophrenia involves a shared bioenergetic vulnerability

connecting brain function and peripheral metabolic control.

The same NMDAR / mitochondrial / insulin-signalling deficits driving symptoms also impair hypothalamic glucose sensing.

→ Dysglycemia is part of the disease — not merely a medication side effect.

→ Targeting metabolism may treat the disease, not just manage iatrogenic harm.

Hamel L, et al. Rev Endocr Metab Disord 2026. Pillinger T, et al. JAMA Psychiatry 2017. Perry BI, et al. Lancet Psychiatry 2016.

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SECTION 5

Putting It Into Practice

Implementation, deprescribing, and synergistic care

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PATIENT SELECTION

Who benefits from a ketogenic diet— and who needs caution

✓ STRONG CANDIDATES

- Inadequate response to standard care
- Low energy, cognitive slowing, ↓ motivation
- Comorbid metabolic dysfunction (obesity, MAFLD, IR/diabetes, HTN, PCOS)
- Neuropsychiatric comorbidity (cognitive impairment, autism, seizures)
- Medication intolerance / desire to reduce psychotropic burden
- H/o behavioral follow-through with prior commitments

! USE CAUTION

- Advanced kidney disease
- Heart failure
- Pancreatic insufficiency, gallbladder disease/removal
- Post-bariatric surgery
- Type 1 diabetes (specialist oversight)
- SGLT2 inhibitor use (DKA)

✗ AVOID / CONTRAINDICATED

- Acute medical instability
- Pregnancy or breastfeeding
- Underweight / active anorexia nervosa
- Genetic disorders of fat metabolism
- Severe psychiatric decompensation

Sethi et al. Nature Mental Health 2026.

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GLP-1 RECEPTOR AGONISTS — THE PSYCHIATRIC QUESTION

Semaglutide · tirzepatide: major weight loss, CV-risk reduction, insulin sensitization — but mixed psychiatric data

ENCOURAGING SIGNALS

- Improvements in cardiometabolic markers known to drive SMI mortality
- Weight-independent insulin sensitization aligns with psychiatric mechanism
- Emerging signals in addiction/reward behaviors
- May complement (not replace) ketogenic/lifestyle approaches

CONCERNING SIGNALS

- Recent post-marketing cohort analyses suggest possible ↑ depression, anxiety, suicidality risk in some patients (Kornelius et al. 2024)
- Psychiatric outcomes inconsistent across studies
- Long-term psychiatric impact remains uncertain
- Effects on central bioenergetics not characterized
- Loss of muscle mass needs to be prevented

CLINICAL POSITIONING

Not primary psychiatric treatments. *May serve as adjuncts for metabolic comorbidity or short-term support during dietary transition (3–12 months). Pair with nutrition and lifestyle intervention. Monitor for psychiatric symptom changes and lean mass loss.*

Kornelius E, et al. Sci Rep 2024;14:24433. McNamara KP, et al. Med J Aust 2022;217(S7):S29–S33.

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MONITORING: WHAT TO ORDER

Shift the lens from weight to metabolic function

CORE PANEL · EVERYONE

Insulin resistance:
Fasting insulin · HOMA-IR

Glycemic control:
HbA1c · fasting glucose

Lipid metabolism:
Fasting lipid panel (incl. triglycerides, HDL)

Anthropometric:
Waist circumference · BMI · vitals

EXPANDED · WHEN INDICATED

Inflammation:
hs-CRP · ferritin · homocysteine

Thyroid:
TSH · free T3/T4 · reverse T3 · antibodies

Nutritional:
B12 · folate · vitamin D · carnitine · iron

Other:
Comprehensive metabolic panel · uric acid
Continuous glucose monitoring (short-term, optional)
Body Composition testing (optional)

Metabolic dysfunction is dynamic and reversible. *Repeated measures enable early detection of treatment response, dose adjustment, and precision intervention.*

Sethi et al. Nature Mental Health 2026.

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DEPRESCRIBING IN PSYCHOSIS: HOW YOU TAPER MATTERS

Shared Decision-Making May Be The Key Factor

Open-label, shared-decision reduction (18 mo) →	**Functional recovery doubles — 40.4% vs 17.6% (OR 3.49).** The advantage emerged only at 7 years. *Wunderink 2013 · n=128 · 7 yr*
Guided but fixed schedule (12 mo, single-blind) →	**Real early relapse risk (OR 2.84), including 3-vs-1 deaths by suicide;** clinician-rated function better by yr 3–4 (β=6.13). *HAMLETT / Sommer 2026 · n=347 · 4 yr*
Blinded placebo substitution — no patient input →	**Worse clinical outcome at 10 years.** *Hui 2018 · n=178 · 10 yr*

The likely active ingredient is shared decision-making itself. *Wunderink's open-label, symptom-guided reduction gave patients and clinicians real agency — which plausibly explains both why that group sustained lower doses and why they recovered better. The more prescriptive or blinded the taper (HAMLETT's fixed schedule; Hui's placebo substitution), the smaller — or absent — the benefit. ASCP 2026 and INTEGRATE 2025 endorse supervised, shared dose reduction in remitted patients.*

Wunderink L, et al. JAMA Psychiatry 2013. Sommer IE, et al. JAMA Psychiatry 2026 (HAMLETT). Hui CLM, et al. Lancet Psychiatry 2018.

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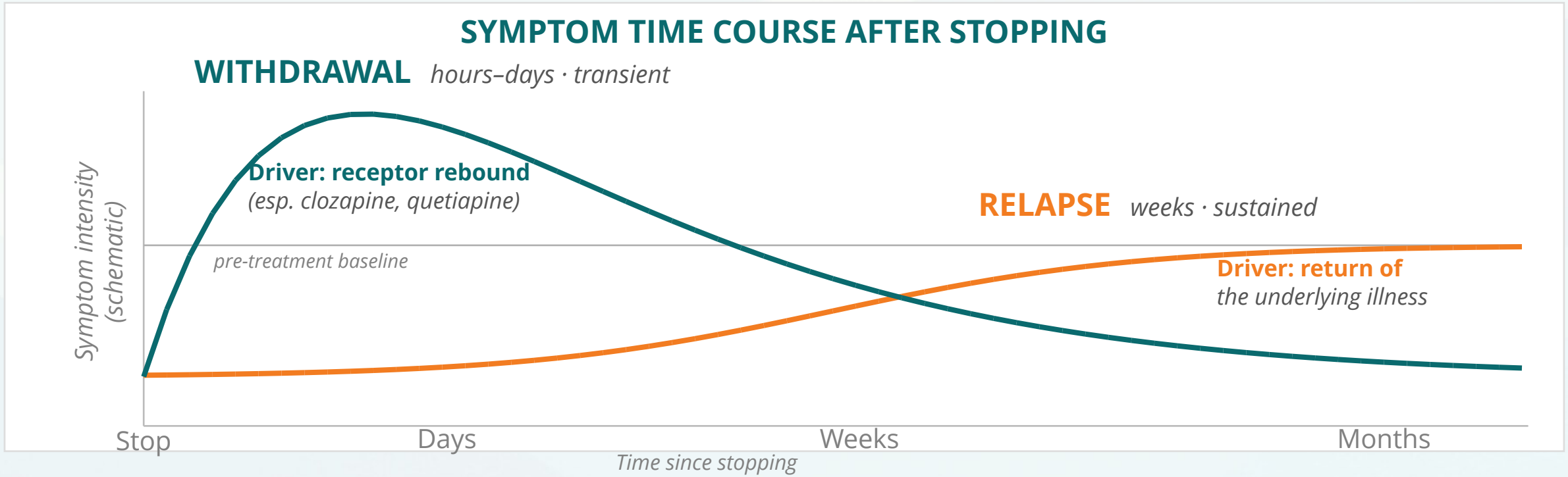
ANTIPSYCHOTIC WITHDRAWAL SYNDROMES ARE REAL — AND OFTEN MISREAD AS RELAPSE

Rapid symptom return after abruptly stopping is often withdrawal, not relapse. Brandt 2020 (5 studies, n=261): withdrawal syndromes are extremely common after abrupt/rapid cessation · OR 7.97 · NNH 3. *Mistaking it for relapse drives the false conclusion that maintenance is required.*



Practical: *taper hyperbolically over ≥6 months (Horowitz 2021; INTEGRATE 2025). ASCP 2026 names withdrawal dyskinesias as a consequence of abrupt cessation.*

Brandt L, et al. Front Psychiatry 2020. Cosci F, Chouinard G. Psychother Psychosom 2020. Horowitz MA, et al. Schizophr Bull 2021. McCutcheon R, et al. Lancet Psychiatry 2025 (INTEGRATE).

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CONVERGENT MECHANISMS

Different therapeutic modalities target the same shared metabolic pathways

INTERVENTIONS	SHARED METABOLIC TARGETS	BRAIN OUTCOMES
Ketogenic metabolic therapy	↑ Mitochondrial function	Mood stabilization
Exercise	↑ Insulin sensitivity	↓ Anxiety, depression
Mind–body practices · meditation	↓ Inflammation / NLRP3	↓ Psychosis severity
Sleep / circadian alignment	↓ Oxidative stress	↑ Cognition, energy
Pharmacology (metformin, GLP-1)	Stabilize neurotransmission	↑ Functional capacity

Different paths · same biology · transdiagnostic potential

Sethi et al. Nature Mental Health 2026. Singh B, et al. Br J Sports Med 2023.

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EXERCISE AS ADJUNCTIVE METABOLIC TREATMENT

Among the most potent interventions for mood — and it shares the ketogenic mechanism

EFFICACY

- Singh 2023 umbrella review: 1,039 trials, 128,119 participants
- Among the most potent evidence-based interventions for depression & anxiety

SHARED MECHANISM

- Exercise + KD both drive mitochondrial biogenesis (PGC-1α; AMPK upstream)
- ↑ insulin sensitivity · ↑ BDNF — reinforcing, not redundant

IN SCHIZOPHRENIA

- +12% hippocampal volume over 3 months of moderate aerobic exercise (Pajonk 2010)
- Fitness and function gains; symptom effects modest

- *Rx: 150 min/week moderate aerobic + 2×/week resistance training*
- *morning fasted exercise on KD maximizes fat oxidation.*

Singh B, et al. Br J Sports Med 2023. Pajonk FG, et al. Arch Gen Psychiatry 2010. Firth J, et al. World Psychiatry 2020.

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CIRCADIAN ALIGNMENT

Circadian disruption is a cause of mood symptoms — not just a symptom

CAUSAL

- Daghlas 2021 Mendelian randomization (n=697,828)
- Earlier sleep midpoint is causally protective: 23% lower MDD risk per hour earlier

BRIGHT LIGHT THERAPY

- 11 RCTs, 858 patients: remission nearly doubled (40.7% vs 23.5%)
- Works in non-seasonal depression · 10,000 lux, 20–30 min after waking

RHYTHM REGULARITY

- A consistent wake time is the key daily anchor
- IPSRT cut 2-year bipolar relapse (HR 0.34) via routine regularity

> *Restoring the daily clock is a genuine treatment target — not optional sleep hygiene tacked onto the end of a visit.*

Daghlas I, et al. JAMA Psychiatry 2021. Menegaz de Almeida A, et al. JAMA Psychiatry 2025. Gottlieb JF, et al. Bipolar Disord 2019.

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MIND-BODY PRACTICES & METABOLIC HEALTH

Reducing allostatic load to rebuild the energy reserve for repair

THE ENERGY LOGIC

- Chronic stress raises allostatic load — energy is diverted from growth, maintenance, and repair (McEwen)
- Mind-body practice rebuilds the reserve

OUTCOMES

- Medium-to-large effects across mood and anxiety
- Strongest signal in anxiety (Strauss 2014, SMD ≈ −0.5 to −0.6)

WHAT TO PRESCRIBE

- 8-week MBSR / MBCT (most replicated)
- 10–20 min daily beats long infrequent sessions; HRV-guided slow breathing (~6/min)

Exercise + circadian + mind-body + KD compound rather than substitute — each addresses a different layer of allostatic load.

McEwen BS. N Engl J Med 1998. Strauss C, et al. Behav Res Ther 2014. Galante J, et al. PLOS Med 2021.

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WHAT WE DON'T YET KNOW

Honest limits of the current evidence

- **The evidence base is thin and early.**
  The strongest psychiatric KD studies are pilots and open-label cohorts (Sethi n = 21; Danan; Campbell). No active-comparator RCTs yet (Two larger RCTs in SMI are due to be published in late 2026)

- **We can't yet predict who responds.**
  No reliable biomarker or clinical phenotype tells us in advance who will benefit most.

- **Optimal duration is unknown — but a pediatric precedent is tantalizing.**
  In pediatric drug-resistant epilepsy responders, 62.9% maintained response at mean 2.5 years AFTER discontinuing the diet — but only about one-third of those without any additional anti-seizure medications (Schoeler 2024, n = 97). Caveat: kids with epilepsy ≠ adults with SMI — different population, different disease, different brain. The durability signal is biologically suggestive, not transferable.

- **Adherence in the real world is the open question.**
  Inpatient and residential adherence is achievable; sustained outpatient adherence after stabilization is largely unstudied.

Schoeler NE, et al. Seizure 2024;121:78–84. Psychiatric KD evidence: see slides 17–21.

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CARRYING THIS FORWARD

Where to start with the patients you're already seeing

1 CONSIDER

- Metabolic dysfunction in every patient, from day 1
- Reassess every regimen at least annually (ASCP 2026)

2 ORDER

- HbA1c, fasting insulin, lipids, waist, BP — at intake + 6 months
- TSH / free T4 / hs-CRP, plus vitamin D
- Insulin resistance often shows up many years before diabetes

3 PRESCRIBE & REASSESS

- Match antipsychotic to metabolic burden (consider switching high-burden agents)
- GLP-1 for AP weight gain
- Lifestyle is psychiatric care, not adjunctive
- Discuss gradual dose reduction in remitted patients

BUILD YOUR REFERRAL NETWORK NOW — BEFORE YOU NEED IT

Metabolic Mind — metabolicmind.org
The Metabolic Collective — metaboliccollective.org
Society of Metabolic Health Practitioners — thesmhp.org
Accord Mental Health — accordmh.com
Advanced Ketogenic Therapies (Denise Potter) — advancedketogenictherapies.com
Georgia Ede MD — clinician directory & KMT training (free version launching July 2026) — diagnosisdiet.com

IMPLEMENTATION READING

Modified Delphi consensus
on KMT in serious mental illness

Ede G, Bernstein M, et al.
Front Nutr 2026;13:1749406 · open access

Goldberg JF, et al. JAMA Netw Open 2026 (ASCP). Siskind D, et al. Diabetes Obes Metab 2019. Firth J, et al. World Psychiatry 2020. Wunderink L. Psychiatr Rehabil J 2024.

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THANK YOU

Questions & Discussion

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REFERENCES: FOUNDATIONS & DEPRESSION/MOOD MECHANISM

Sethi S, Berk M, Andreazza AC, et al. Metabolic psychiatry targeting metabolic dysregulation in mental health. Nature Mental Health 2026. doi:10.1038/s44220-026-00609-5

Berk M, Walder K, Kim JH. Past, present and future of research on brain energy metabolism in bipolar disorder. World Psychiatry 2025;24(1):47–49.

Chesney E, Goodwin GM, Fazel S. Risks of all-cause and suicide mortality in mental disorders: a meta-review. World Psychiatry 2014;13(2):153–160.

Penninx BWJH, et al. Immuno-metabolic depression: from concept to implementation. Lancet Reg Health Eur 2024.

Vancampfort D, et al. Risk of metabolic syndrome and its components in people with schizophrenia and related psychotic disorders, bipolar disorder and major depressive disorder. World Psychiatry 2015.

Watson K, et al. Incident major depressive disorder predicted by three measures of insulin resistance. Am J Psychiatry 2021.

Fernandes BS, et al. Insulin resistance in depression: a large meta-analysis of metabolic parameters and variation. Neurosci Biobehav Rev 2022.

Cen M, et al. Associations between metabolic syndrome and anxiety, and the mediating role of inflammation: findings from the UK Biobank. Brain Behav Immun 2024;116:1–9.

Chourpiliadis C, et al. Metabolic profile and long-term risk of depression, anxiety, and stress-related disorders. JAMA Netw Open 2024.

Goldstein BI, et al. The burden of obesity among adults with bipolar disorder in the United States. Bipolar Disorders 2011;13(4):387–395.

Perry BI, et al. Longitudinal trends in childhood insulin levels and body mass index and associations with risks of psychosis and depression in young adults. JAMA Psychiatry 2021;78(4):416–425.

Giménez-Palomo A, et al. Does metabolic syndrome or its component factors alter the course of bipolar disorder? A systematic review. Neurosci Biobehav Rev 2021.

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REFERENCES: SCHIZOPHRENIA, STRESS & ANTIPSYCHOTICS

Hamel L, Pereira S, Yang Z, Garrido AN, Agarwal SM, Lam TKT, Hahn MK. From brain bioenergetics to hypothalamic glucoregulation: A shared-systems hypothesis for intrinsic dysglycemia in schizophrenia. Rev Endocr Metab Disord 2026. doi:10.1007/s11154-026-10034-9

Pillinger T, Beck K, Gobjila C, et al. Impaired glucose homeostasis in first-episode schizophrenia: a systematic review and meta-analysis. JAMA Psychiatry 2017;74(3):261–269.

Perry BI, McIntosh G, Weich S, et al. The association between first-episode psychosis and abnormal glycaemic control: systematic review and meta-analysis. Lancet Psychiatry 2016;3(11):1049–1058.

Rajkumar AP, Horsdal HT, Wimberley T, et al. Endogenous and antipsychotic-related risks for diabetes mellitus in young people with schizophrenia: a Danish population-based cohort study. Am J Psychiatry 2017;174(7):686–694.

Chouinard V-A, Henderson DC, Dalla Man C, et al. Impaired insulin signaling in unaffected siblings and patients with first-episode psychosis. Mol Psychiatry 2019;24(10):1513–1522.

Sullivan CR, O'Donovan SM, McCullumsmith RE, Ramsey A. Defects in bioenergetic coupling in schizophrenia. Biol Psychiatry 2018;83(9):739–750.

Henkel ND, Wu X, O'Donovan SM, et al. Schizophrenia: a disorder of broken brain bioenergetics. Mol Psychiatry 2022;27(5):2393–2404.

Whitehurst T, et al. The role of mitochondria in the pathophysiology of schizophrenia: a critical review of the evidence focusing on mitochondrial complex one. Neurosci Biobehav Rev 2022;132:449–464.

Sapolsky RM, et al. How do glucocorticoids influence stress responses? Endocr Rev 2000;21(1):55–89.

McEwen BS. Physiology and neurobiology of stress and adaptation: central role of the brain. Physiol Rev 2007.

Felitti VJ, et al. Relationship of childhood abuse and household dysfunction to many of the leading causes of death in adults: the Adverse Childhood Experiences (ACE) Study. Am J Prev Med 1998.

Chow RT, et al. An umbrella review of adverse effects associated with antipsychotic medications. Neurosci Biobehav Rev 2023.

Sahay S, et al. Metabolic insights into neuropsychiatric illnesses and ketogenic therapies. Int J Mol Sci 2024.

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REFERENCES: KETOGENIC & METABOLIC THERAPIES

Sethi S, Wakeham D, Ketter T, et al. Ketogenic Diet Intervention on Metabolic and Psychiatric Health in Bipolar and Schizophrenia: A Pilot Trial. Psychiatry Research 2024;335:115866.

Danan A, Westman E, Saslow L, Ede G. The Ketogenic Diet for Refractory Mental Illness: A Retrospective Analysis of 31 Inpatients. Front Psychiatry 2022;13:951376.

Campbell IH, Needham N, et al. A pilot study of a ketogenic diet in bipolar disorder: clinical, metabolic and magnetic resonance spectroscopy findings. BJPsych Open 2025;11:e34.

Calkin C, Chengappa KNR, et al. Treating Insulin Resistance With Metformin as a Strategy to Improve Clinical Outcomes in Treatment-Resistant Bipolar Depression (TRIO-BD): A Randomized, Quadruple-Masked, Placebo-Controlled Clinical Trial. J Clin Psychiatry 2022;83(2):21m14022.

Anderson J, et al. The Ketogenic Diet as a Transdiagnostic Treatment for Neuropsychiatric Disorders: Mechanisms and Clinical Outcomes. Curr Treat Options Psychiatry 2025;12:1.

Włodarczyk A, Cubała W, Stawicki M. Ketogenic Diet for Depression: A Potential Dietary Regimen to Maintain Euthymia? Prog Neuropsychopharmacol Biol Psychiatry 2021;109:110257.

Palmer C. Ketogenic Diet in the Treatment of Schizoaffective Disorder: Two Case Studies. Schizophr Res 2017;189:208–209.

Palmer C, Gilbert-Jaramillo J, Westman E. The Ketogenic Diet and Remission of Psychotic Symptoms in Schizophrenia: Two Case Studies. Schizophr Res 2019;208:439–440.

Palmer CM. Brain Energy: A Revolutionary Breakthrough in Understanding Mental Health. BenBella Books 2022.

Newman JC, Verdin E. β-Hydroxybutyrate: A Signaling Metabolite. Annu Rev Nutr 2017;37:51–76.

Youm Y-H, et al. The ketone metabolite β-hydroxybutyrate blocks NLRP3 inflammasome–mediated inflammatory disease. Nat Med 2015;21(3):263–269.

Sethi S, Ford J. The Role of Ketogenic Metabolic Therapy on the Brain in Serious Mental Illness: A Review. J Psychiatr Brain Sci 2022;7(5).

Rawat K, Singh N, Kumari P, Saha L. A Review on Preventive Role of Ketogenic Diet (KD) in CNS disorders from the Gut Microbiota perspective. Rev Neurosci 2020;32(2):143–157.

Calabrese L, Scolnick B, Zupec-Kania B, et al. Ketogenic diet and ketamine infusion treatment to target chronic persistent eating disorder psychopathology in anorexia nervosa: a pilot study. Eat Weight Disord 2022;27:3751–3757.

Juby A, Blackburn T, Mager D. Use of medium chain triglyceride (MCT) oil in subjects with Alzheimer's disease: a randomized, double-blind, placebo-controlled, crossover study. Alzheimers Dement 2022;8:e12259.

Mattson MP, Moehl K, Ghena N, Schmaedick M, Cheng A. Intermittent metabolic switching, neuroplasticity and brain health. Nat Rev Neurosci 2018;19:81–94.

Mattson MP. An evolutionary perspective on why food overconsumption impairs cognition. Trends Cogn Sci 2019;23(3):200–212.

Teicholz N, Croft SM, et al. Myths and facts regarding low-carbohydrate diets. Nutrients 2024;16(6):1047.

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REFERENCES: LIFESTYLE & ADJUNCTIVE THERAPIES

McNamara KP, et al. Should antidiabetic medications be considered to reduce cardiometabolic risk in patients with serious mental illness? Med J Aust October 2022;217(7 Suppl).

Kornelius E, et al. The risk of depression, anxiety, and suicidal behavior in patients with obesity on glucagon-like peptide-1 receptor agonist therapy. Sci Rep 2024;14:24433.

Hallberg / Athinarayanan SJ, Hallberg SJ, McKenzie AL, et al. Long-term effects of a novel continuous remote care intervention including nutritional ketosis for the management of type 2 diabetes: A 2-year non-randomized clinical trial. Front Endocrinol 2019;10:348.

Saslow LR, Daubenmier JJ, et al. Twelve-month outcomes of a randomized trial of a moderate-carbohydrate versus very low-carbohydrate diet in overweight adults with type 2 diabetes mellitus or prediabetes. Nutr Diabetes 2017;7(12):304.

Yancy WS, Olsen MK, Guyton JR, Bakst RP, Westman EC. A low-carbohydrate, ketogenic diet versus a low-fat diet to treat obesity and hyperlipidemia: A randomized, controlled trial. Ann Intern Med 2004;140(10):769–777.

Westman EC, Tondt J, Maguire E, Yancy WS Jr. Implementing a low-carbohydrate, ketogenic diet to manage type 2 diabetes mellitus. Expert Rev Endocrinol Metab 2018;13(5):263–272.

Bueno NB, de Melo ISV, de Oliveira SL, da Rocha Ataide T. Very-low-carbohydrate ketogenic diet v. low-fat diet for long-term weight loss: a meta-analysis of randomised controlled trials. Br J Nutr 2013;110(7):1178–1187.

Volek JS, Phinney SD, et al. Carbohydrate restriction has a more favorable impact on the metabolic syndrome than a low fat diet. Lipids 2009;44(4):297–309.

Santos FL, Esteves SS, da Costa Pereira A, Yancy WS, Nunes JP. Systematic review and meta-analysis of clinical trials of the effects of low carbohydrate diets on cardiovascular risk factors. Obes Rev 2012;13(11):1048–1066.

Zembic A, Eckel N, et al. An empirically derived definition of metabolically healthy obesity based on risk of cardiovascular and total mortality. JAMA Netw Open 2021;4(5):e218505.

Singh B, Olds T, Curtis R, et al. Effectiveness of physical activity interventions for improving depression, anxiety and distress: an overview of systematic reviews. Br J Sports Med 2023;57(18):1203–1209.

Gordon BR, McDowell CP, Lyons M, Herring MP. Resistance exercise training for anxiety and worry symptoms among young adults: a randomized controlled trial. Sci Rep 2020;10:17548.

Yang W, Chen H, Liu W, Qu S, Ge Y, Song J. Efficacy of vigorous physical activity as an intervention for mitigating depressive symptoms in adolescents and young adults: A comprehensive systematic review and meta-analysis. Front Behav Neurosci 2025;19:1479326.

Pascoe MC, Thompson DR, Ski CF. Yoga, mindfulness-based stress reduction and stress-related physiological measures: A meta-analysis. Psychoneuroendocrinology 2017;86:152–168.

Cipriani A, Furukawa TA, Salanti G, et al. Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: A systematic review and network meta-analysis. Lancet 2018;391(10128):1357–1366.

Torres JA, Kruger SL, Broderick C, et al. Ketosis ameliorates renal cyst growth in polycystic kidney disease. Cell Metabolism 2019;30(6):1007–1023.e5.

Teicholz N. The Big Fat Surprise: Why Butter Meat and Cheese Belong in a Healthy Diet. Simon and Schuster 2014.

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APPENDIX

Backup Material

Backup material — available for Q&A

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ANTIPSYCHOTICS COMPOUND AN ALREADY-PRESENT VULNERABILITY

Medication amplifies — but does not fully explain — the metabolic burden

Antipsychotic-naïve first-episode patients already show: ↑ fasting insulin · IR indices · abnormal glucose tolerance · ↓ glycolytic enzymes *(Pillinger 2017; Perry 2016; Sullivan 2018).*

Antipsychotics **amplify** this vulnerability — they don't create it from scratch.

METABOLIC

- ↑ Weight, visceral adiposity
- ↑ Insulin resistance
- ↑ Dyslipidemia

MOVEMENT

- EPS, akathisia
- Tardive dyskinesia

SEDATION & SLEEP

- Daytime sedation
- Disrupted sleep architecture

Layered cellular impact: ↑ *metabolic strain* · ↑ *mitochondrial stress* · ↓ *ATP availability — on top of the intrinsic deficits.*

Umbrella review of 32 meta-analyses (Chow 2023): metabolic and movement effects are the most consistent adverse domains across antipsychotics and mood stabilizers.

Chow RT, et al. Neurosci Biobehav Rev 2023. Hamel L, et al. Rev Endocr Metab Disord 2026.

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HISTORICAL CONVERGENCE: A CENTURY OF EVIDENCE

Early findings now mechanistically validated

EARLY OBSERVATIONS · 1920s onward

- Reduced oxygen consumption
- Elevated lactate
- Altered glutathione levels

→ Suggested impaired energy metabolism in psychosis and schizophrenia

Initially dismissed; under-recognized for decades.

MODERN VALIDATION

- Mitochondrial dysfunction (proteomic + post-mortem)
- Cerebral glucose hypometabolism (FDG-PET)
- Oxidative stress and neuroinflammatory signaling

Across: *schizophrenia · bipolar disorder · MDD*

→ Psychiatric illness reflects persistent system-level disruption in cellular energy and metabolic signaling.

Sethi et al. Nature Mental Health 2026.

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OXIDATIVE STRESS IN PSYCHIATRIC DISORDERS

A shared pathway of cellular damage

Lipid peroxidation

membrane instability

Protein oxidation

enzymatic dysfunction

DNA oxidation

genomic instability

NEUROBIOLOGICAL CONSEQUENCES

Impaired synaptic plasticity · reduced neurogenesis · amplified mitochondrial–inflammatory crosstalk

Associated with greater illness severity, chronicity, and reduced cellular resilience across major psychiatric disorders.

Why this matters clinically: *Ketogenic metabolism increases NAD^+/NADH ratio and engages endogenous antioxidant systems — directly targeting this shared pathway.*

Sethi et al. Nature Mental Health 2026.

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CALKIN 2022: SUBGROUP CONVERSION ANALYSIS

Additional detail on insulin sensitivity conversion drives clinical response

Subgroup analysis of TRIO-BD *(metformin vs. placebo, 26 weeks, n = 45):*

- 11 participants converted to insulin sensitive by ≥ 14 weeks

10 metformin vs. 1 placebo (P = 0.0009)

- Converters showed:

Greater MADRS reduction (separation begins ~ week 6 → sustained to week 26; P = 0.031 → 0.008)
Large effect sizes for depression response
↑ Global functioning (GAF), ↓ anxiety (HAM-A)

Mechanistic relevance *(CNS effects):*

- Crosses blood–brain barrier
- Improves central insulin signaling and glucose utilization
- Supports mitochondrial function and TCA cycle efficiency
- Reduces inflammatory signaling and oxidative stress

Calkin C, et al. J Clin Psychiatry 2022;83(2):21m14022.

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