



GAD Care Reimagined:
**Current Best Practices and the
Emerging Role of Psychedelics**

Supported by an educational grant from Definium Therapeutics

MasterClass

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Faculty Disclosures

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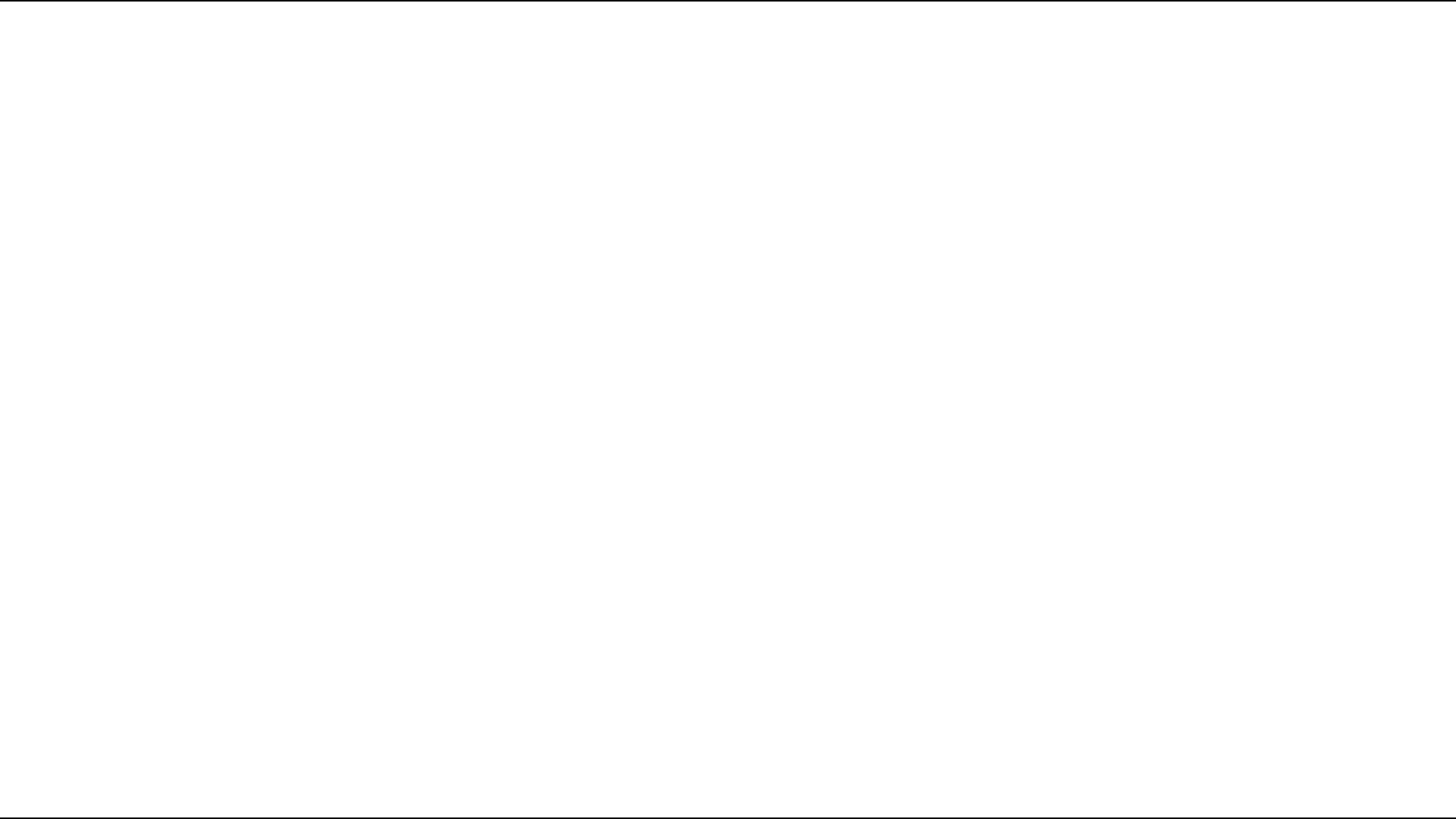
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Learning Objectives

- Summarize the prevalence, functional burdens, common comorbidities, and key neurobiological mechanisms underlying GAD
- Distinguish GAD from conditions with overlapping presentations using DSM-5-TR criteria and validated screening tools
- Compare the benefits and limitations of traditional therapies for GAD, including unmet needs with current strategies
- Describe the pharmacological and neurological basis of psychedelic compounds and the evidence supporting their potential role in GAD
- Evaluate emerging clinical evidence, safety profiles, and MOAs of investigational psychedelic compounds in GAD





CC: “There is something wrong with me.”



- 19 year old college sophomore with a past medical history of migraine headaches who presents to student mental health s/p ER visit for syncopal episode due to dehydration.
- **Symptoms:** Acute on chronic (2+ years) excessive worry about classes, exams, public speaking and fear of failure. Frequently feels a sense of dread. Difficulty relaxing. Difficulty falling asleep due to worry. Chronic, daily muscle tension and frequent headaches. Recently had first panic attack.
- **Substance use:** infrequent social alcohol use – “I am afraid of getting in trouble,” no tobacco use; has never tried a drug
- **Past psychiatric history:** None
- **Social history:** Straight A high achieving student, has stable friend group and long term boyfriend, involved in multiple clubs on campus, works as a resident advisor, math and English tutor; volunteers at the local nursing home; no trauma history
- **“I stay up too late studying and haven’t been taking great care of myself. I am making a D in physics, and I think I need to give up pre-med. I feel like a failure. What should I do?”**

The Worry Continuum: From Normal Worries to GAD



Epidemiology of GAD

GAD is Common and Underrecognized

Chronic, Waxing-Waning Course:

- Onset peaks in late adolescence to early adulthood, with a second peak in middle age
- Often relapsing without treatment
- Remission rates are lower for GAD than for other anxiety disorders

~2%–3.8%

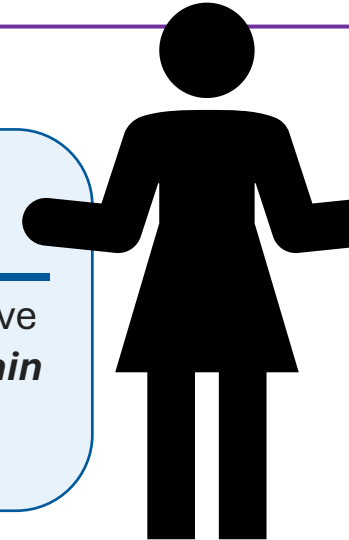
Global 12-month prevalence of DSM-5 GAD across countries

~5%–9%

Lifetime prevalence in high-income countries

1 in 4

US adults screen positive for GAD, *yet most remain undiagnosed*



Women have 1.8x higher risk of developing GAD vs men

DSM-5-TR = Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision; GAD = generalized anxiety disorder. MDD = major depressive disorder.
Ruscio AM, et al. JAMA Psychiatry. 2017;74(5):465-475. Morjig S. Psychiatry Advisor. May 14, 2024. American Psychiatric Association. DSM-5-TR. 2022. Ruscio AM, et al. JAMA Psychiatry. 2017;74(5):465-475. Javaid SF, et al. Middle East Curr Psychiatry. 2023;30(1):44. Zhang Z, et al. J Affective Disord. 2025;120299. Ruscio et al. JAMA Psychiatry 2017;74(5):465-475

The Burden of GAD is Significant

Significantly increase the likelihood of suicide attempts

- Risk of suicide attempt is further elevated when GAD co-occurs w/ MDD



Family



Physical health

Finances



Work performance



Associated with **chronic physical disorders** including arthritis, asthma, cancer, diabetes, pain, cardiovascular disease, HTN, dementia & **1.6x increased risk of all cause mortality**

Associated with significant occupational impairment, healthcare utilization, social impairment, and **reduced quality of life**

- Patients with GAD average more missed workdays and report lower health-related QoL than those with other anxiety disorders

Frequent co-occurrence with MDD accelerates disability and **worsens outcomes for both conditions**

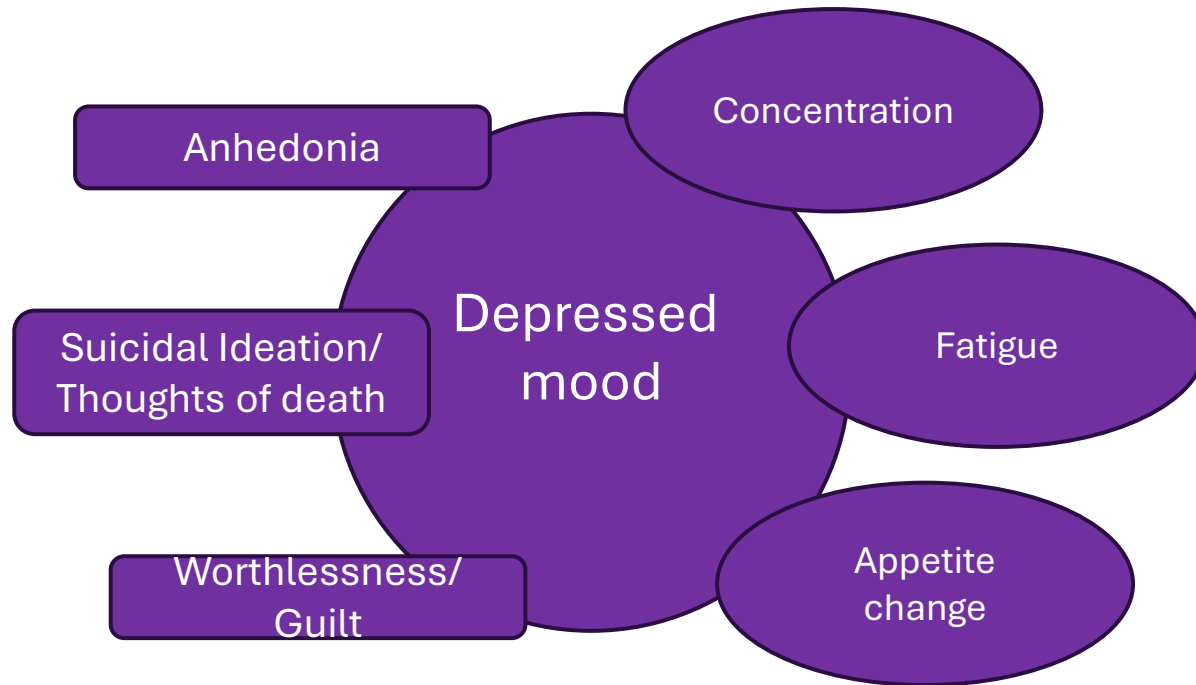
DALYs = disability-adjusted life years; GI = gastrointestinal; QoL = quality of life.

Zhang Z, et al. *J Affective Disord*. 2025;120299. Nepon J, et al. *Depress Anxiety*. 2010;27(9):791-798. Kessler RC, et al. *Epidemiol Psychiatr Sci*. 2015;24(3):210-226. Nepon J, et al. *Depress Anxiety*. 2010;27(9):791-798. Meier et al. *Br J Psychiatry* 2016;209(3):216-221

Neurobiology of GAD

The prevailing view is that pathological anxiety arises from an over-reactivity of the amygdala in response to threat stimuli and a lack of cortical regulation of these responses.

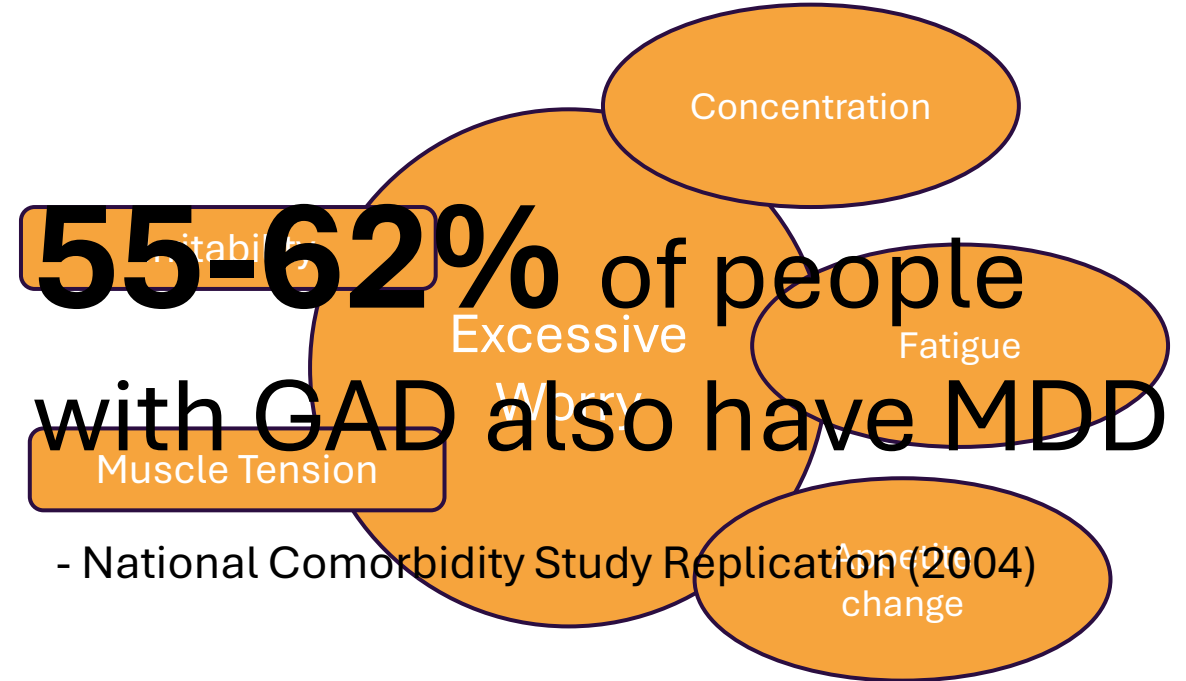
CC: “I’m sad” Dx: MDD
CC: “I’m worried” Dx: GAD?



Major Depressive Disorder (MDD)

*Disrupted reward circuits/ diminished inhibition
(ventral striatum/DLPFC/sgACC)*

Kessler RC, et al. Arch Gen Psychiatry. 2005;62(6):617–627.



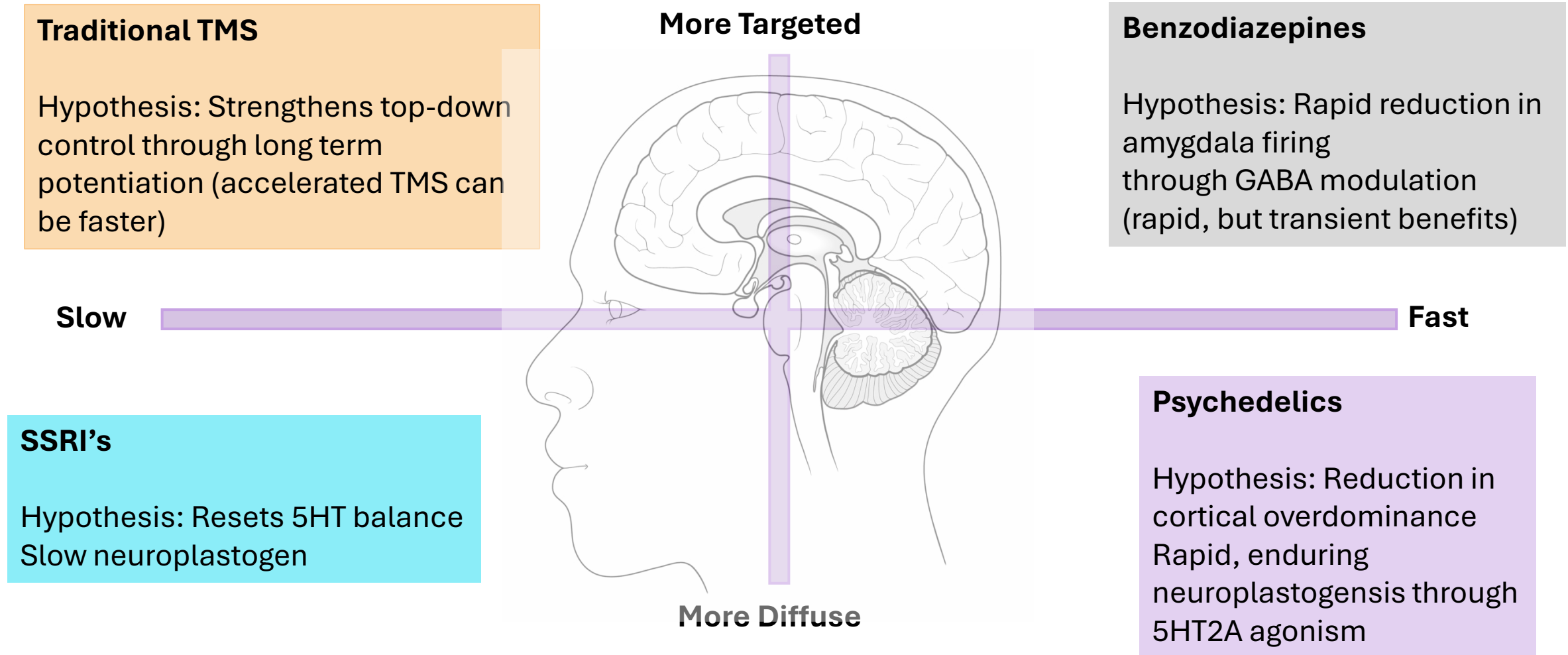
**55-62% of people
with GAD also have MDD**

- National Comorbidity Study Replication (2004)

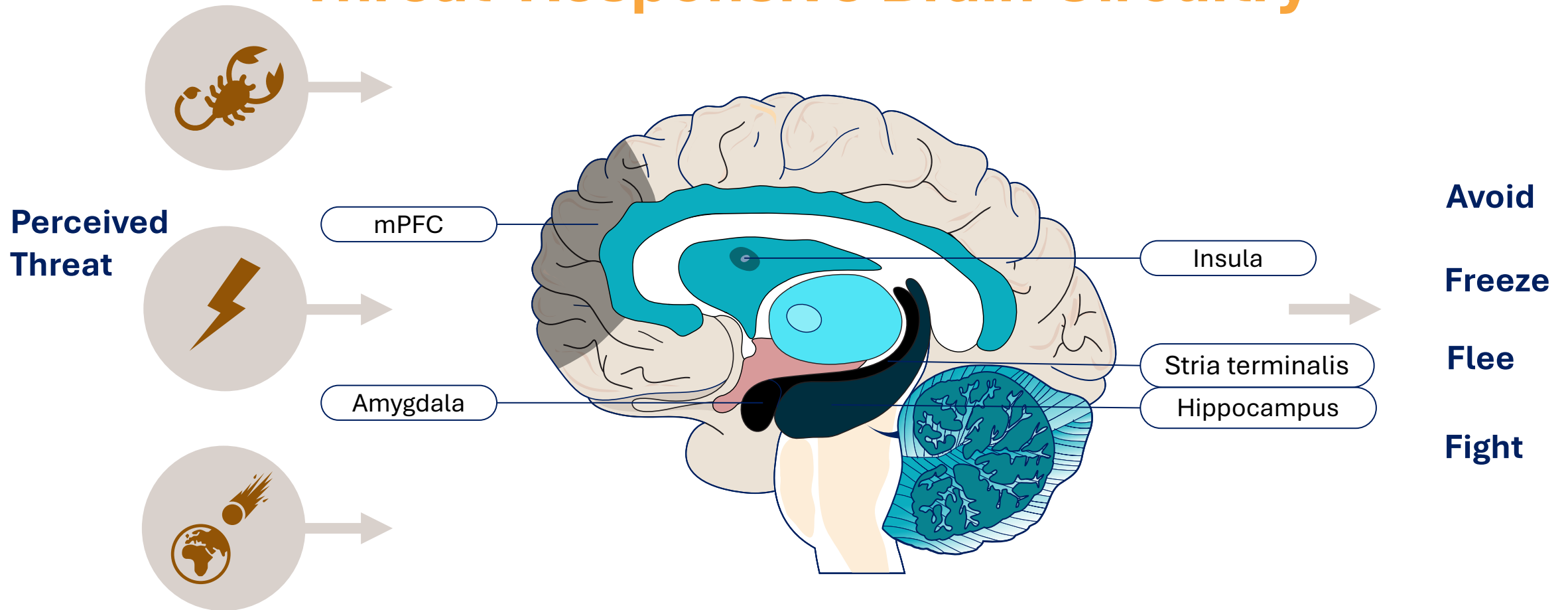
Generalized Anxiety Disorder (GAD)

*Excessive risk assessment/ diminished inhibition
(amygdala/ VMPFC)*

Different routes to the same goal



Etiology of Fear & Anxiety: Threat-Responsive Brain Circuitry

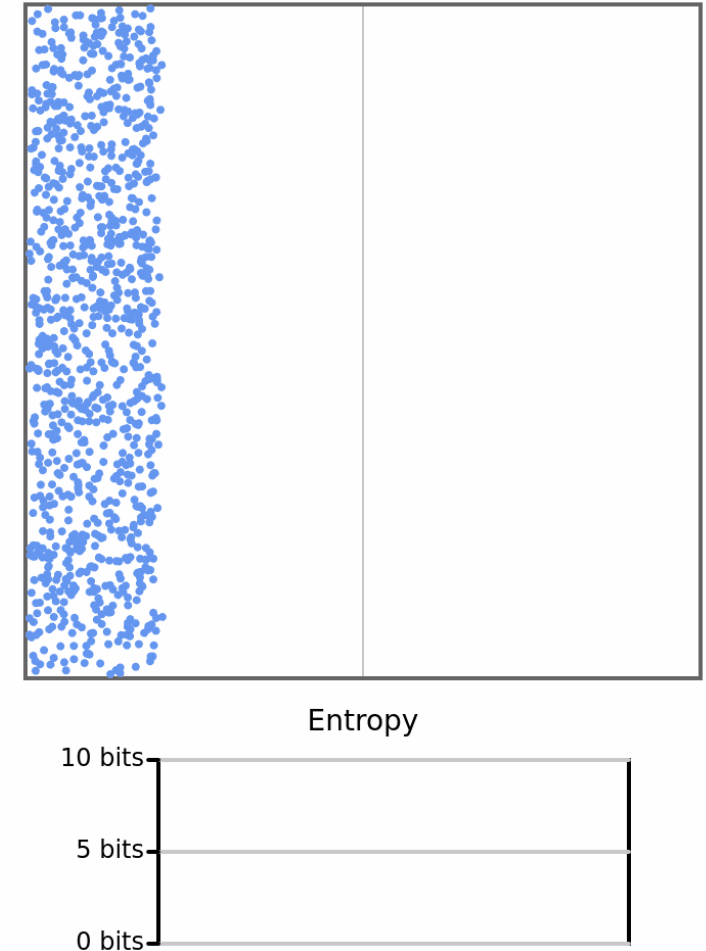


mPFC=medial prefrontal cortex

Penninx et al. Lancet 2021;397(10277):914–927. Domschke. Biol Psychiatry Glob Open Sci 2022;2(4):314–315. Carey et al. J Parkinsons Dis 2023;13(6):989–998. Image = This work is adapted from 'Anxiety in Parkinson's Disease is associated with changes in brain structural connectivity' by Carey et al., used under CC-BY. This work is licensed under Creative Commons license CC-BY-SA by The Lundbeck Foundation.

Is anxiety as the price of successfully resisting entropy?

- The second law of thermodynamics says that systems **tend to go from a state of order to disorder** (i.e. entropy)
- **The body has many systems in place to maintain order** and conserves energy (i.e. homeostasis)
 - **This applies to survival *behavior* as well** (e.g. being eaten by a tiger is the ultimate example of going from a state of order to disorganization)
- **We make predictions about what will happen in the world to try to conserve energy, and reduce uncertainty**
- These predictions may be efficient but may be incorrect. One useful framework is that anxiety involves overly persistent threat predictions and reduced updating when those predictions are incorrect. This can lead to behaviors that are ultimately maladaptive, but difficult to change (a state of low entropy).



*I can't get
it to stop!*

What happens when we are anxious?

– Loss of top-down inhibition model



You live upstairs

Loss of Top-Down Inhibition



But what if?!
I wonder if they're mad at me?
What if I mess up?
What's gonna happen?
Is something wrong with me?

The Downstairs Neighbors
“The Worriers”

Williams, N (2022) Psychedelics and Neurostimulation for Brain Rewiring, Huberman Podcast

<https://podcasts.apple.com/us/podcast/psychedelics-neurostimulation-for-brain-rewiring-dr/id1545953110?i=1000582122440>

What happens when we are depressed?

– Loss of top-down inhibition

**What's wrong with you?!
You're terrible!
Everything is awful!**

Dorsolateral prefrontal cortex

*I can't get
it to stop!*

You live 2 stories up

Loss of Top-Down Inhibition

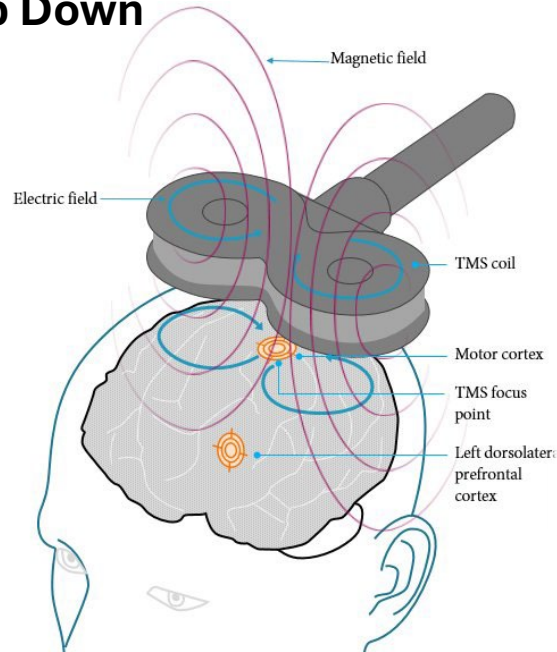
**The Downstairs Neighbors
“The Ruminators”**

Subgenual anterior cingulate (sgACC)/Amygdala

TMS Restores the Ability of the DLPFC to Inhibit the Overactive sgACC/amygdala

Can you guys keep it down?

Top Down



Dorsolateral prefrontal cortex (DLPFC)

You live 2 stories up

Restoration of Top-Down Inhibition

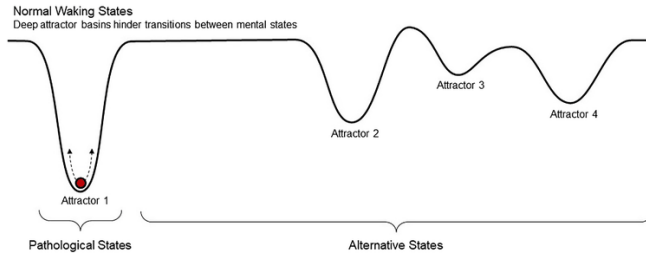
The Downstairs Neighbors
“The Ruminators” &
“The Worriers”



Subgenual anterior cingulate (sgACC)/Amygdala

What happens when we are depressed?

– DMN overdominance model



Default mode network: vmPFC. Posterior Cingulate, sgACC

Depression may be a state of low entropy, where prior experiences overdominate, and change is difficult, like a ball in a deep rut (the rut is the prior experience)

“We’re a new, good experience”

**The new, bottom-up (limbic) emotional experience
“The Friendly Visitors”**

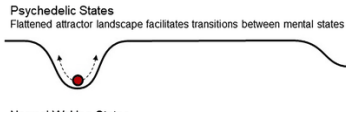
It never goes well

DMN overweights prior experiences

Psychedelics introduce greater DMN entropy - reducing dominance of priors and erroneous predictions

Welcome!

Default mode network: vmPFC. Posterior Cingulate, sgACC



Psychedelics introduce transient entropy,
“flattening the rut,” allowing for new experiences.

“We’re a new, good experience”

The new, bottom-up (limbic) emotional experience
“The Friendly Visitors”

Bottom Up



With greater DMN entropy,
new experiences can land



Relaxed
Beliefs
Under/After
Psychedelics
(REBUS/REBAS)

Key Learning Points



- GAD affects approximately **3%-6%** of the global population across a lifetime; in the United States, nearly **1 in 4 adults screen positive**, yet most are undiagnosed
- GAD follows a **chronic, relapsing course** with onset typically in early-to-mid adulthood, and is associated with substantial functional impairment, QoL reductions, and elevated mortality risk, including suicide
- Core pathophysiology involves **corticolimbic dysregulation**: amygdala hyperactivation, reduced PFC-amygdala connectivity, and HPA axis hyperactivation, driving serotonin and NE dysregulation
- TMS may increase the brain's ability to regulate activity. Psychedelics may temporarily increase the brain's ability to update what it is regulating.

Differential Diagnosis and Assessment of GAD

DSM-5-TR Criteria: Generalized Anxiety Disorder

Excessive anxiety and worry (>6 months) for several /activities, occurring more days than not

Difficulty controlling or stopping the constant cycle of worry.

Anxiety or worry is associated with ≥ 3 of 6 physical or cognitive symptoms

- Restlessness or feeling keyed-up or on-edge
- Being easily fatigued
- Difficulty concentrating or mind going blank
- Irritability
- Muscle tension
- Sleep disturbances (difficulty falling or staying asleep, or restless unsatisfying sleep)

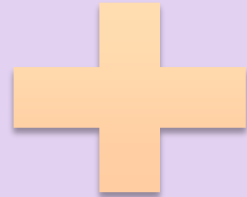
Lead to clinically significant distress or functional impairment

Not accounted for by another mental/medical/developmental disorder or physiological effects of a substance (drug misuse/medication/alcohol)

Key Properties of GAD

Symptoms

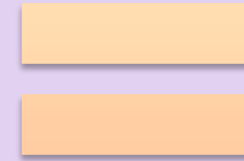
- excessive worry out of proportion to actual threat
- restlessness, fatigue, dyssomnia, muscle tension



Functional Impairment

- activities avoided
- opportunities missed

> 6 months



GAD



Shortness of breath



Difficulty concentrating



Insomnia



Fatigue



Agitation



Muscle cramps



Headaches

Somatic symptoms are common!



GI Distress

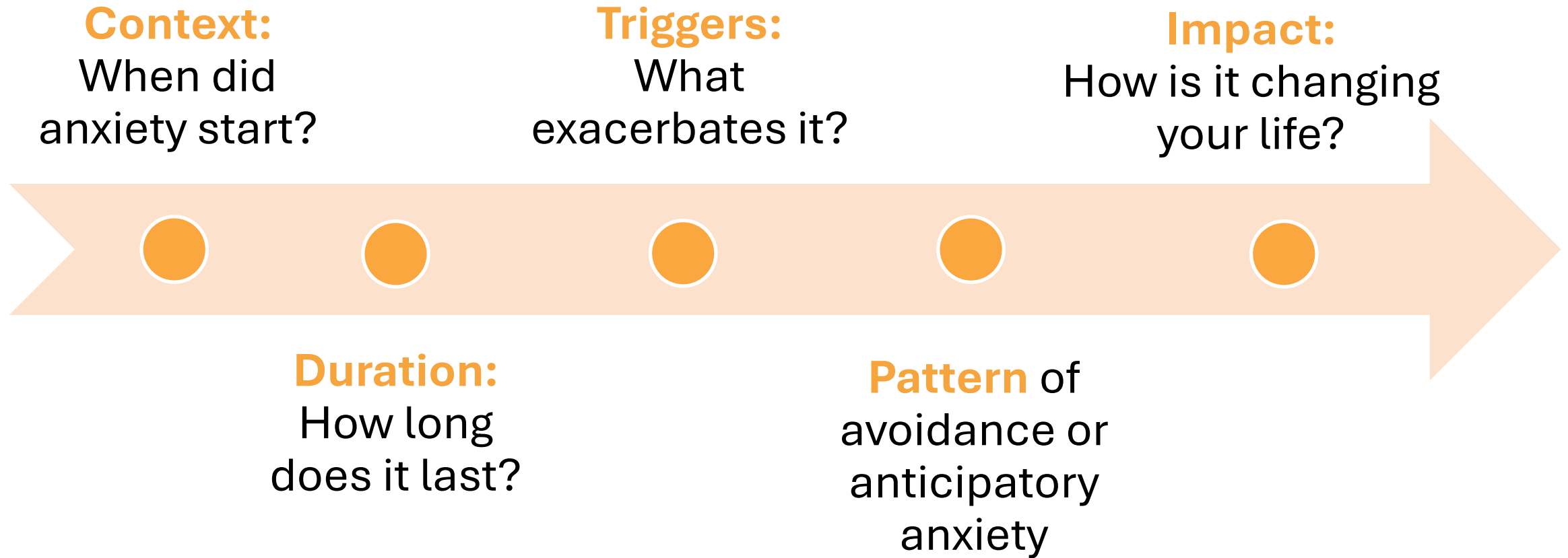


Heart Palpitations



Restlessness

Diagnostic Assessment: Anxiety



The 7-Item Generalized Anxiety Disorder (GAD-7) Scale

How to Use

- Self-report tool: Patients circle 1 of the 4 numbers (representing severity) associated with 7 problems.
- Brief—only 7 questions
- Multiple languages
- Couple minutes to complete

Sensitivity and Specificity

- Sensitivity: 89%
- Specificity: 82%

Over the last 2 weeks, how often have you been bothered by the following problems?		Not at all	Several Days	More than half the days	Nearly every day
1	Feeling nervous, anxious, or on edge	0	1	2	3
2	Not being able to stop or control worrying	0	1	2	3
3	Worrying too much about different things	0	1	2	3
4	Trouble relaxing	0	1	2	3
5	Being so restless that it is hard to sit still	0	1	2	3
6	Becoming easily annoyed or irritable	0	1	2	3
7	Feeling afraid, as if something awful might happen	0	1	2	3
TOTAL SCORE (add the marked numbers):					

The GAD-7 was developed by Drs. Robert L. Spitzer, Janet B. W. Williams, Kurt Kroenke, and colleagues, with an education grant from Pfizer, Inc.

Interpreting the GAD-7

How to Score

Add the values for each column and then add the total for each column to get the total score.

**Don't forget to
do a PHQ-9!**

As GAD + MDD
occur together
commonly

The Generalized Anxiety Disorder 7-Item (GAD-7) Scale

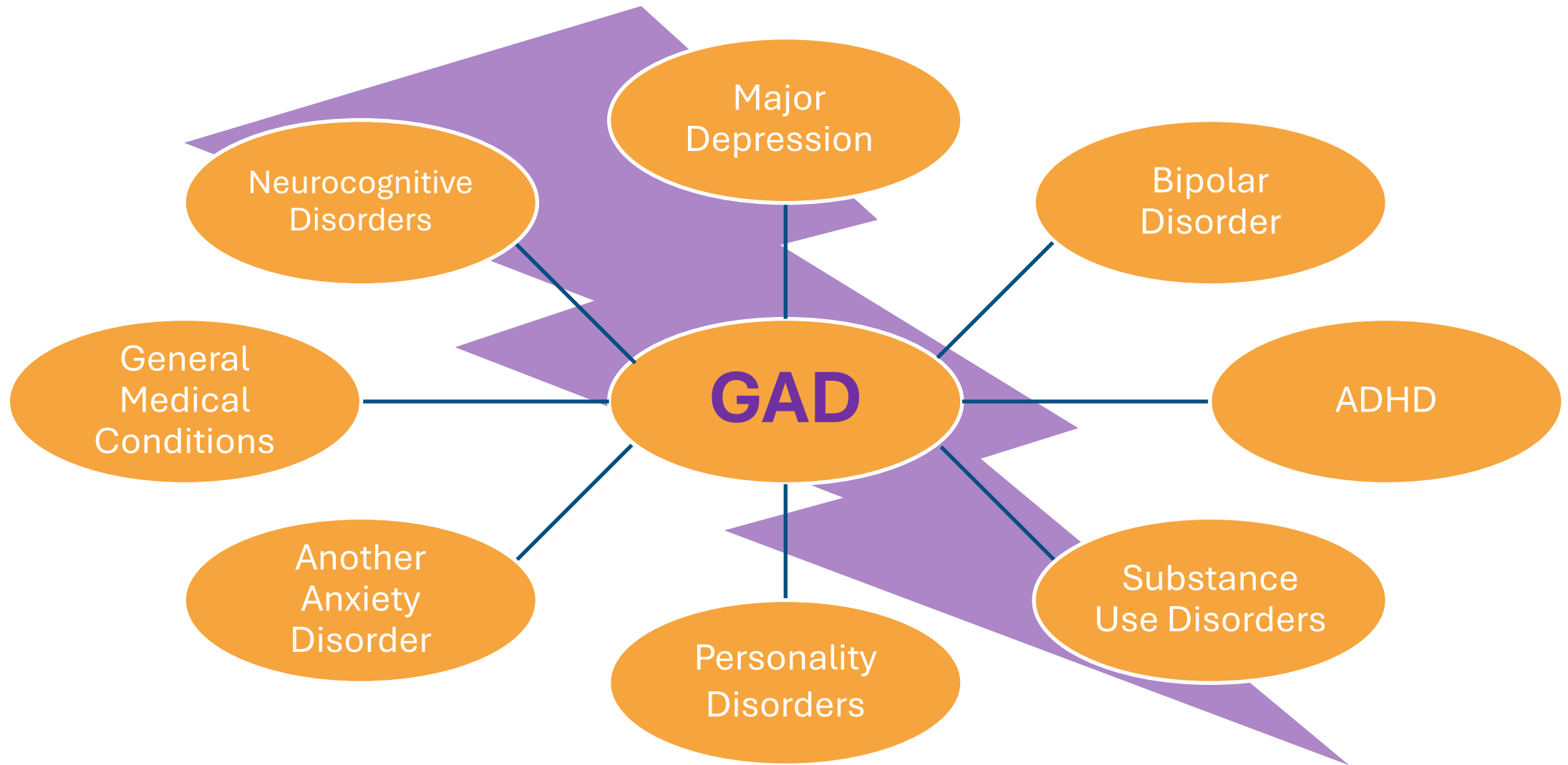
Name: _____ Date: _____

Over the last 2 weeks, how often have you been bothered by the following problems?

	Not at all	Several days	More than half the days	Nearly every day
1. Feeling nervous, anxious or on edge	0	1	2	3
2. Not being able to stop or control worrying	0	1	2	3
3. Worrying too much about different things	0	1	2	3
4. Trouble relaxing	0	1	2	3
5. Being so restless that it is hard to sit or stay still	0	1	2	3

Total Score	Interpretation
≥ 10	Probable diagnosis of GAD; confirm by further evaluation
5	Mild anxiety
10	Moderate anxiety
15	Severe anxiety

Common Comorbidities with GAD



Differentiating GAD from Other Psychiatric Conditions

Condition	Core Feature	Key Distinguisher from GAD
GAD vs MDD	MDD: low mood or anhedonia	In anxious MDD, anxiety arises within depressive episode; in comorbid GAD+MDD, GAD predates or outlasts it
GAD vs SAD	SAD: fear/avoidance in social situations	GAD worry spans multiple life domains; SAD is limited to social or performance contexts
GAD vs Panic Disorder	PD: episodic, acute attacks	GAD: chronic diffuse worry, no discrete panic episodes; PD: sudden intense surges with prominent physical symptoms
GAD vs OCD	OCD: ego-dystonic obsessions + compulsions	GAD: ego-syntonic worries felt as realistic concerns; no compulsive rituals

Key question: Is the anxiety transient and tied to a specific trigger (SAD, PD, OCD) or pervasive across multiple areas of daily life (GAD)?

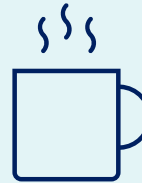
Rule Out Substance, Medication, & Medical Causes of Anxiety Symptoms

Medical Conditions



- * Hyperthyroidism: tremor, palpitations, weight loss, heat/cold intolerance
- * Pheochromocytoma: diaphoresis, headaches, palpitation, hypertension
- * Hypoglycemia
- * Cardiac disease: mitral valve prolapse, angina, arrhythmias presenting with autonomic arousal
- * Chronic pain
- * Autoimmune disorders
- * Respiratory disorders such as asthma or COPD
- * Menopause
- * Neurological disorders such as seizure

Substances



- * Stimulants: caffeine, sympathomimetics, amphetamines
- * Alcohol, benzodiazepine, cannabis, and opioid withdrawal can precipitate or worsen anxiety
- * Cannabis use

Medications



- * Corticosteroids
- * thyroid hormone
- * Bronchodilators
- * decongestants
- * Some SSRIs/SNRIs (early treatment activation effect)
- * Testosterone

Obtain comprehensive medical history and medication review before initiating psychiatric treatment

Tests: TSH; consider CBC, metabolic panel, UDS, ECG

Key Learning Points

- The **GAD-7 (cutoff ≥ 10)** and **PHQ-9** should be administered together to capture the high rate of GAD+MDD comorbidity; both tools are brief, validated, and practical for routine use
- **GAD must be differentiated** from **MDD with anxious distress** (by mood episode timing and core symptom), **social anxiety disorder** (restricted vs pervasive worry), **panic disorder** (episodic vs chronic), and **OCD** (ego-dystonic vs ego-syntonic)
- Rule out substance and medical causes of anxiety: always screen for **thyroid disease, stimulant use, and anxiety-inducing medications** before making a GAD diagnosis
- Clinical interview should **assess worry domains, duration (≥ 6 months), ability to control worry, functional impairment, and physical symptoms** to confirm a GAD diagnosis

The Current GAD Treatment Landscape

GAD Treatment Guidelines: APA, NICE, CANMAT, AAFP



Cognitive Behavioral Therapy

- first-line psychotherapy across all guidelines
- evidence for both individual and group formats



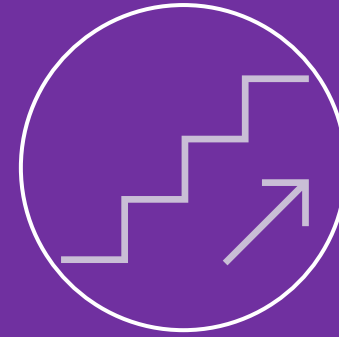
SSRIs/SNRIs:

- first-line pharmacotherapy endorsed by all major guidelines



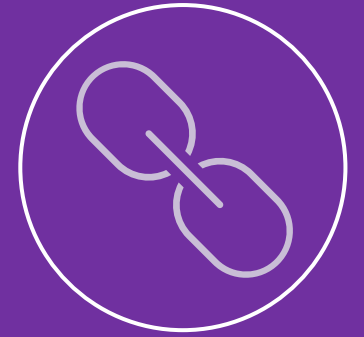
Benzodiazepines:

- most guidelines limit use to acute/short-term situations due to dependence risk;
- role as adjunct during antidepressant initiation



Sequential step-up:

- 1) CBT first
- 2) then SSRI/SNRI
- 3) buspirone or hydroxyzine as adjuncts
- CANMAT (2014)



Pharmacotherapy + CBT:

- offers superior outcomes for patients with moderate-to-severe GAD or significant comorbidity

CANMAT = Canadian Network for Mood and Anxiety Treatments; CBT = cognitive behavioral therapy; NICE = National Institute for Health and Care Excellence; AAFP = American Academy of Family Physicians. DeGeorge KC, et al. Am Fam Physician. 2022;106(2):157-164.

Katzman MA, et al. BMC Psychiatry. 2014;14(Suppl 1):S1. American Psychiatric Association. Practice Guideline for Anxiety Disorders. 2020.

Key Elements of Cognitive Behavioral Therapy

Psychoeducation

Realistic goal-setting

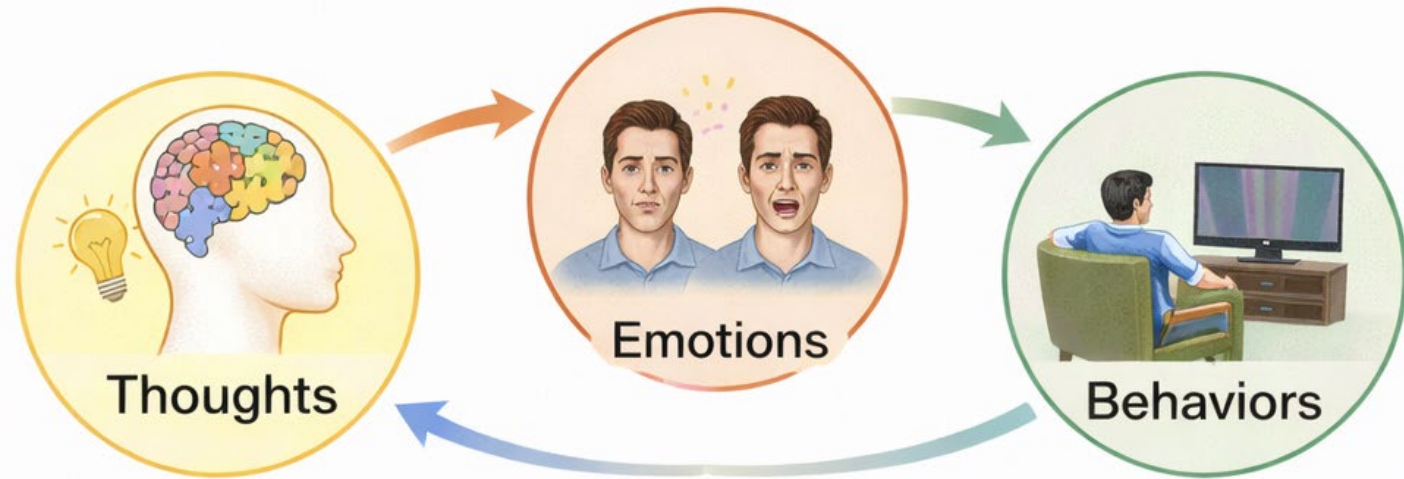
Relaxation training

Behavioral pacing

Relapse prevention

Communication skills training

Identifying dysfunctional thought patterns



What we THINK (thoughts) affects how we feel and act
What we FEEL (emotions) affects how we think and act
What we DO (behaviors) affects how we think and feel



Cognitive
Restructuring



Behavioral
Activation

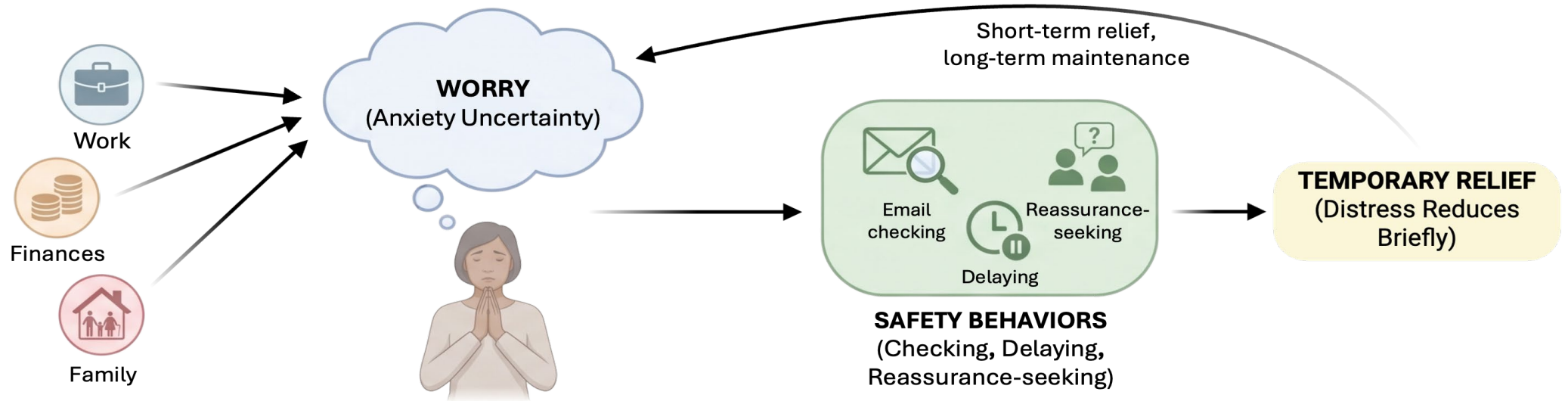


Exposure
Therapy

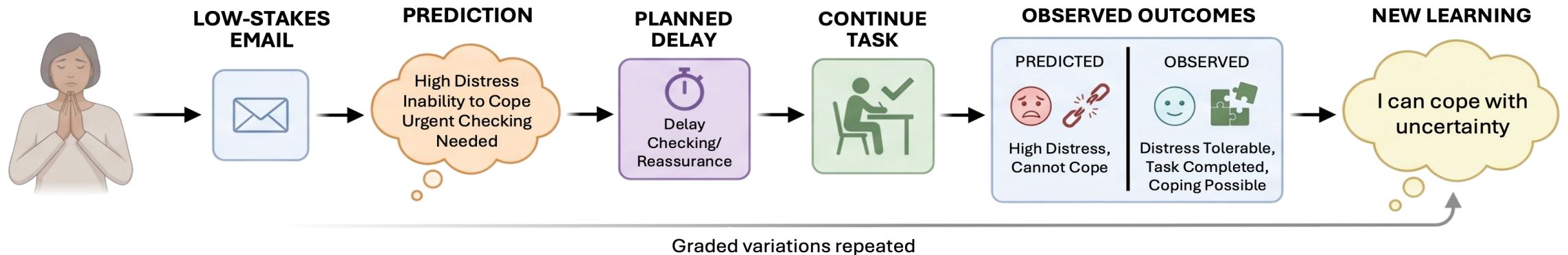


Skills
Training

CBT Worry Cycle in GAD

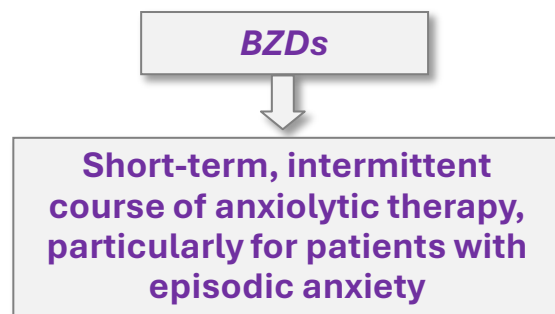


CBT BEHAVIORAL EXPERIMENT FOR ANXIETY: TESTING UNCERTAINTY

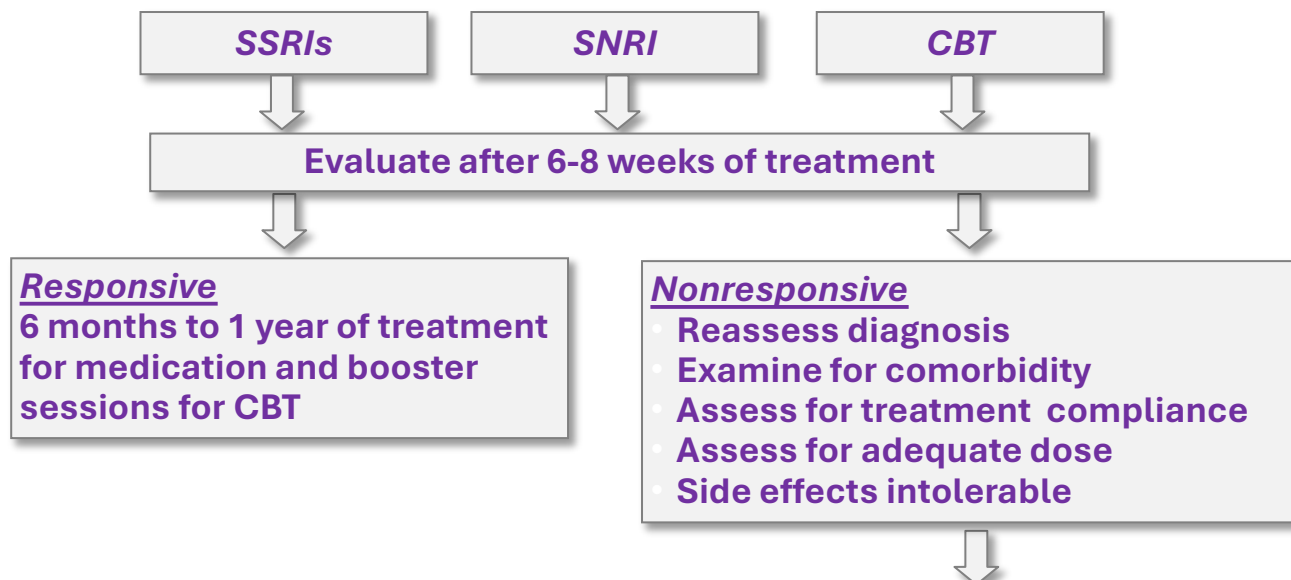


Medication Treatment Algorithm for GAD

Treatment for Acute Transient Anxiety



Prolonged Treatment Indicated



Treatment Options

- Switch to another first-line treatment
- Augmentation with CBT if on medication only or the reverse if started with CBT
- Augmentation with a BZD
- Augmentation with buspirone, bupropion, pregabalin, gabapentin, propranolol, or an antipsychotic

BZD = benzodiazepines; SSRI = selective serotonin reuptake inhibitor; SNRI = serotonin norepinephrine reuptake inhibitor; CBT = cognitive behavioral therapy.

Rynn MA, Brawman-Mintzer O. Generalized anxiety disorder: acute and chronic treatment. *CNS Spectr*. 2004 Oct;9(10):716-23.

First-Line GAD Pharmacotherapy: SSRI/SNRI

FDA Approved

- Paroxetine
- Venlafaxine ER
- Escitalopram
- Duloxetine
- Alprazolam
- Diazepam
- Oxazepam
- Lorazepam
- Buspirone



SSRIs and SNRIs demonstrated superior efficacy over placebo for response + remission in GAD

- According to a large network meta-analysis (Slee et al., Lancet, 2019)



SNRIs showed numerically higher response rates than SSRIs for GAD, particularly at higher doses

- According to a 3-level network meta-analysis (Gosmann et al., 2021)



Duloxetine, escitalopram, paroxetine, sertraline, and venlafaxine are among the agents with the strongest evidence base for GAD



Vilazodone and vortioxetine have positive studies in GAD

SSRI/SNRIs: *Early and Stepwise Reassessment*

- Early symptomatic improvement (typically within the first 4 weeks of therapy) is a reliable prognostic indicator for anxiety treatment outcomes
- Monitor improvement at maximally tolerated dose for at least 6 weeks prior to making changes; Onset of SSRI/SNRI anxiolytic effect typically takes 2–4 weeks; full benefit may require 6–12 weeks
- Not all SRIs are created equal! Tolerability profiles differ among agents; switching within class is appropriate before escalating to second-line

Week	Clinical Action
Week 1-2	Assess tolerability
Week 4	Check for any improvement ; increase dose if symptomatic
Week 6	If only mild response , consider increasing dose again.
Week 12	If no response , increase again or switch agent or class

When changing medications, consider potential for discontinuation symptoms or treatment-emergent symptoms of anxiety, irritability, and panic

Benzodiazepines: *Pros and Cons*



Advantages:

- Rapid onset
- Reasonable tolerability
- Low cost
- Useful for breakthrough symptoms
- May enhance adherence to treatment and alleviate initial activating symptoms of SRIs

Disadvantages:

- Initial sedation
- Memory impairment
- Falls
- Possibility of abuse, dependence, overdose, and withdrawal



The Charge:

- Use selectively & cautiously
- Ideal for acute expected anxiety or when rapid onset is needed
- Use for brief periods or infrequently as needed

SRI = serotonin reuptake inhibitor.

Hirschtritt ME, et al. *JAMA*. 2021;325(4):347-348. Blanco C, et al. *J Clin Psychiatry*. 2018;79(6):18m12174.

Potts NL, Krishnan KR. *Can Fam Physician*. 1992;38:149-153.

Benzodiazepines: *Know When to Say No*

Not recommended as first line for GAD

Appropriate for short-term adjunctive use when:

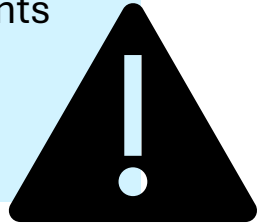
- Severe acute distress
- Bridging until SSRI/SNRI efficacy onset
- Treatment-resistant + closely monitored

Risks include:

- Tolerance
- Dependence
- Cognitive dulling
- Fall risk (esp. older adults)
- Rebound anxiety or withdrawal
- Overdose which can lead to
- Respiratory depression and death

Use with caution:

- History of substance use disorder
- Co-morbid CNS depressant agents
- Patients 65+
- Certain jobs
- Pregnancy / breastfeeding



Generic Drug	Approximate Dosage Equivalents (mg)	Time to Peak Plasma Level (Hours)	Elimination Half-Life (Hours)
Alprazolam	0.5	1–2	12–15
Chlordiazepoxide	10–25	2–4	24–48 (>96)
Clonazepam	0.25–0.5	1–4	30–40
Diazepam	5	1–2	44–48 (50–100)
Lorazepam	1	1–6	10–20
Temazepam	15	2.5	10–20

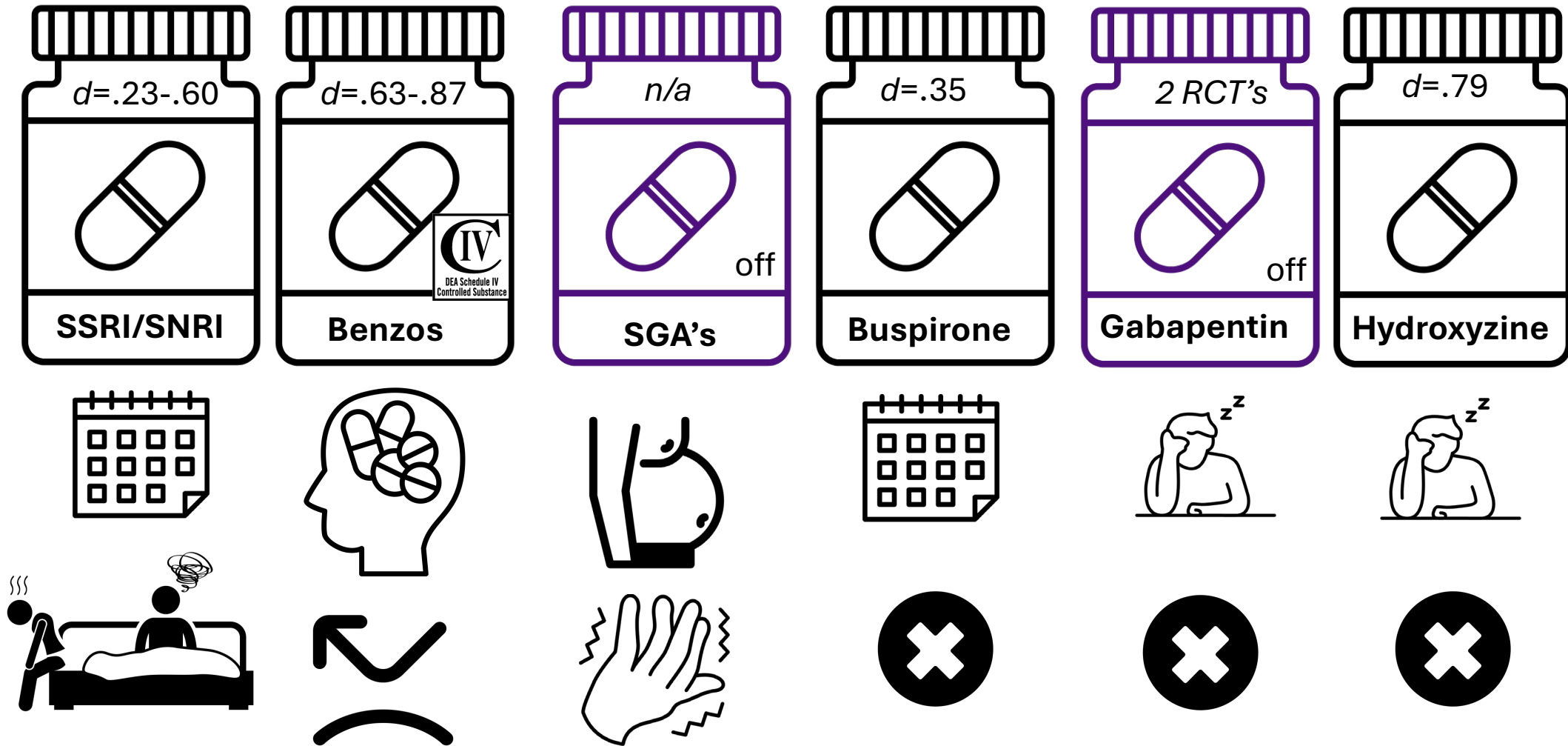
How Long to Continue Treatment *in Patients Who Respond to GAD Therapy*

For patients who respond to medication without significant adverse effects, the drug should be continued for at least 1 year after response to reduce relapse.

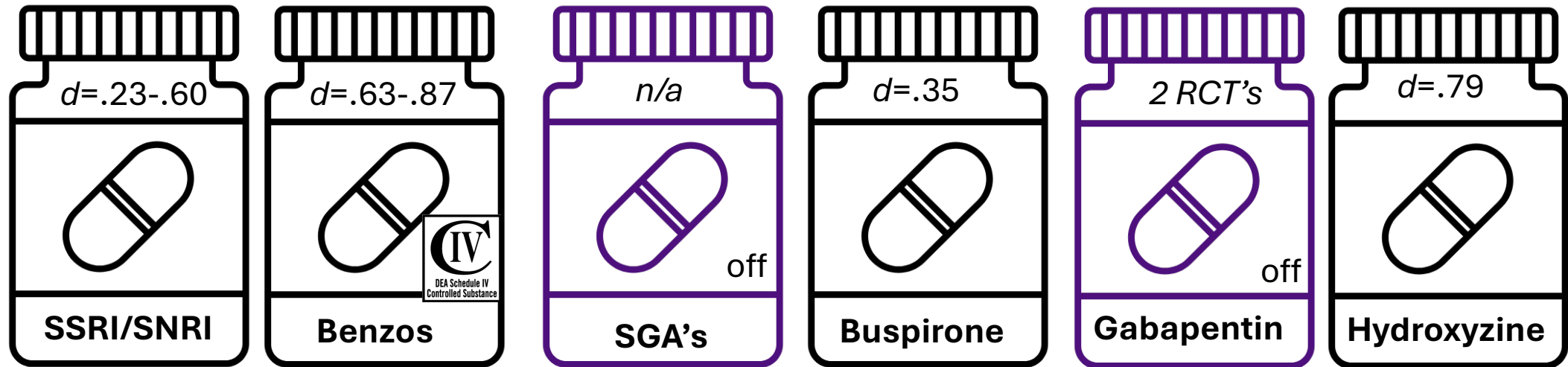
Clinicians should monitor patients during gradual discontinuation of medication over weeks to months to help avoid confusion between withdrawal symptoms and disorder relapse.

For CBT, a full course of treatment is typically 8 to 20 weekly sessions. If patients experience a relapse of symptoms, boosting sessions to reinforce previously learned skills or troubleshooting obstacles can be effective.

Current GAD Pharmacopeia and Their Shortcomings



But what's the biggest problem with all of these?



Less than 50% remit on SSRI/SNRI!

None of the meds work once the drug wears off

What if we could treat and not have to take a daily med?



SGA = second generation antipsychotic.

Slee A, et al. Lancet. 2019;393(10173):768-777. Kong W, et al. Front Pharmacol. 2020;11:580858. Szuhany, K. L., & Simon, N. M. (2022). Anxiety Disorders: A Review. JAMA, 328(24), 2431-2445. Slee A, et al. Lancet. 2019;393(10173):768-777. Kong W, et al. Front Pharmacol. 2020;11:580858. Gosmann NP, et al. PLoS Medicine. 2021;18(6):e1003664.

Key Learning Points

- Major treatment guidelines (APA, NICE, CANMAT, WFSBP, AAFP) converge on SSRIs/SNRIs and CBT as first-line treatments
- First-line pharmacotherapies, including SSRIs/SNRIs, are limited since the anxiolytic response generally does not persist once treatment is discontinued
- Second-line and adjunctive options: buspirone (non-habit-forming, delayed onset), hydroxyzine (rapid, no dependence), and pregabalin
- Benzodiazepines have a role in short-term management of acute exacerbations or during antidepressant initiation, but carry risks with chronic, daily use
- Significant unmet needs remain: first-line response rates are ~40%–60%, relapse is common after discontinuation, and tolerability issues frequently limit long-term adherence



The Science of Psychedelics and Their Potential Role in GAD

How did we get to psychedelics as medicines?



Early studies 1943-1970's

*Controlled Substance
Act (1970)*



**Contemporary Investigator
Initiated studies**

2000's-

*Breakthrough status
(2017-)*

Phase 3 Esketamine/TRD

FDA Approved 2019

Phase 3 MDMA/PTSD

Declined by FDA 2024, resubmit 2026

Phase 3 Psilocybin MDD, TRD

FDA NDA Q4 2026 – Q1 2027

Phase 3 LSD MDD, GAD

FDA NDA Q3/4 2026

Phase 3 Deuterated DMT/MDD

TBD

Industry Sponsored studies

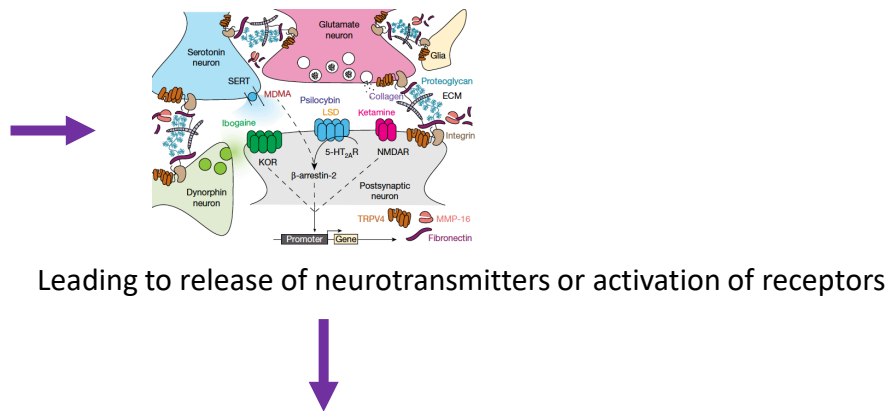
2010-present

*Executive Order
(2026)*

Geyer M. A. (2024). A Brief Historical Overview of Psychedelic Research. *Biological psychiatry. Cognitive neuroscience and neuroimaging*, 9(5), 464–471. <https://doi.org/10.1016/j.bpsc.2023.11.003>. Harvey, P.D., Nemeroff, C.B. Psychedelic therapeutics in psychiatric conditions. *Neuropsychopharmacol.* (2026). <https://doi.org/10.1038/s41386-026-02335-z>



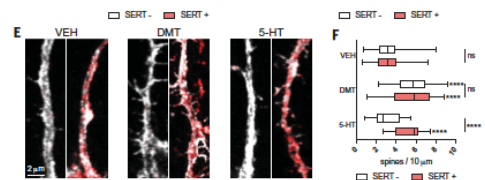
A drug is ingested



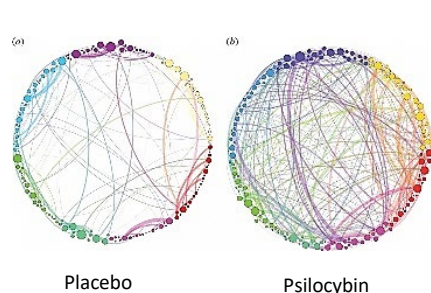
How can psychedelics be therapeutic?



Changing our story/ Emotional Breakthrough
Feeling connected to a larger whole
Finding meaning/spirituality



Growing new brain connections (neuroplasticity)



Changing the way the brain
talks to itself and predicts events (increased DMN entropy)



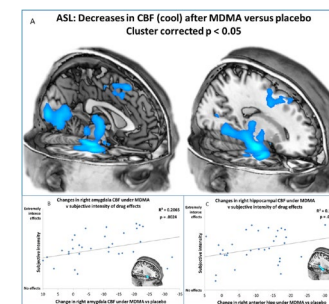
Therapeutic Response



Re-opening of critical
learning periods



Increased tolerance of difficult emotions



Reduction in limbic hyperactivation

5HT2A Agonism is the hallmark of "classical" psychedelic action, but it's not the only receptor activated

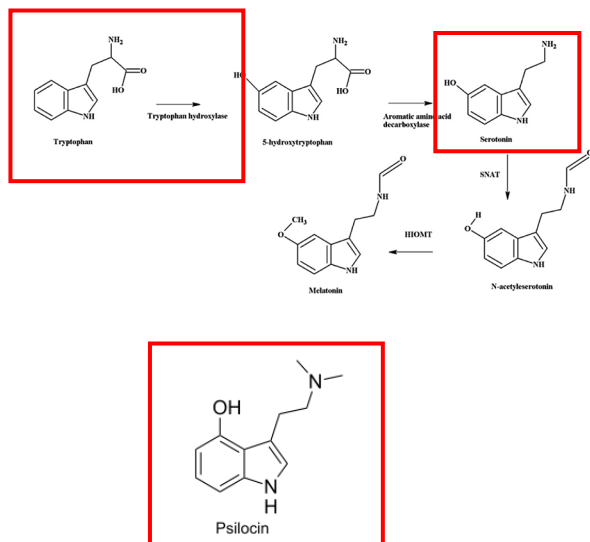
- All 5HT receptors are G-coupled protein receptors (GCPR) except 5HT3
- 5HT2A activity is essential for subjective psychedelic effects (and can be blocked by pre-dosing with ketanserin)
- LSD acts on several other key 5HT receptors, including
 - 5HT1A (buspirone, vilazodone, vortioxetine)
 - 5HT1B (triptans)
 - 5HT2B (fenfluramine - concern for VHD with chronic agonism)
 - LSD: 5HT1B>5HT2B>5HT1A>5HT2A
 - Blocking 5HT2B in rats before LSD administration eliminates anxiolytic and antidepressant effects (role in human is unclear, but may lead to VHD)

Table I
Affinity of LSD for rat, mice and human 5-HT_{1A/B} and 5-HT_{2A/B/C} Receptors.

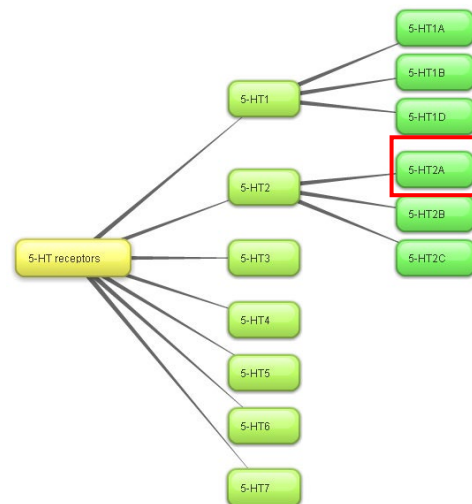
Receptors	Species	Ki	Action	Sources
5-HT _{1A}	Rat	1.1	Partial Agonist	[89]
	Mouse	30		[90]
	Human	3.5		[91]
5-HT _{1B}	Rat	3.9	Partial Agonist	[92]
	Mouse	18.8		[93]
	Human	0.63		[94]
5-HT _{2A}	Rat	3.5	Partial Agonist	[92]
	Mouse	2.3		[95]
	Human	4		[96]
5-HT _{2B}	Rat	30	Partial Agonist	[92]
	Mouse	0.9 (EC50)		[97]
	Human	0.97		[98]
5-HT _{2C}	Rat	5.5	Partial Agonist	[92]
	Mouse	N/A		—
	Human	15		[96]

Bouloufa, A., Delcourte, S., Rovera, R., Delannay, T., Duquet, A., Mouledous, L., Dkhissi-Benyahya, O., Guiard, B. P., & Haddjeri, N. (2025). LSD's rapid antidepressant effects are modulated by 5-HT_{2B} receptors. *Biomedicine & pharmacotherapy = Biomedecine & pharmacotherapie*, 190, 118348. <https://doi.org/10.1016/j.biopha.2025.118348>

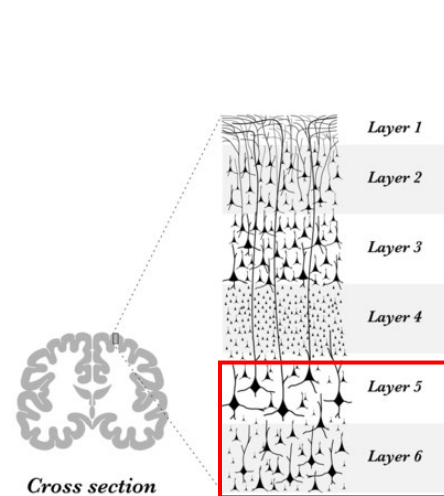
Serotonin 2A (5HT2A) = a key for human (and cellular) adaptivity? *Is GAD/MDD a form of maladaptation?*



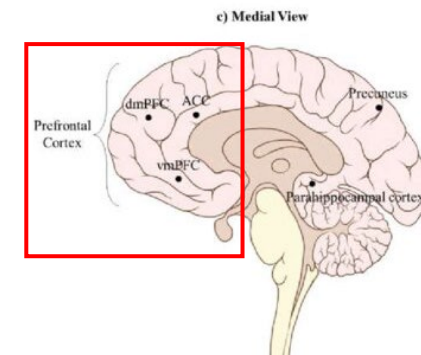
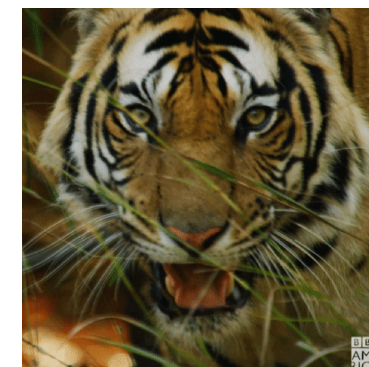
Serotonin (5HT) is synthesized from tryptophan



Psychedelics activate many 5HT receptors, but 5HT2A appear to be one key



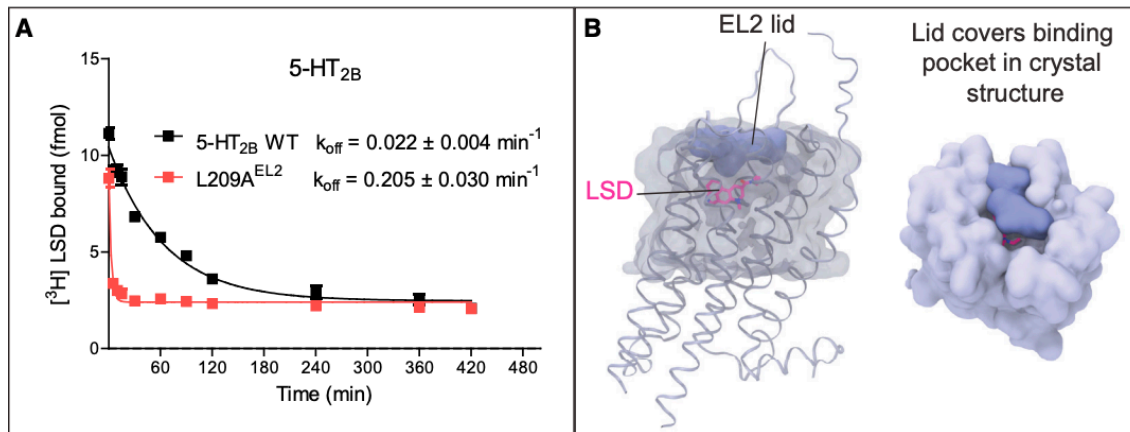
5HT2A is richly expressed in layers 5-6 of the cortex



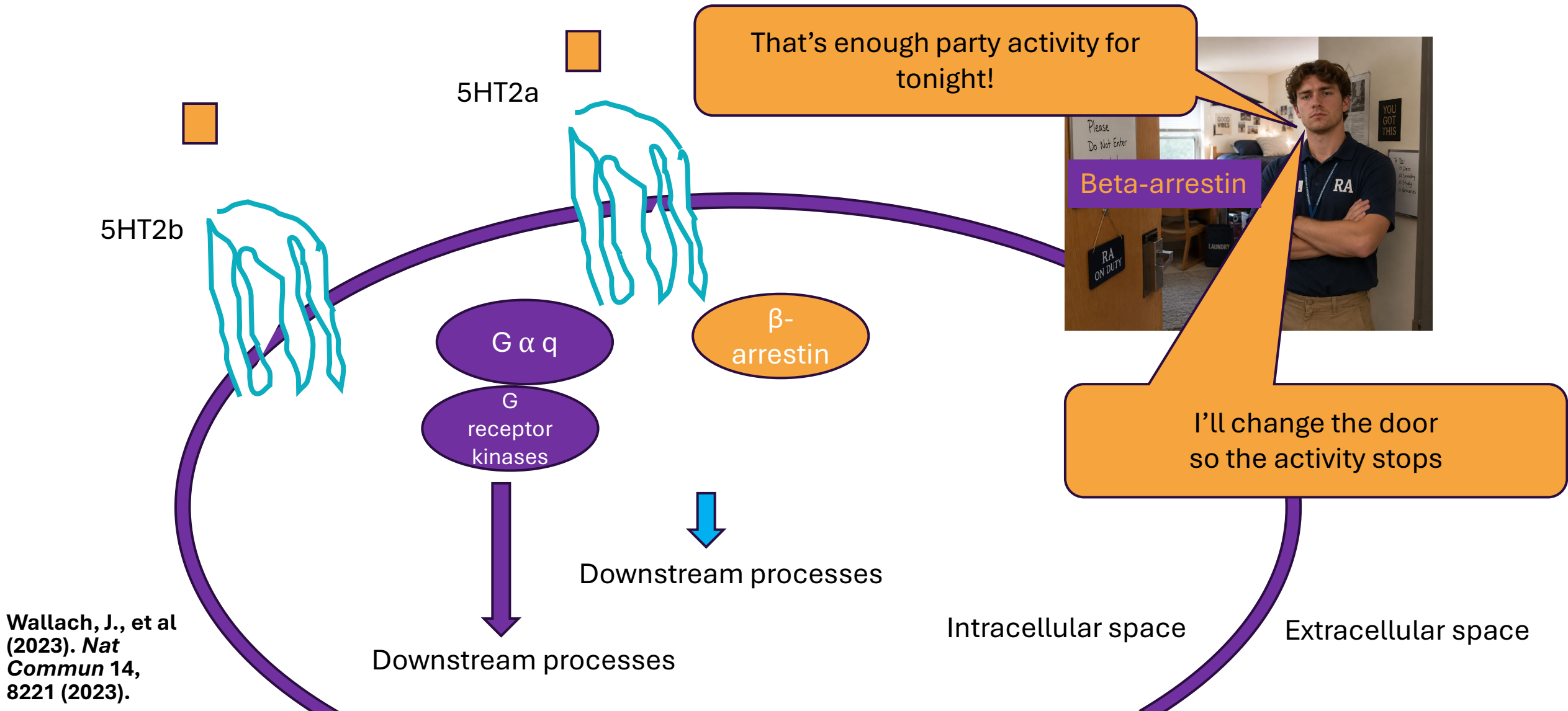
There are many 5HT2A receptors in the prefrontal cortex = stress adaptation

Once it's attached to extracellular 5HT receptors, LSD does interesting things

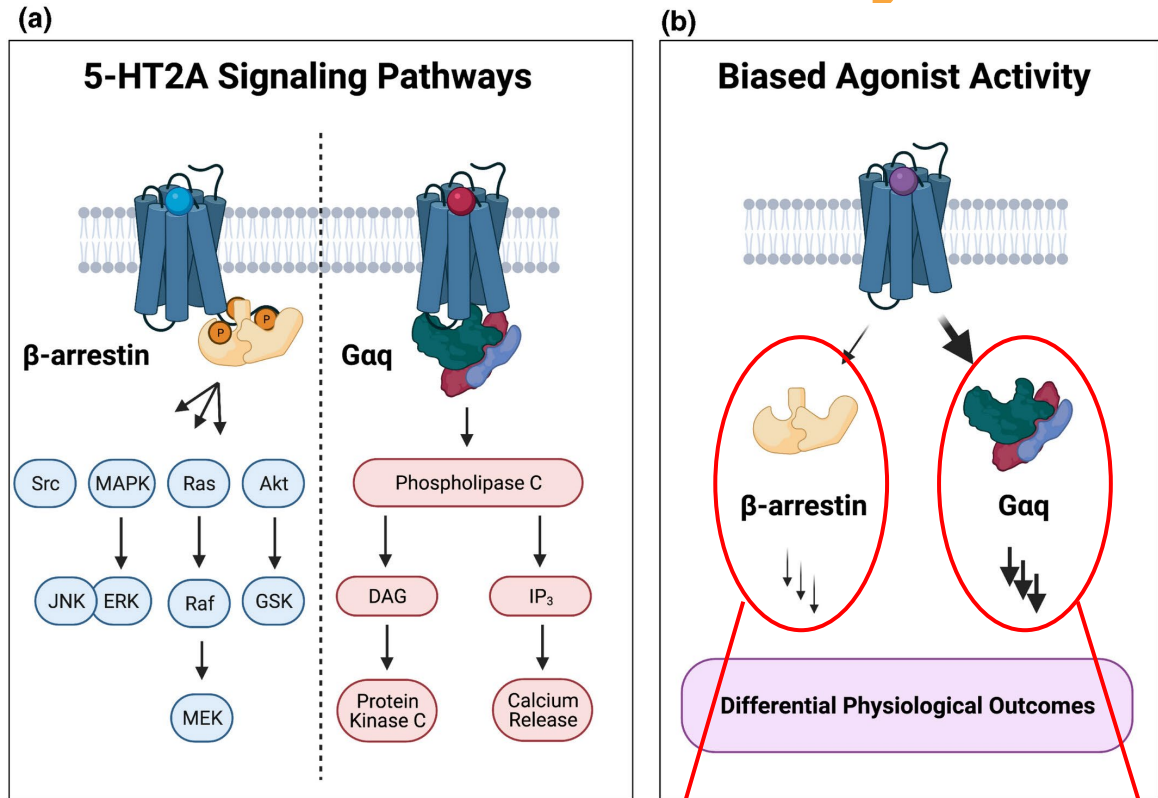
- LSD binds to the orthosteric site of the receptor
- LSD causes a conformational change of the proteins of the 5HT2a and 2b receptor, creating a "lid" over the receptor
- This prevents LSD from disassociating from the receptor, maintaining activation of the receptor
- Lab models demonstrated presence of LSD in the receptor for 40+ minutes, allowing for prolonged activation of the 5HT2a and 2b receptors



β -arrestin can contribute to receptor desensitization/internalization, but it also acts as a signaling scaffold and can initiate downstream signaling of its own.

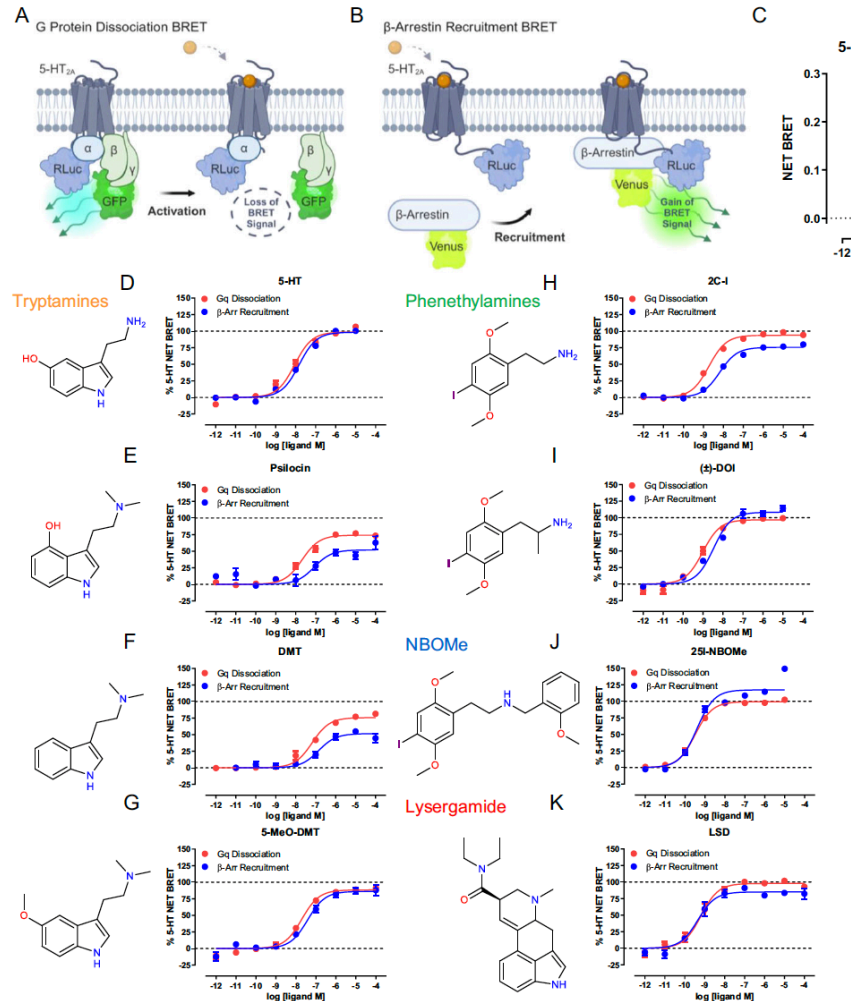


How the molecule influences *intracellular* processes determines the subjective effects – biased agonism



- **5-HT_{2A} signaling is multidimensional**
 - **Gq/11-dependent signaling**
 - PLC/IP₃/DAG pathways
 - cortical excitation and downstream signaling
 - **β-arrestin-associated signaling**
 - receptor desensitization/internalization
 - additional intracellular signaling
- Most subjectively psychedelic drugs activate both β-arrestin and Gαq – they are “unbiased agonists”
- How these pathways interact remains under investigation

Most psychedelics are non-biased agonists of β -arrestin and $G\alpha_q$



- Both β -arrestin and $G\alpha_q$ pathways lead to neurogenesis outcomes, through different pathways
- “Non hallucinatory psychedelics” are attempting to create drugs that bias towards β -arrestin signaling to create neuroplastic effects without psychedelic “side effects”

Preclinical evidence suggests intracellular 5-HT2A signaling may contribute to psychedelic-induced neuroplasticity

- 5HT2A receptors are expressed on the *outside* of neurons (GCPR's) and *inside* neurons (intracellular)
- Activation of intracellular 5HT2Ar's by DMT may initiate cascade of AMPA, TrKB, and mTOR signaling starting within hours, resulting in neuroplasticity that may last for days to weeks
- This neuroplastic event, when blocked before giving a psychedelic, diminishes the antidepressant effects in animal models.

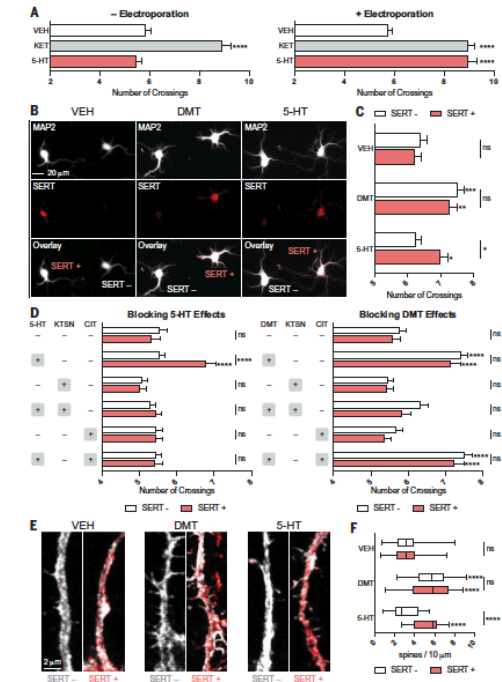


Fig. 4. Cellular uptake of serotonin induces structural plasticity in vitro. (A) Rat embryonic cortical neurons were administered compounds (1 μM) with (+) and without (-) electroporation. N_{cross} values obtained from Sholl plots (DIV6) demonstrate that unlike ketamine, serotonin only promotes growth when administered with electroporation ($N = 49$ to 59 neurons per treatment). (B) Widefield images of embryonic rat cortical cultures (DIV6) sparsely transfected with CaMKII-SERT-eYFP and treated with compounds. (C) N_{cross} values obtained from Sholl plots demonstrate that serotonin (10 μM) can only increase the dendritic arbor complexity of SERT-positive neurons, whereas DMT (10 μM) can promote the growth of both SERT-positive and SERT-negative neurons ($N = 69$ to 93 neurons per treatment). (D) KTSN pretreatment (10 μM) blocks the plasticity-promoting effects of serotonin (1 μM) in SERT-positive neurons and DMT (1 μM) in both SERT-positive and SERT-negative neurons. CIT (10 μM) only blocks the plasticity-promoting effects of serotonin (1 μM) in SERT-positive neurons ($N = 59$ to 100 neurons per treatment). (E) Confocal images of CaMKII-SERT-eYFP positive and negative dendrites (DIV5) treated with compounds (10 μM). (F) Serotonin only promotes spine growth in SERT-positive neurons ($N = 11$ to 35 neurons per treatment). Error bars in (A), (C), and (D) represent standard error of the mean. ns is not significant, * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, and **** $p < 0.0001$, as compared with VEH controls in (A) (one-way ANOVA followed by Dunnett's multiple comparisons test) or compared with VEH controls from the same genotype in (C), (D), and (F) (two-way ANOVA followed by Tukey's multiple comparisons test). For box-and-whisker plots in (F), the center line represents the median, box limits are upper and lower quartiles, and whiskers are minimum and maximum values.

Is psychedelic change biological or psychological? Yes.

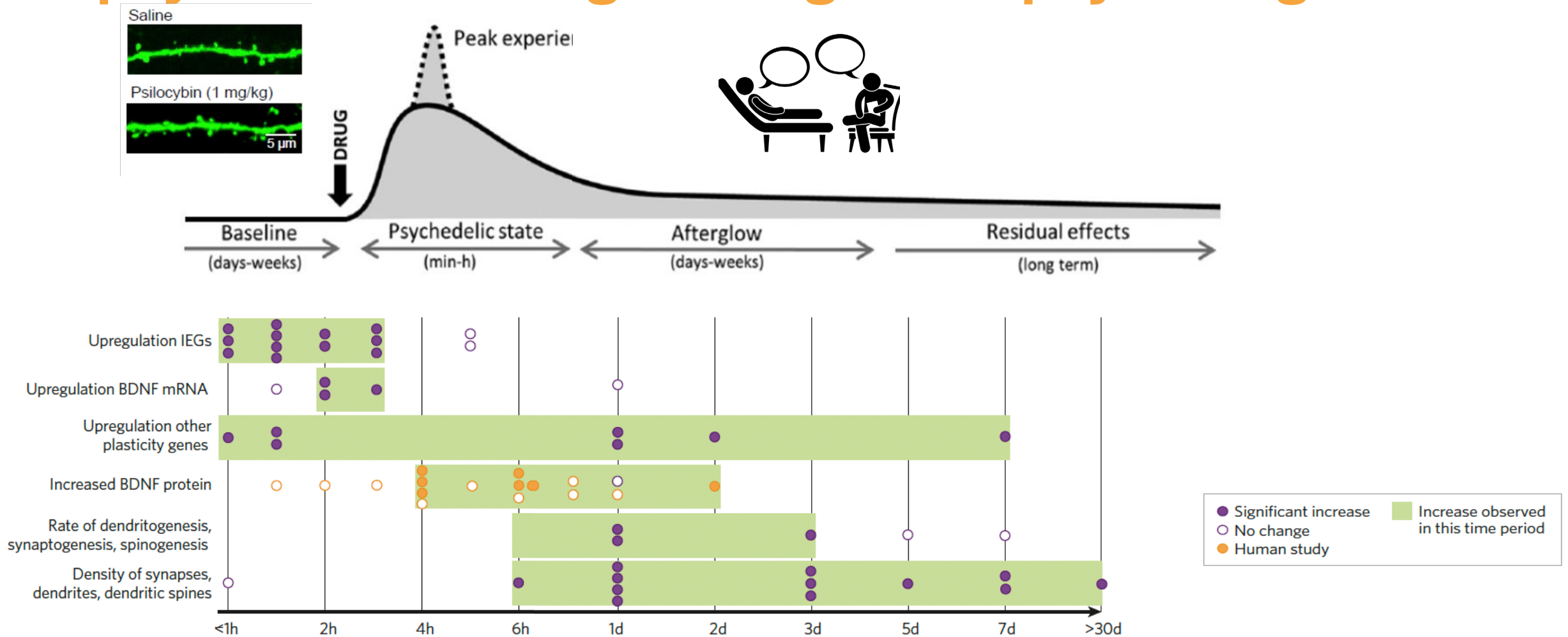


Fig. 1 Timeline showing the earliest and latest observations of various changes in neuroplasticity following treatment with a single dose of the serotonergic psychedelics LSD, psilocybin/psilocin, DMT, or DOI. One dot represents one study and time point. Human studies are shown in yellow; animal and in vitro studies are shown in purple. BDNF = brain-derived neurotrophic factor, IEGs = immediate early genes. Based on data for synaptic density, it is assumed that rates of dendritogenesis and synaptogenesis also increase at 6 h post-treatment. See Table S1 for citations.

Part of the Psychological effect may be the evocation feared emotions, creating an adaptive stressor



Tends to suppress emotions



Tends to evoke emotions



Adaptive Stressor

Experiential avoidance

Suppression: controlling or eliminating immediate experiences of unwanted thoughts, feelings, memories, or physical sensations.

Situational escape/avoidance: modifying contextual factors associated with undesirable personal experiences.

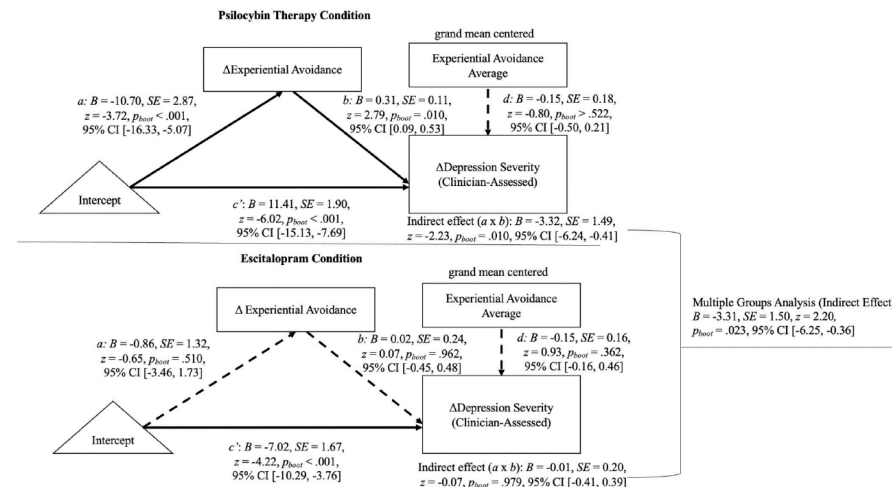


Fig. 2. Decreases in Clinician-Assessed Depression Severity via Reductions in Experiential Avoidance (Psilocybin Therapy Condition vs. Escitalopram Condition). Note. Solid arrows represent significant effects ($p < .05$) and dashed lines represent non-significant effects ($p > .05$).

Context is critical to a stressor being responded to in a adaptive or maladaptive way

Reduced experiential avoidance correlates with antidepressant response to psilocybin

What's the Psychedelic Experience Like?

“Emotionally it was a roller coaster ride ... The first time it was very brutal, painful, at least emotionally very painful. I could not even say in which direction—it just hurt, like heartache, like being disappointed, like everything you once had experienced as a negative feeling. ... It was pure pain. Pain of memories, well, or memory of pain. ... it was quite hard.

During the second time it was sublime. Really. Love, expansion, holding, I knew that this sometimes happens, that participants talk about spiritual experiences. I thought they just meant this dissolution of oneself – everything is okay, everything is great. That was a very important experience for me. Very, very important.” [85] [LSD, end-of-life anxiety].



Awe-Joy/Psychotherapeutic
Narrative/ perspective -
autobiographical shifts

“I think right after the trips ... certain changes happened ... Same things were not equally important anymore. A shift in values. ... To take time to listen to music, to listen to music consciously. Maybe that material values were not that important anymore. That other values have priority. Health and family, such things... When you have a job and the job has priority and the family comes last. You don't even notice it anymore. To realize there, stop, what is actually important? That the family is fine, that the kids are doing well ...” [85] [LSD, end-of-life anxiety].

Key Learning Points

- Psychedelics vary in their receptor activity, but 5HT1a, 1b, 2b, and 2a appear critical for both subjective and therapeutic effects
- Psychedelics have a multimodal activity including neuroplastic effects, transiently introducing entropy to both brain networks and thought/emotional/behavioral patterns
- Psychedelics tend to be evocative of emotions, which may serve to help address affective avoidance by means of introducing an adaptive stressor

Harnessing Psychedelics for the Treatment of GAD

Investigator-Initiated Studies (Recruiting)

- **Safety, Tolerability, and Preliminary Efficacy of Psilocybin Oral Solution in Adults With Generalized Anxiety Disorder**
(NCT06969170) – (Low dose 3mg, RCT) Canada
- **Psilocybin-Assisted Therapy for Intergenerational Trauma**
(NCT06899165) – (Open label, 25mg), NY
- **Open-Label Psilocybin Study in Transdiagnostic Population**
(NCT06442423) – (Open label, 25mg), Yale

In The Pipeline: Emerging Psychedelics for GAD

Phase 2

HLP004
(IM Deuterated DMT)

RE02
(5-HT1A agonist)*

RE104
(SC Luvesilocin)

PSX-001 (Psilocybin)

Low dose Psilocybin

Phase 3

DT120
(LSD D-tartrate
ODT)

<https://reunionneuro.com/programs/> accessed Aug 22, 2026

*Originally developed/described as a sublingual 5-MeO-DMT formulation; current sponsor materials describe RE02 as a non-psychedelic, neuroplasticity-promoting 5-HT1A agonist

DT120 ODT: New Phase 3 Signal for a Single-Dose Psychedelic Approach in GAD



Phase 3, randomized, double-blind, placebo-controlled trial (N = 193 adults with GAD) for a single dose of DT120 ODT (100 µg)[†]

94% met end-of-session criteria by 8 hours

DT120 ODT was reported as **generally well tolerated**; mild to moderate transient TEAEs predominately occurred on dosing day

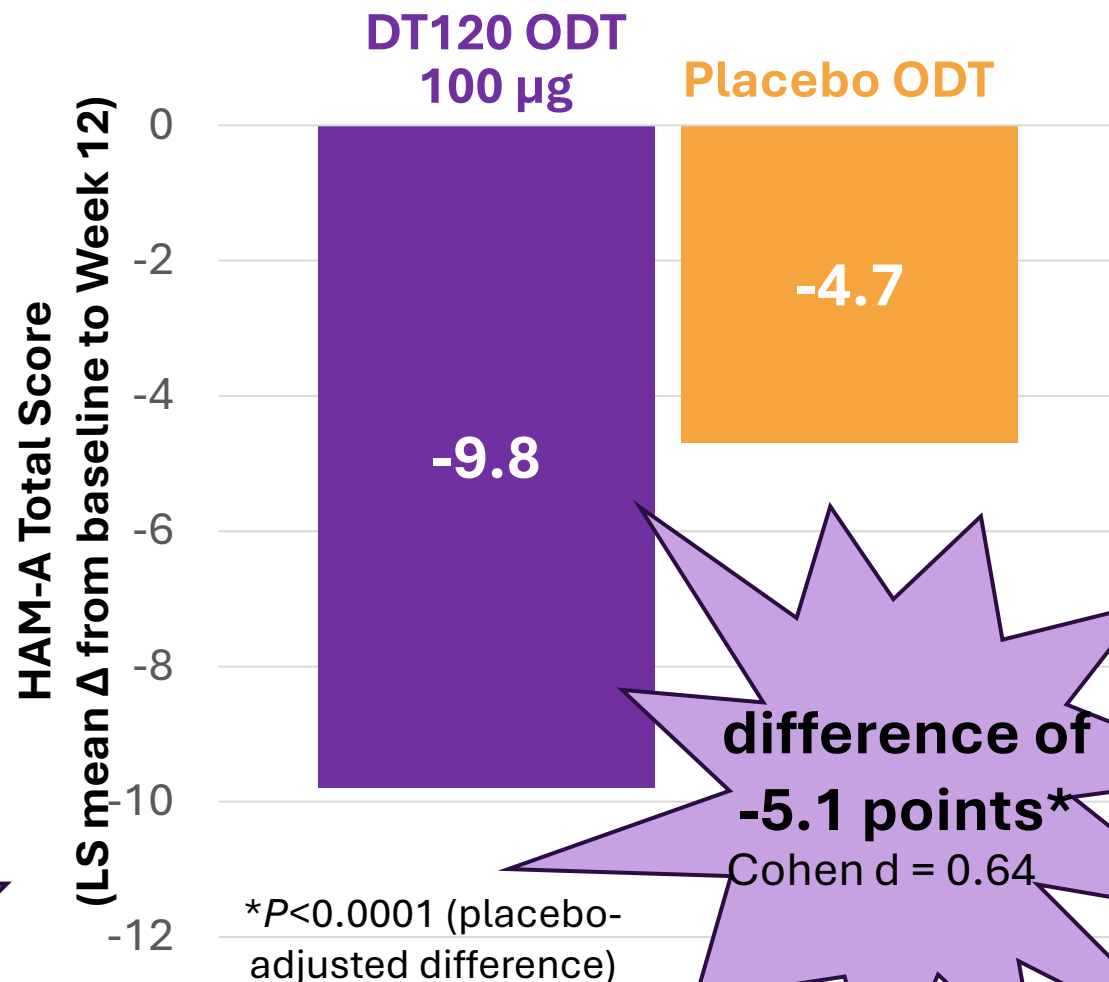
Response Rate at Week 12:

32% vs 14%

Remission Rate at Week 12:

15% vs 4%

Improvement in anxiety symptoms

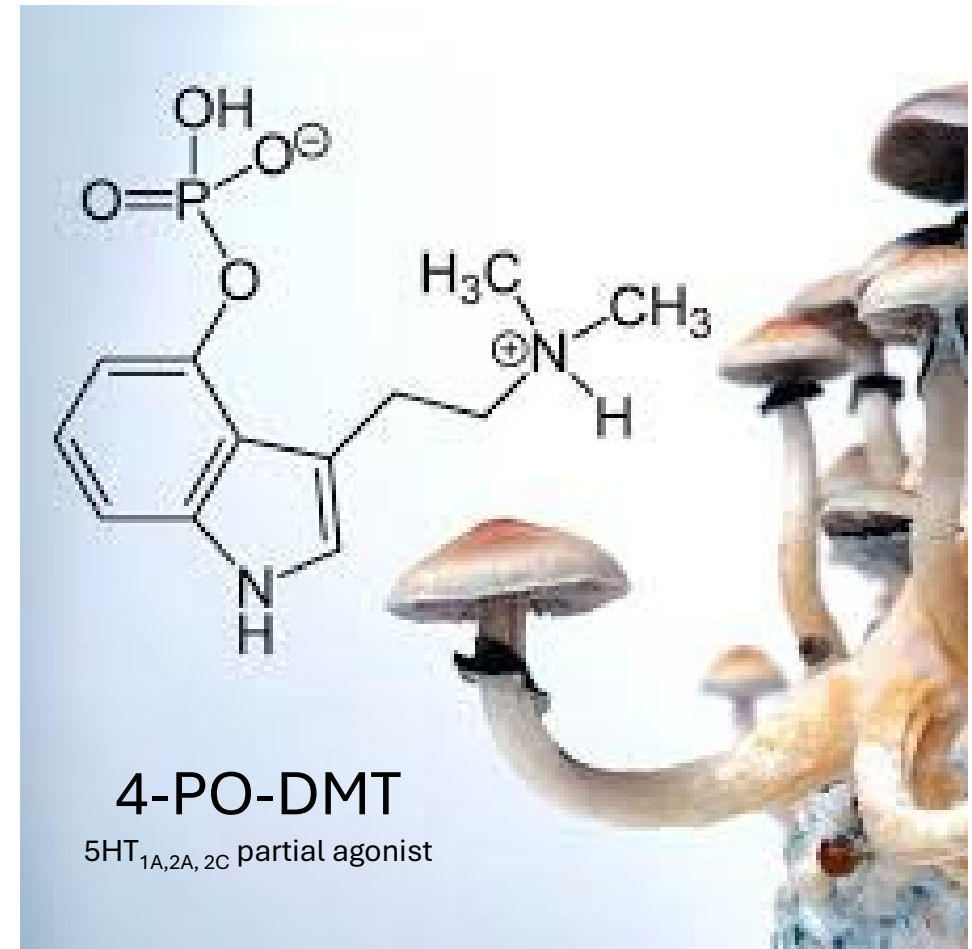


[†]Note: company-reported topline data; not yet peer-reviewed

ODT = Orally Disintegrating Tablet; HAM-A = Hamilton Anxiety Rating Scale; TEAE = treatment-emergent adverse event. Definium Therapeutics. Definium Therapeutics announces positive topline results from Phase 3 Panorama study of DT120 ODT in generalized anxiety disorder. Published September 14, 2026. Accessed September 18, 2026.

2026: Ph 2 Psilocybin (PSX-001)

- **Drug:** PSX-001 (Synthetic Psilocybin)
- **Size:** N=73 (PsiGAD1)
N = 94 (PsiGAD2)
- **Type:** DB RCT or placebo
- **Key Findings:** (2025 Topline, yet not published) 44% had a 50% or more reduction in GAD-7. PSX-001 was well tolerated with no SAEs. Awaiting publication



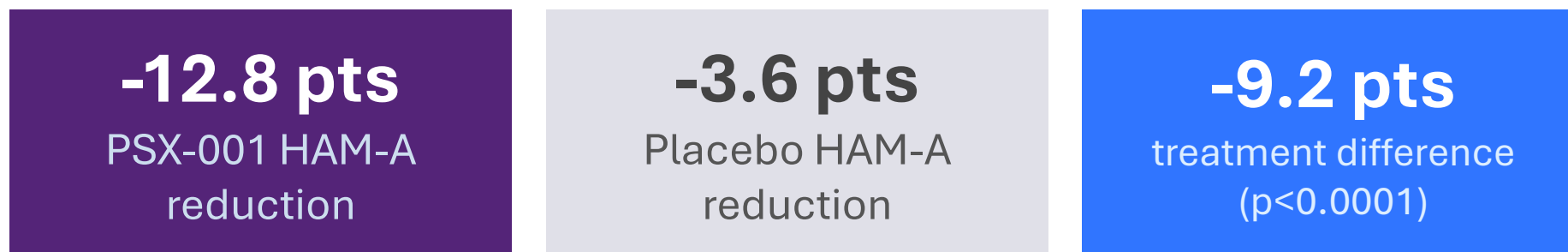
SAE = Serious Adverse Event.

Kuntz L (2025) *Psychiatric times*, accessed 5/22/26 from <https://www.psychiatrictimes.com/view/psychedelic-psx-001-for-generalized-anxiety-disorder-a-conversation-with-lou-barbato-md> <https://incannex.com/pipeline/psx-001-generalized-anxiety-disorder/> accessed 5/22/26

PSX-001: Phase 2 Psi-GAD Trial Design



Primary Endpoint Result



HAM-A = Hamilton Anxiety Rating Scale; PAP = psilocybin-assisted psychotherapy.
Incannex Healthcare Inc. Incannex Reports Positive Results from Phase 2 Clinical Trial of PSX-001 (Psi-GAD) for Generalised Anxiety Disorder.
August 26, 2025. <https://ir.incannex.com/news-releases/news-release-details/incannex-reports-positive-results-phase-2-clinical-trial-psx-001>

PSX-001: Response, Remission, and Breadth of Effect

Breadth of Effect (Secondary Endpoints)

GAD-7

-7.4 vs -3.5 pts
($p < 0.0004$)

PHQ-9

Sig. improvement,
antidepressant co-
benefit

SDS

Sig. improvement,
functional
disability reduced

PWI

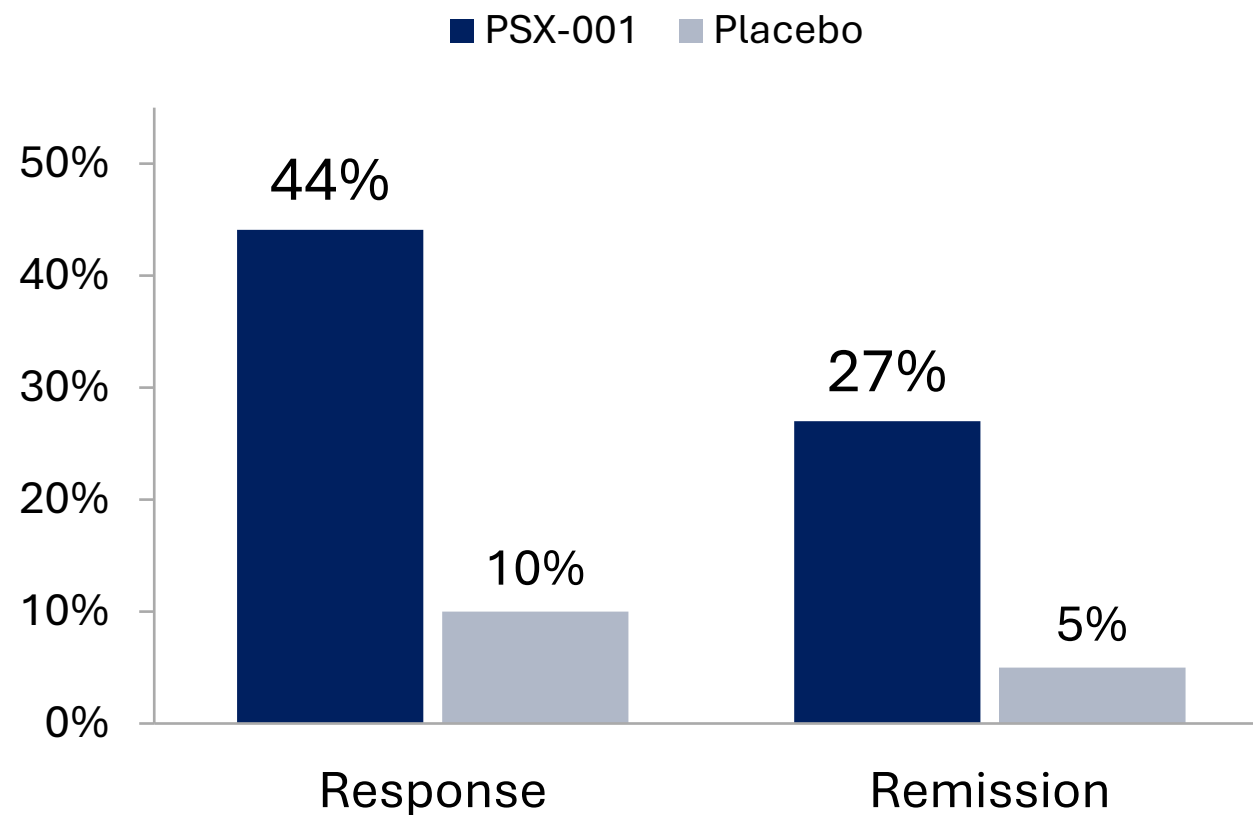
Sig. improvement
in quality of life

Safety: No SAEs; no suicidality signals.
Phase 3 planning underway

SAE = serious adverse event

Incannex Healthcare Inc. Incannex Reports Positive Results from Phase 2 Clinical Trial of PSX-001 (Psi-GAD) for Generalised Anxiety Disorder.
August 26, 2025. <https://ir.incannex.com/news-releases/news-release-details/incannex-reports-positive-results-phase-2-clinical-trial-psx-001>

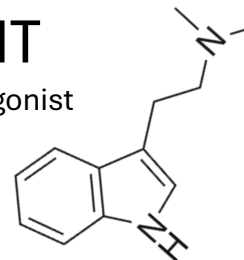
Response and Remission Rates (%)



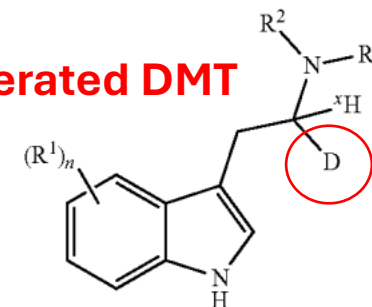
2026: Phase 2a (HLP004)

- **Drug:** HLP004 (Deuterated N,N-DMT)
- **Indication:** Moderate – Severe GAD (HAM-A average 22, GAD-7 ≥ 10)
- **Size:** N=36
- **Type:** DB RCT or placebo (IM 20mg vs 2mg HLP004), 2 doses, 2 weeks apart, 12-week endpoint on HAM-A. Manualized psychotherapy (EMBARC)
- **Key Findings:** (Topline, not yet published) - 10.4-points ($p < 0.0001$) HAM-A in 20mg group from baseline at 6 weeks. At 6 months, the pooled study population had 67% responding, 39% remission by HAM-A criterion
- **Effects** lasting about 90 minutes, d/c in 3 hours
- **Awaiting publication; topline results are not peer-reviewed**

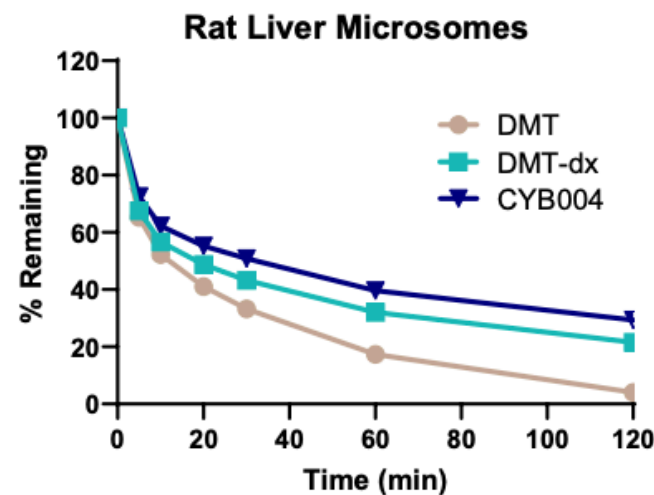
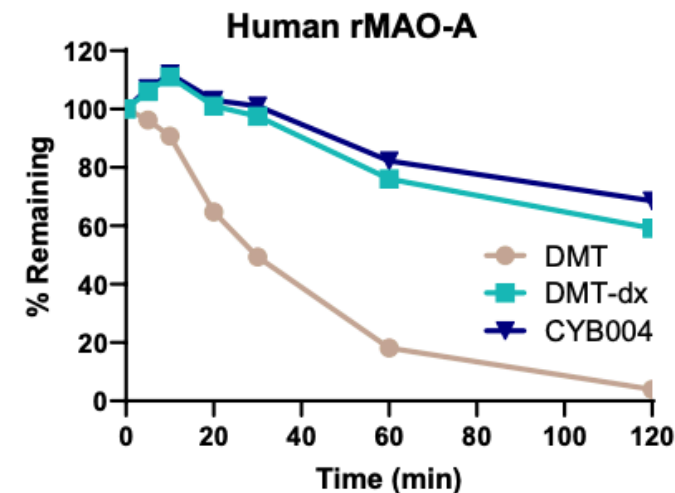
N,N-DMT
5HT_{1,2,6,7} partial agonist



Deuterated DMT



The Effect of Deuteration on In Vitro Metabolism



DMT= dimethyltryptamine.

Helus Pharma. *Helus Pharma announces topline results in Phase 2 signal detection study for HLP004 in patients with generalized anxiety disorder.* Published March 5, 2026. Accessed August 9, 2026. Varty GB et al., Poster presented at: 62nd Annual Meeting of the American College of Neuropsychopharmacology; December 3-6, 2023; Tampa, FL. Accessed May 22, 2026.

HLP004: Phase 2 Signal Detection Trial Design

HLP004 is Novel Serotonergic Agonist (NSA)

Study Design	Screening	HLP004 IM	Week 6 Primary	Week 12 + 12-month
	GAD-7 $\geq$ 10 on SoC, N=36	Adjunct to SoC	HAM-A change from	Secondary HAM-A;
	(2:1, active:placebo)	(~90 min effect)	baseline	QoL follow-up

Key Differentiator:

~90-min acute window vs hours for LSD/psilocybin
reduces treatment-day burden, improves scalability

MEQ30 = Mystical Experience Questionnaire-30; NSA = novel serotonergic agonist; PK = pharmacokinetics; SoC = standard of care.
Helus Pharma. Topline Results: Phase 2 Signal Detection Study for HLP004 in GAD. March 5, 2026. National Library of Medicine. NCT06051721.
Accessed March 12, 2026. Cybin Corp. Cybin Announces Positive Topline Data from Phase 1 Studies of CYB004 and SPL028. January 8, 2024.

HLP004: Phase 2 Topline Efficacy and Safety Results

~10 pts

HAM-A improvement on SoC
($p < 0.0001$ at 6 weeks)

67%

Responder rate at 6 months

39%

Remission rate at 6 months

Effects durable through at least 6 months of follow-up, evaluated as adjunct in treatment-resistant GAD patients on SoC

Safety: Generally well-tolerated; no drug-related SAEs; no suicidality signals. ~90-min acute window.

Program Outlook

- * Advancing HLP004 toward Phase 3 in GAD
- * HLP003 (DMT analog for MDD) data anticipated Q4 2026

3 Models – Varying doses of therapy/drug combo

DT120
GAD/MDD

Drug +
Supportive
Setting

PSX-001
GAD

Drug +
Psychological
support

HLP004
GAD

Drug +
Structured
Therapy

The Current GAD-Psychedelic Pipeline

	DT120	PSX-001	HLP004
Drug class	LSD	Psilocybin	DMT analog
Acute window	Long	Long	Short
Therapy	Support	Structured PAP	EMBARK
Population	GAD	GAD	Treatment-resistant GAD
Study size	198 / 214	73	36
Evidence	Phase 2 + Phase 3 topline	Phase 2 topline	Phase 2 topline
Key question	Dose/durability	Therapy/drug contribution	Scalability/durability

What remains unknown?

- Retreatment frequency
- Durability beyond controlled follow-up
- Contribution of psychological support
- Generalizability
- Patient considerations
- Absence of direct comparisons with established treatments
- Treatment operations, billing codes, insurance prior authorizations, insurance reimbursement, staffing considerations
- ... and many more!

Key Learning Points

- Three distinct psychedelic mechanistic classes (LSD-based: DT120; psilocybin-based: PSX-001; DMT-based: HLP004) are in active clinical development for GAD, each with phase 2/3 data showing promise
 - Significantly greater response and remission rates vs placebo for Ph3 study for DT120; 94% of patients were discharged within 8 hours
- Psychedelics may address key unmet needs in GAD (speed of onset, durability, and treatment-resistant populations) through 5-HT_{2A}-mediated neuroplasticity mechanisms and brain network activity changes
- Psychedelics in GAD treatment appear well tolerated, with most side effects occurring on the day of dosing



Patient Case Discussion

Case F/U: 19yo College Student with Excessive Worry



“I think I need to give up my dream of becoming a doctor.”

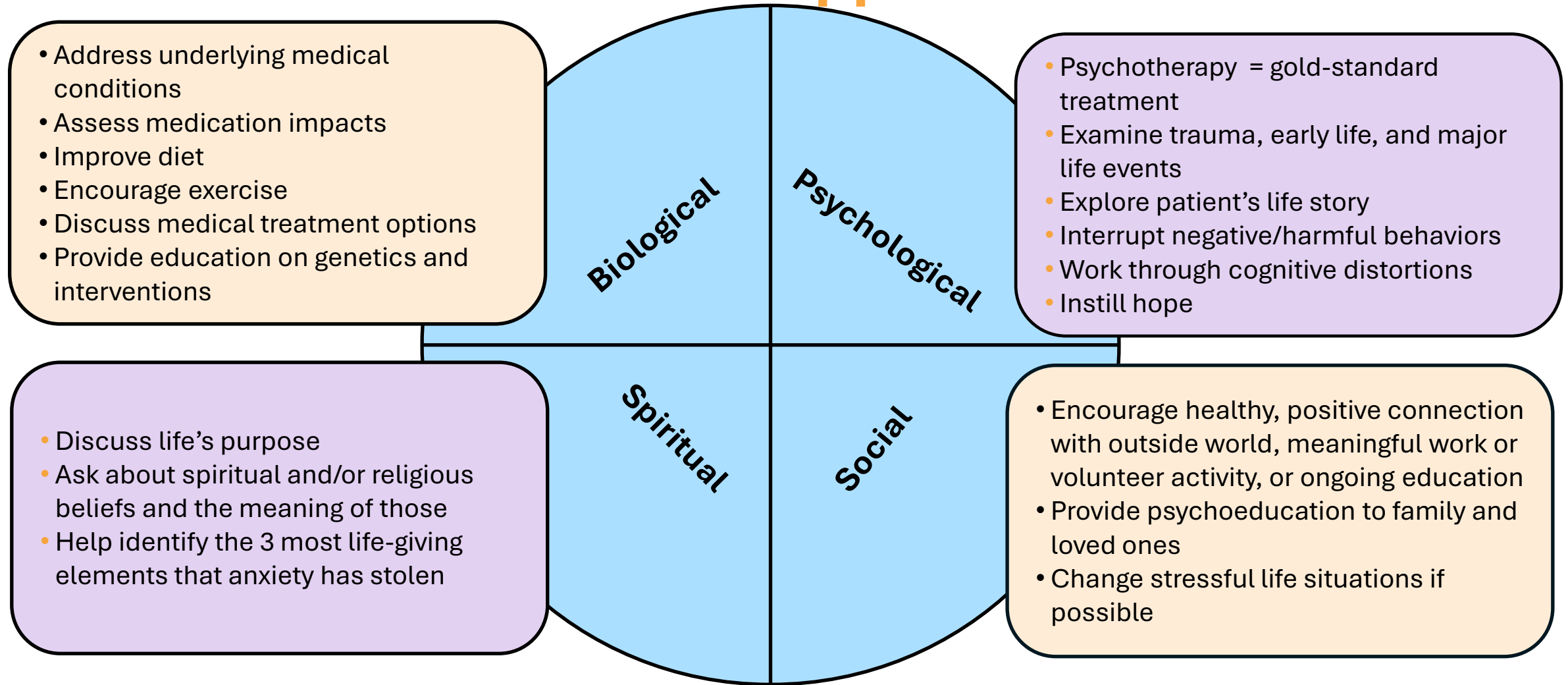
- **Assessment and Plan:**

- She was diagnosed with GAD and started on PRN alprazolam for test taking anxiety. She did not like the way it made her feel but carried it around with her “just in case.”
- She saw the campus counselor who provided psychoeducation and supportive psychotherapy. She withdrew from the physics class on recommendation of the counselor and her anxiety improved.
- She never had a dog, her boyfriend got her a Pomeranian, which significantly helped her anxiety symptoms.

- **Update:**

- In medical school, the GAD significantly exacerbated. She was started on citalopram by student mental health, which caused nausea initially and “took the edge off.”
- Several years later, she wanted to get pregnant and was worried about the impact of the citalopram in pregnancy. She slowly self discontinued citalopram and feared her symptoms would come back.

Patient-Centered Approach to GAD



Future Therapeutic Potential of Psychedelics in GAD

GAD is a chronic, relapsing, and highly prevalent yet underdiagnosed disorder that typically onsets in early-to-mid adulthood and causes substantial functional impairment, reduced quality of life, and elevated mortality

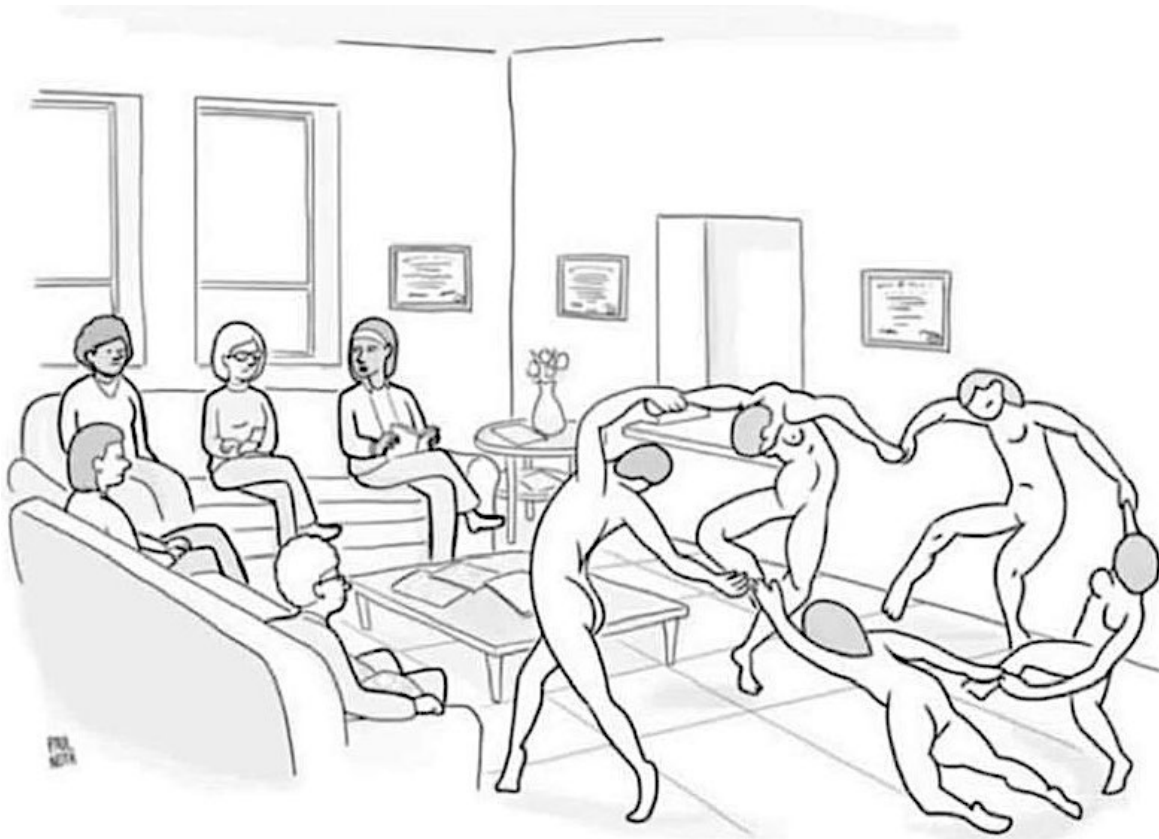
GAD commonly co-occurs with other psychiatric and medical conditions and often presents with somatic symptoms; GAD-7 is an effective screening tool

PRACTICAL TAKEAWAYS

Evidence-based psychotherapy (especially CBT) and SSRIs/SNRIs are the usual first-line treatments, which need to be selected using a shared decision-making approach

Infrequent psychedelic therapies may address key unmet treatment needs in GAD: speed of onset, durability, tolerability, and efficacy via through 5-HT_{2A}-mediated neuroplasticity mechanisms and brain network activity changes

Psychedelic-Assisted Therapy Studies: The Problem with Blinding

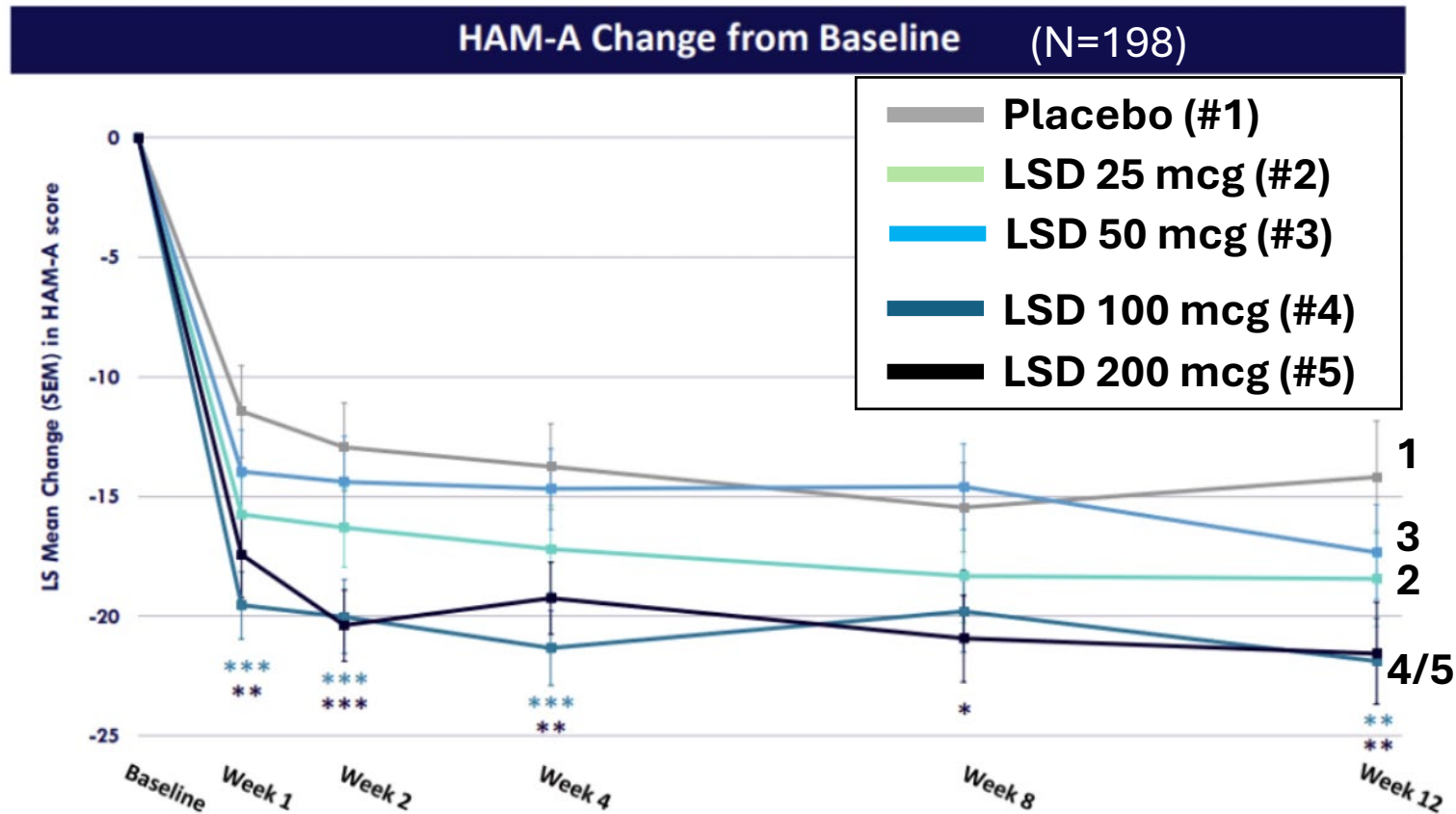


“The majority (81/86; 94%) of studies were blinded, though only 14 (17.3%) included blind assessment; **only 8 of these 14 studies assessed participants’ blinding. Blinding success, assessed in highly varied ways, was generally poor.**”

“So I’m guessing we’re in the placebo group.”

Unblinding, While Problematic, May Not Explain The Long-Term Benefit of Psychedelics

(Phase 2 DT120 (LSD) for GAD)



Guess of Treatment:

Placebo: 33% thought active LSD; only 50% correctly guessed placebo

LSD 25 mcg: 87.5% correctly guessed LSD

LSD 50 mcg: 90% correctly guessed LSD

LSD 100 and 200 mcg: 100% correctly guessed LSD

Take Home Point: Unblinding about the same between LSD groups, yet significant difference in clinical effect: The dose-response relationship complicates the argument that expectancy alone explains the observed benefit



Q&A