Reframing the Future in GAD:
Improving Current Clinical Practices and Evaluating Novel Approaches

MasterClass

Supported by an educational grant from Definium.

Faculty

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Faculty Disclosures

Brittany Albright, MD, MPH, DABOM: Advisory Board- AbbVie, Bristol Myers Squibb, Compass Pathways, Definium Therapeutics, Eli Lilly, Johnson & Johnson, Neurocrine Biosciences. Consultant - AbbVie, Aidvance, Axsome, Definium Therapeutics, Johnson & Johnson, Osmind, Precision Genetics. Speakers Bureau - AbbVie, Alkermes, Axsome, Bristol Myers Squibb, Johnson & Johnson.

Andrew Penn, MS, PMHNP-BC: Advisory Board—Alkermes PLC, NACCME, Osmind, Definium Theraputics, Otsuka, Tactogen; Consultant—1440 Foundation, Alkermes PLC, Board of Psychedelic Medicine and Therapies, California Institute of Integral Studies, Luciem, Fireside Project, Compass Pathways, Otsuka, Definium; Grant/Research Support—Filament, MAPS, Usona; Employee—UCSF, Salma Health

Learning Objectives

- Describe the epidemiology and neurobiology of GAD, including the main circuits and neurotransmitters implicated in the disorder and its frequent comorbidity with MDD
- Assess patients for GAD according to DSM-5-TR diagnostic criteria, differentiating it from normal worry/anxiety and other psychiatric and medical conditions with similar presentations
- Evaluate current treatment strategies, unmet needs, and the therapeutic potential of investigational psychedelics for GAD, according to their MOAs and recent clinical data

The Worry Continuum: From Normal Worries to GAD

NORMAL WORRY

- Time-limited
- Controllable
- Proportionate to actual threat

EXCESSIVE WORRY

- Persistent
- Difficult to control
- Disproportionate to circumstance

GAD
GENERALIZED ANXIETY DISORDER

- Excessive, uncontrollable worry about multiple domains
- For ≥6 months
- Causing functional impairment

Fear is the emotional response to a real or perceived threat
Anxiety is the anticipation of a future threat

GAD = generalized anxiety disorder. Ruscio AM, et al. JAMA Psychiatry. 2017;74(5):465-475. American Psychiatric Association. DSM-5-TR. 2022.

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

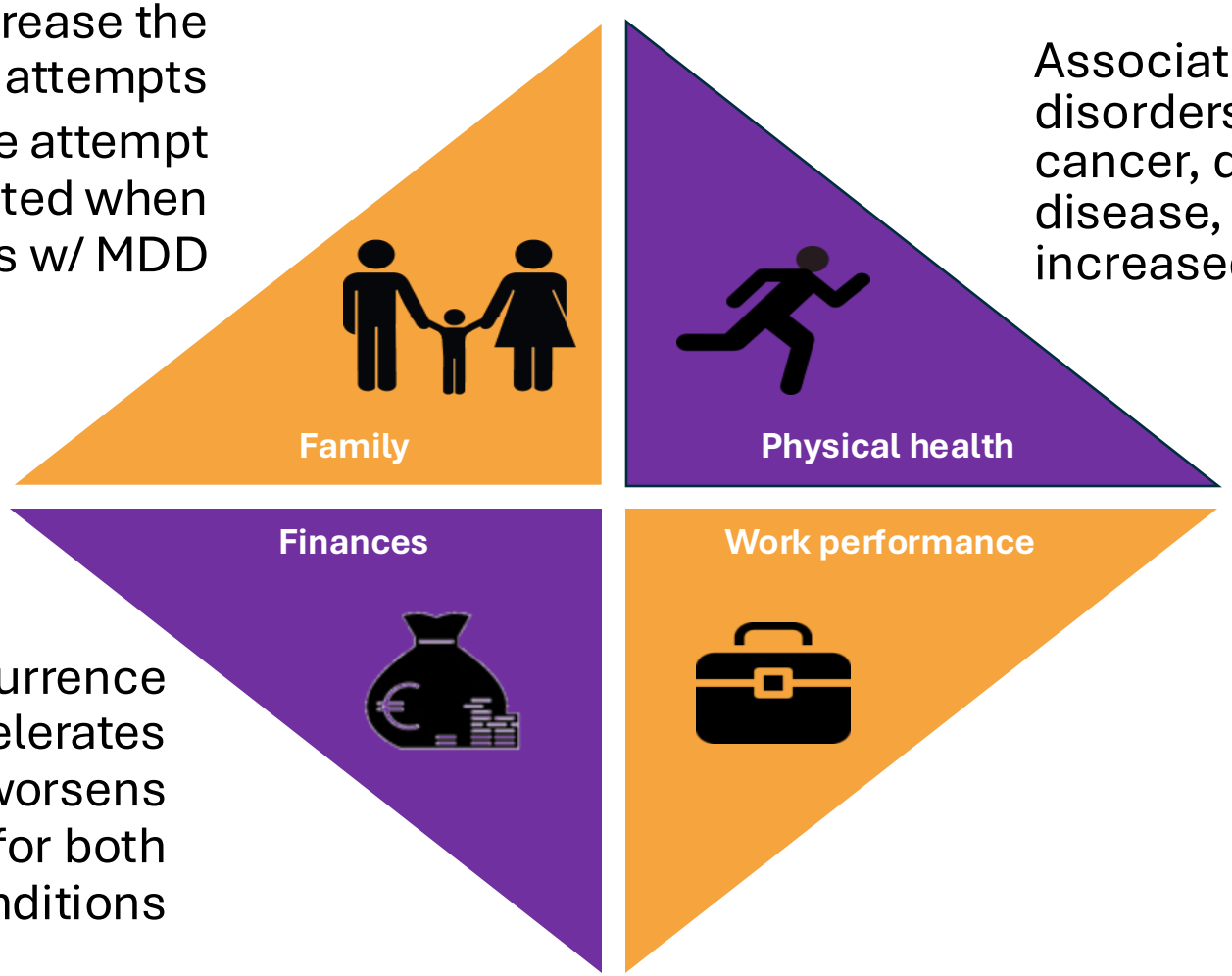
DSM-5-TR = Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision; GAD = generalized anxiety disorder. MDD = major depressive disorder.

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



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

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

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

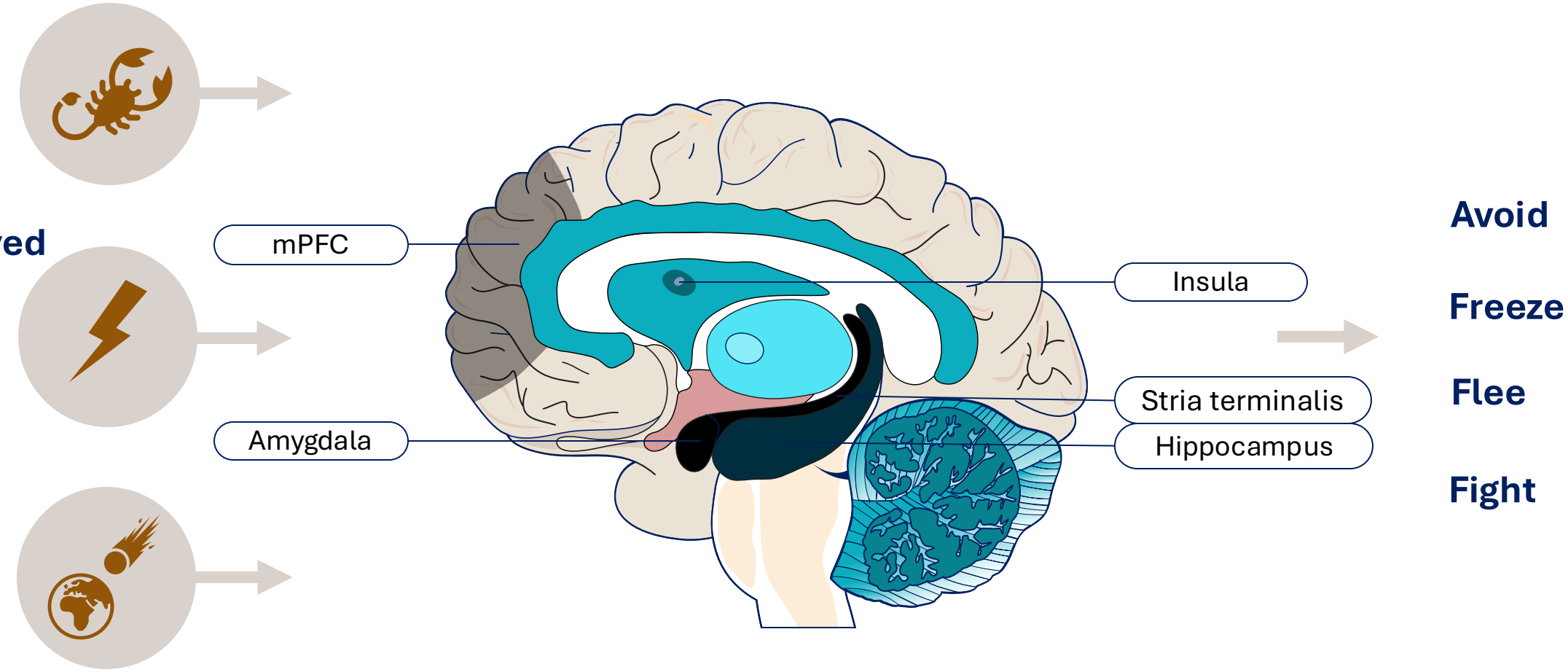
- Patients with GAD average more missed workdays and report lower health-related QoL than those with other anxiety disorders

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

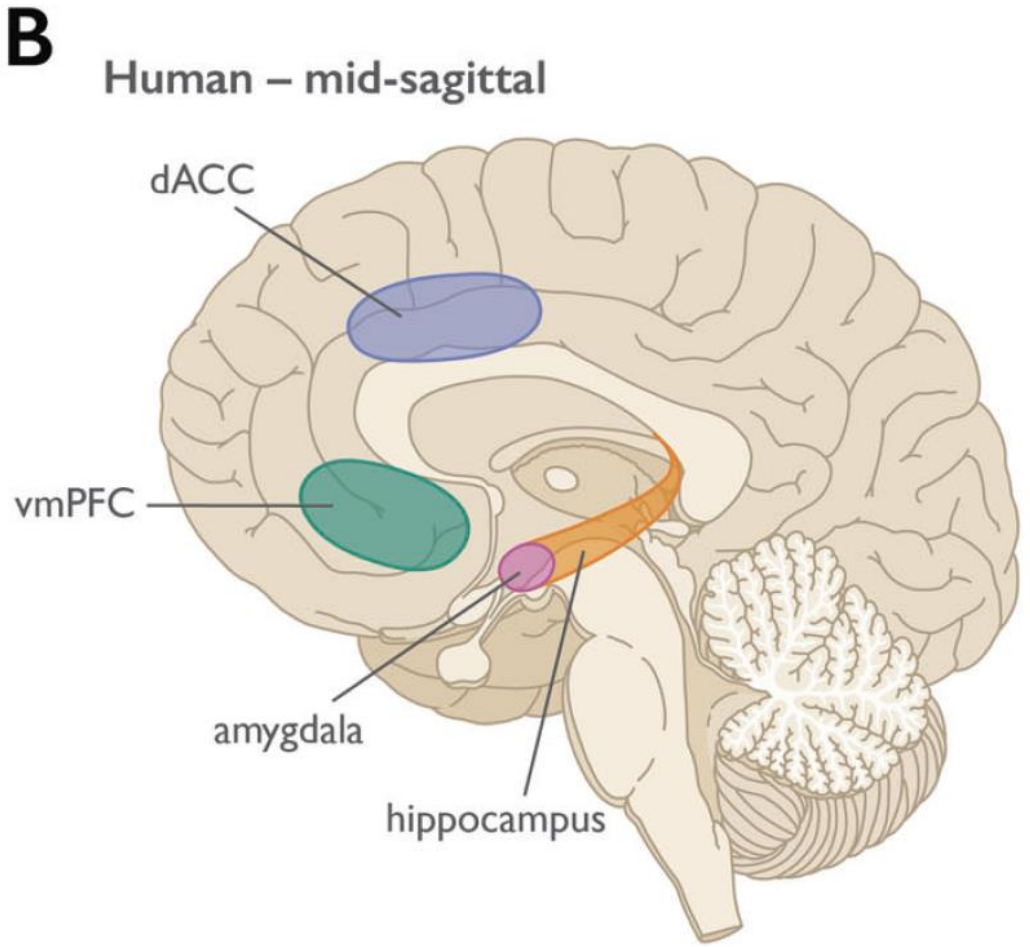
Etiology of Fear & Anxiety: Threat-Responsive Brain Circuitry



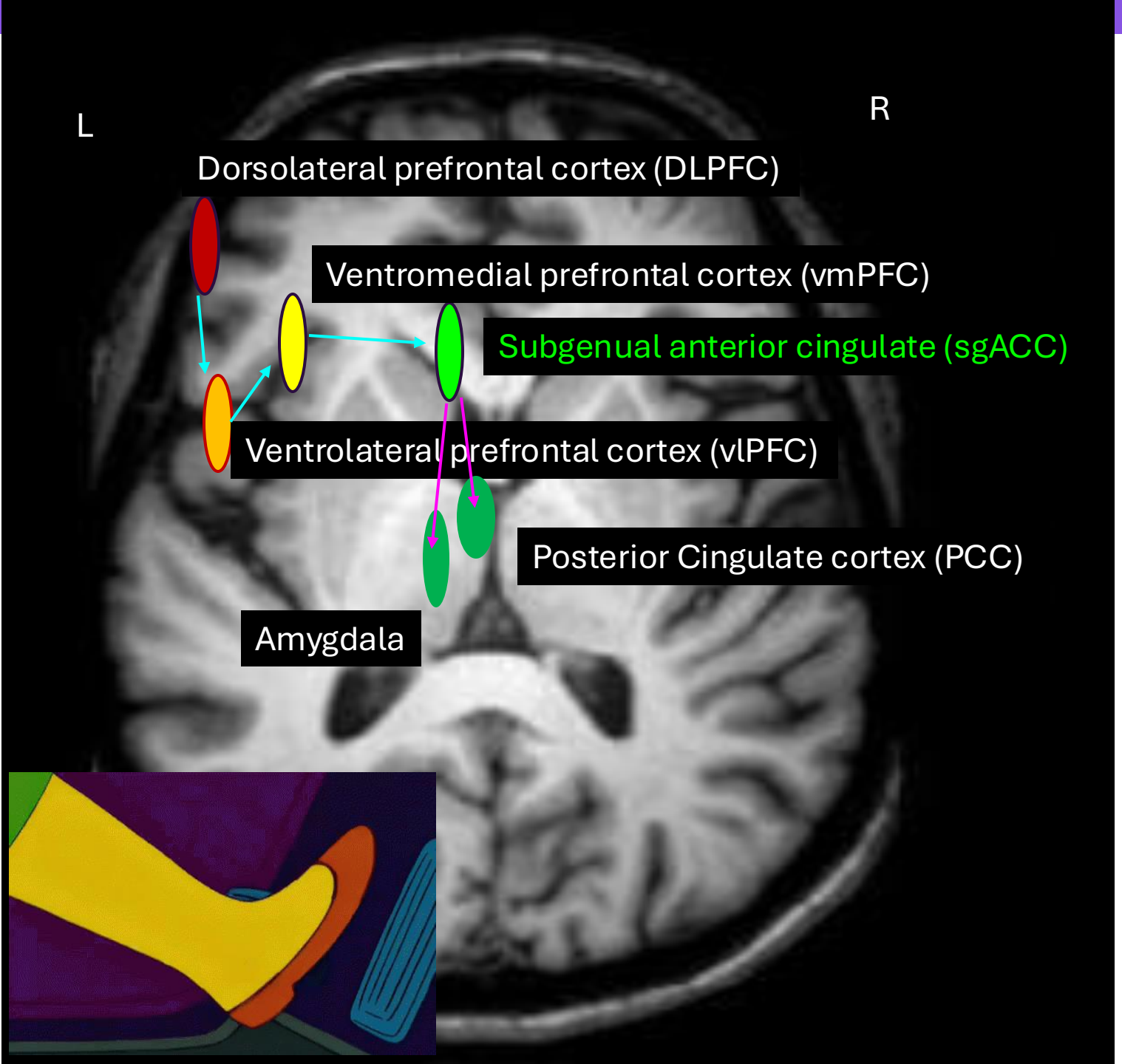
mPFC=medial prefrontal cortex

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.

Critical Concept: Loss of Top-Down Control: Relevant to GAD and MDD



Kredlow, M., Fenster, R.J., Laurent, E.S. *et al*. Prefrontal cortex, amygdala, and threat processing: implications for PTSD. *Neuropsychopharmacol*. 47, 247–259 (2022). https://doi.org/10.1038/s41386-021-01155-7



Inside a non-depressed, non anxious brain

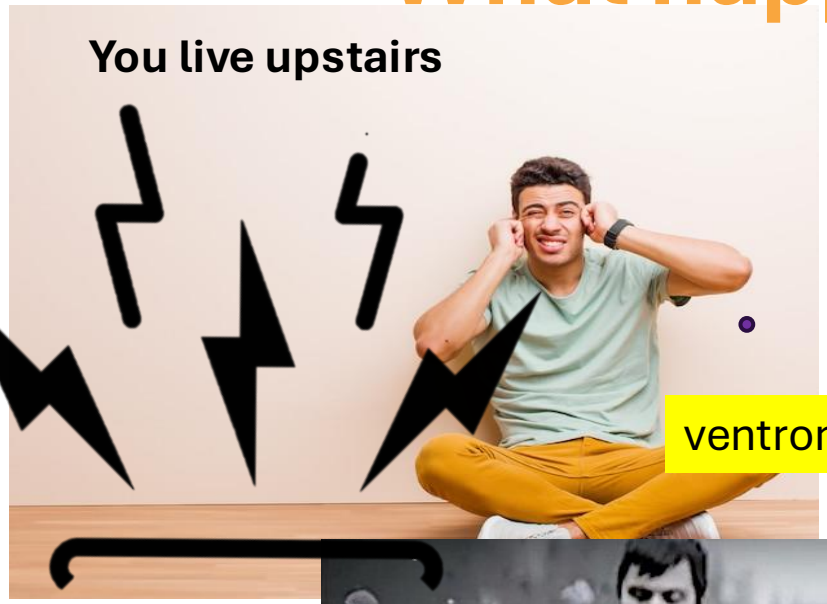
The sgACC is connected to the amygdala and posterior cingulate cortex (**PCC**).

The executive network (*EN*), led by the dorsolateral prefrontal cortex (**dlPFC**), starts a circuit that travels through the ventrolateral prefrontal cortex (**vlPFC**) to the ventromedial prefrontal cortex (**vmPFC**) to control the subgenual anterior cingulate cortex (**sgACC**), which is part of the salience network (*SN*).

This dlPFC circuit helps to regulate the sgACC and amygdala, a form of "top-down cognitive control" or "pumping the brakes."

Kredlow, M., Fenster, R.J., Laurent, E.S. *et al*. Prefrontal cortex, amygdala, and threat processing: implications for PTSD. *Neuropsychopharmacol*. 47, 247–259 (2022).

What happens when we are anxious?



I can't get it to stop!

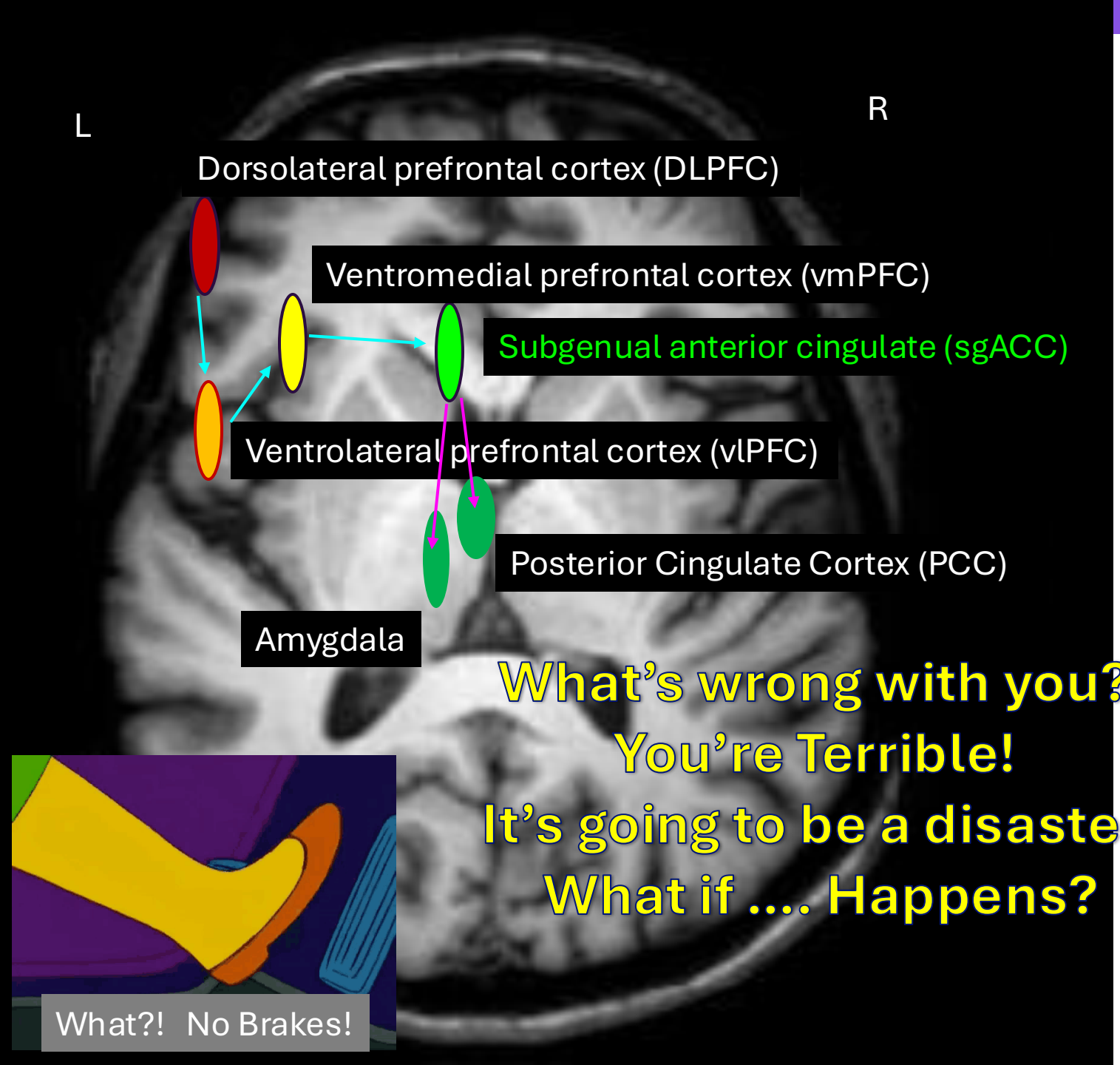
ventromedial prefrontal cortex

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 Neurostiumlation for Brain Rewiring, Huberman Podcast
https://podcasts.apple.com/us/podcast/psychedelics-neurostimulation-for-brain-rewiring-dr/id1545953110?i=1000582122440



What's wrong with you?
You're Terrible!
It's going to be a disaster!
What if .... Happens?

Inside a brain with depression and anxiety

Subgenual anterior cingulate (sgACC), part of the salience network (SN), is connected to other default mode network structures like the **posterior cingulate cortex** and to limbic structures like the **amygdala**, are overactive.

When this sgACC/amygdala/PCC circuit is overactive, rumination and worsening negativity bias occurs, worsening depression. When the amygdala is overactive, anxiety occurs.

The dlPFC and vmPFC are unable to turn off the sgACC overactivity.

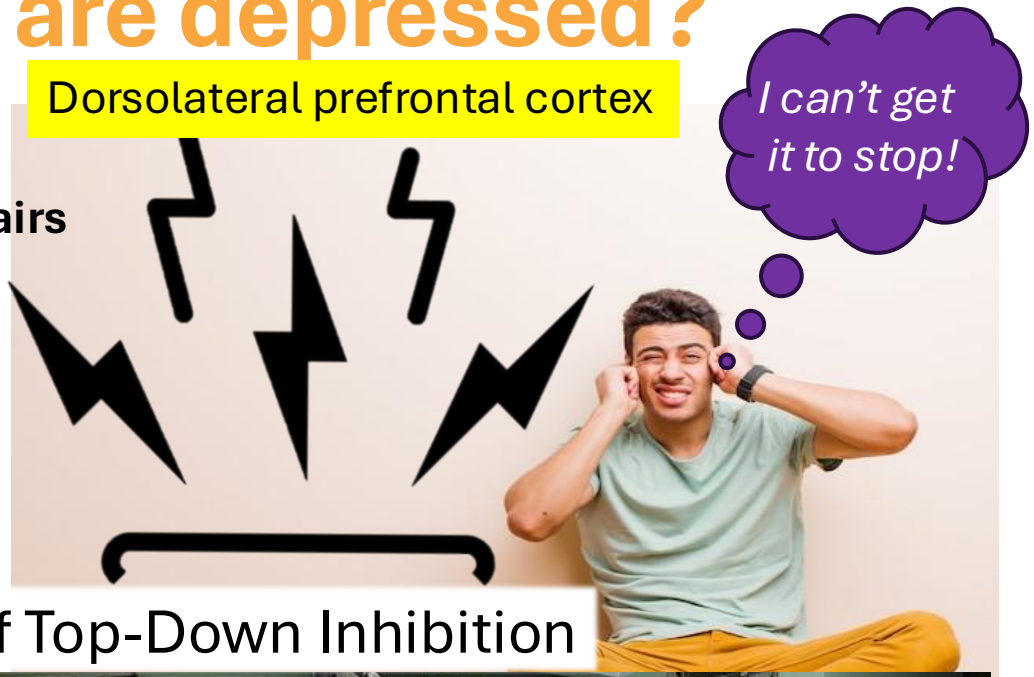
We "lose the brakes" and rumination and anxiety occurs.

What happens when we are depressed?

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

The Downstairs Neighbors
"The Ruminators"

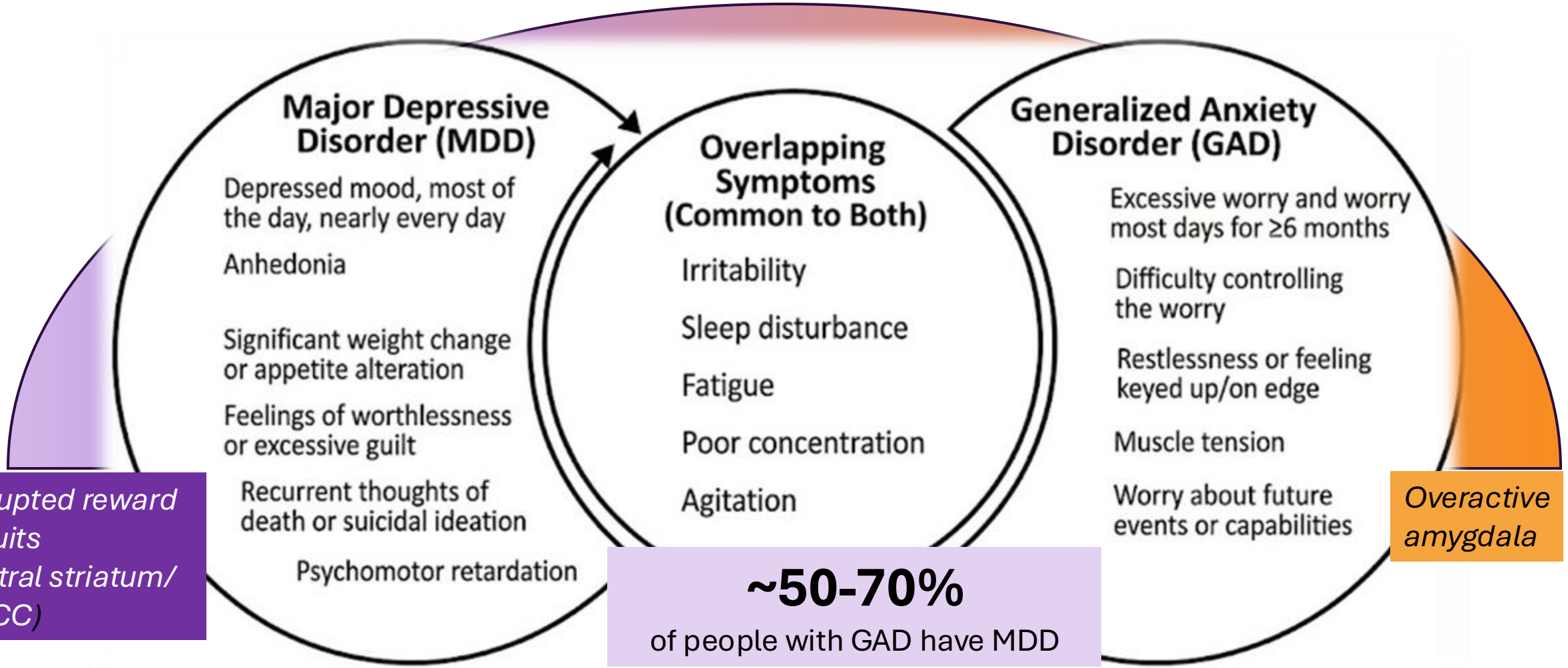
You live upstairs



Loss of Top-Down Inhibition

Williams, N (2022) Psychedelics and Neurostiumlation for Brain Rewiring, Huberman Podcast
https://podcasts.apple.com/us/podcast/psychedelics-neurostimulation-for-brain-rewiring-dr/id1545953110?i=1000582122440

The MDD/GAD Overlap



Disrupted reward circuits (ventral striatum/ sgACC)

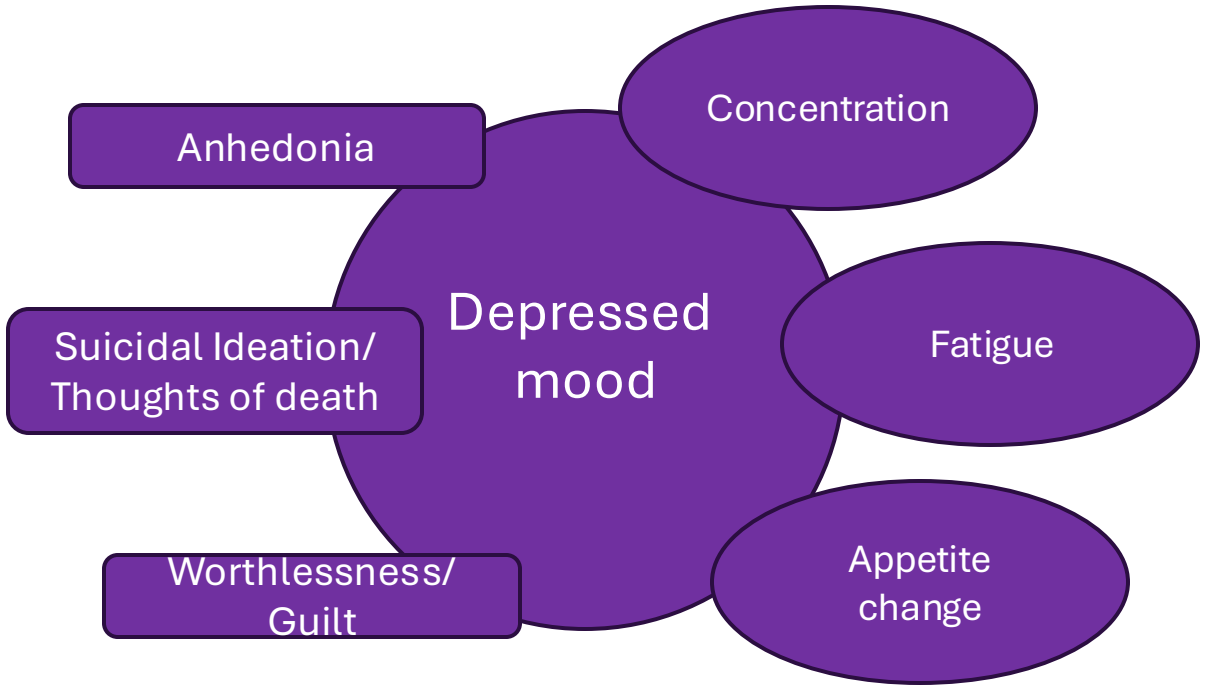
Overactive amygdala

~50-70%

of people with GAD have MDD

Kessler RC, et al. Epidemiol Psychiatr Sci. 2015;24(3):210-226. Beesdo K, et al. Arch Gen Psychiatry. 2010;67(1):47-57. Kessler RC, Chiu WT, Demler O, Walters EE. Arch Gen Psychiatry. 2005;62(6):617–627.

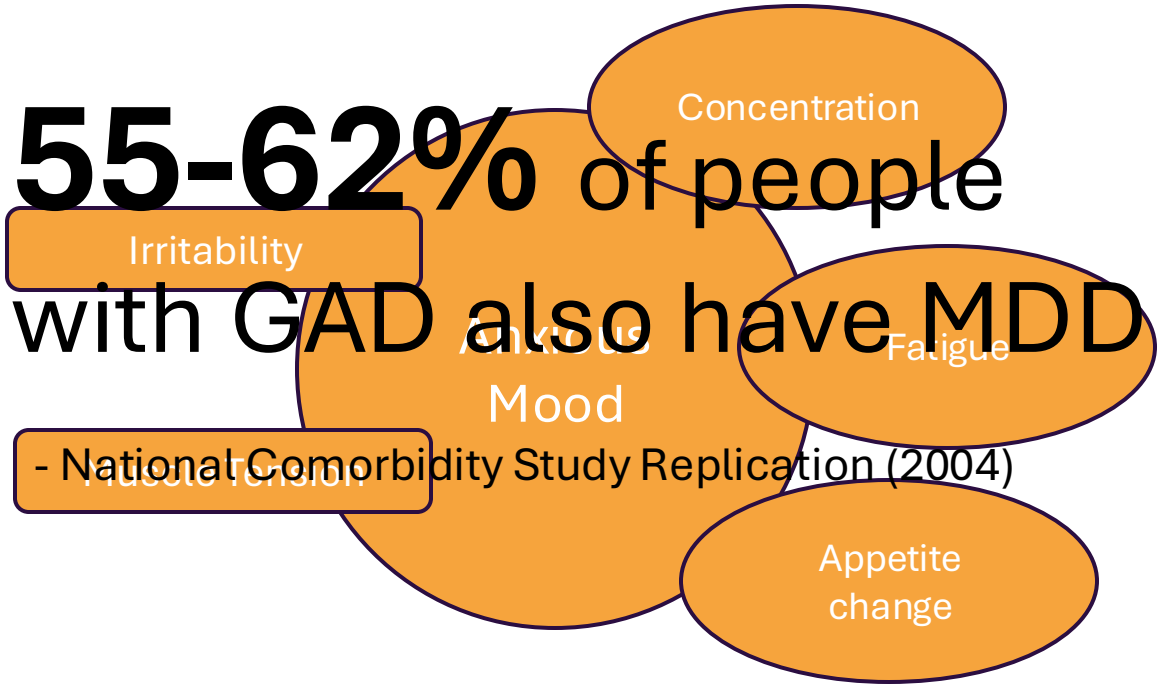
CC: “I’m sad” Dx: MDD
CC: “I’m worried” Dx: GAD?



Major Depressive Disorder (MDD)

55-62% of people with GAD also have MDD

- National Comorbidity Study Replication (2004)



Generalized Anxiety Disorder (GAD)

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

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

- **GAD and MDD share overlapping neurobiological substrates** (serotonin/NE pathways, HPA dysregulation, amygdala hyperactivity), explaining their high rates of co-occurrence (50%-70% lifetime)

Assessment and Differential Diagnosis of GAD

Underdiagnosis and Misdiagnosis of GAD

<50%
of those screening positive in primary care receive a GAD diagnosis

1 in 4
US adults screen positive for GAD, yet most have no formal diagnosis

>10 yrs
mean time from symptom onset to diagnosis in some populations

Why GAD is frequently missed:

Somatic presentation
Headaches, GI, fatigue instead of worry

Clinician misattribution
Symptoms dismissed as stress or medical

Comorbidity masking
MDD or other disorders present more prominently

Stigma & underreporting
Patients normalize or downplay chronic worry

MDD = major depressive disorder.

Morjig S. Psychiatry Advisor. May 14, 2024. Wittchen HU, et al. J Clin Psychiatry. 2002;63(Suppl 8):24-34. Kroenke K, et al. Ann Intern Med. 2007;146(5):317-325.

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):				

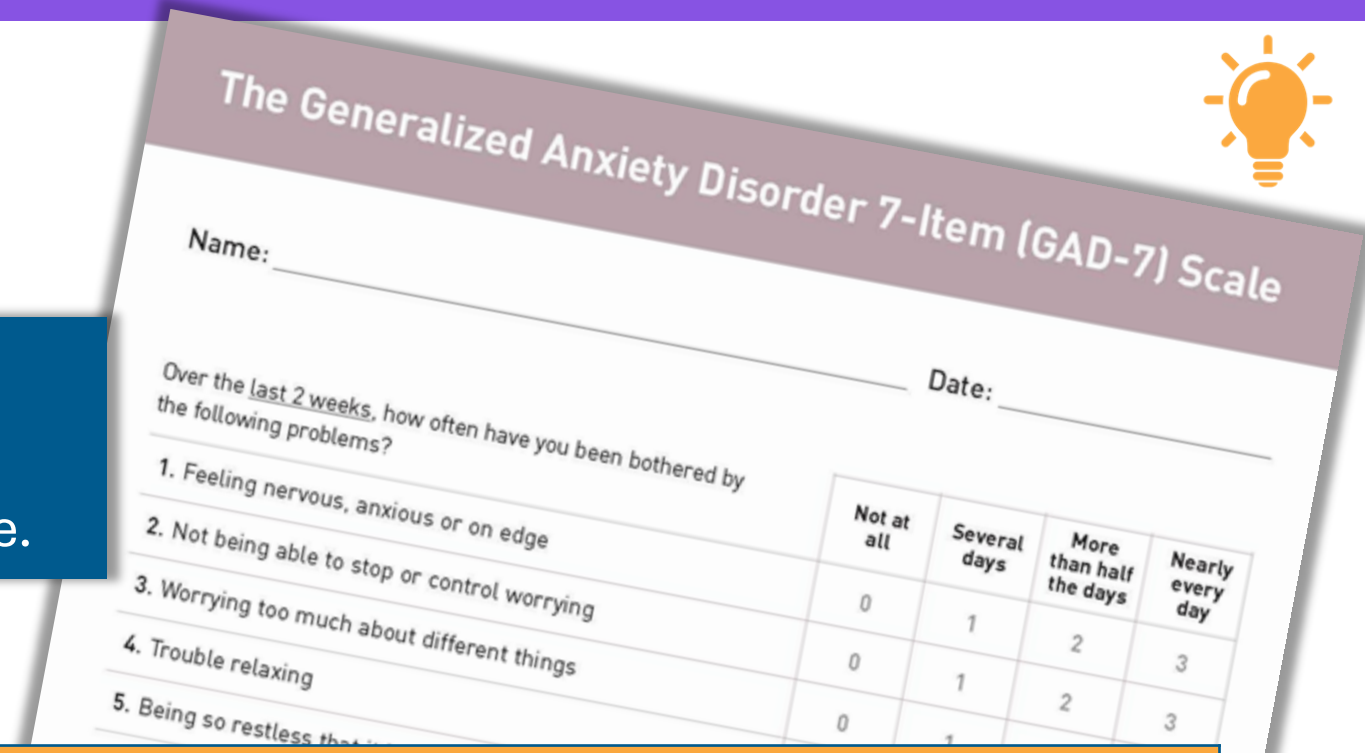
The GAD-7 was developed by Drs. Robert L. Spitzer, Janet B. W. Williams, Kurt Kroenke, and colleagues, with an education grant from Pfizer, Inc.

Spitzer RL, et al. *Arch Intern Med*. 2006;166(10):1092-1097.

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.


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				
5. Being so restless that				

Don't forget to do a PHQ-9!

As GAD + MDD occur together commonly

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

GAD-7 = 7-Item Generalized Anxiety Disorder scale; MDD = major depressive disorder; PHQ-9 = 9-Item Patient Health Questionnaire.

Spitzer RL, et al. *Arch Intern Med*. 2006;166(10):1092-1097.

DSM-5-TR Criteria: Generalized Anxiety Disorder

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

Anxiety or worry is associated with ≥3 of 6 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)

American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. American Psychiatric Association; 2013.

Key Properties of GAD

Symptoms

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

+

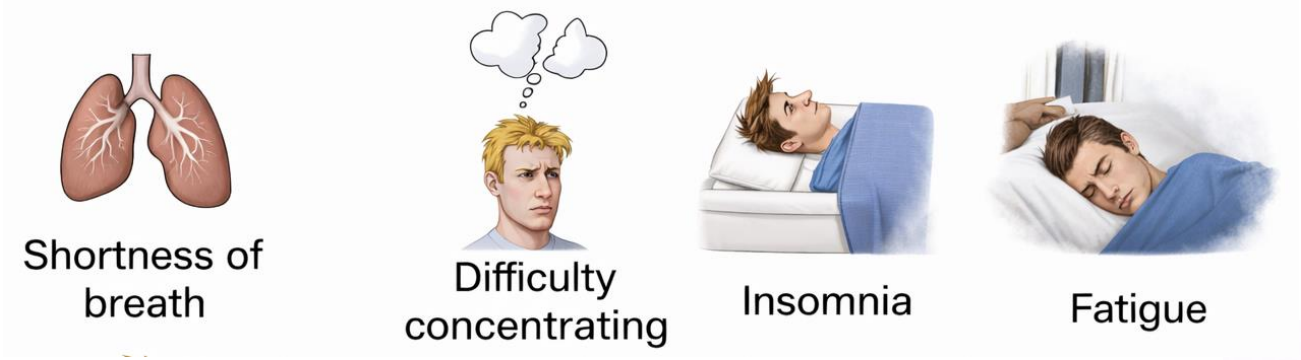
Functional Impairment

- activities avoided
- opportunities missed

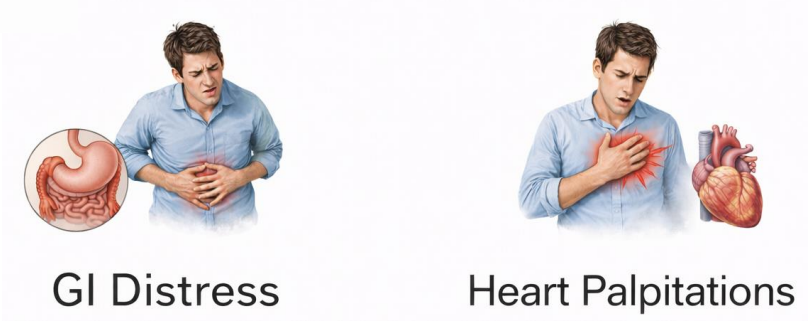
> 6 months

=

GAD

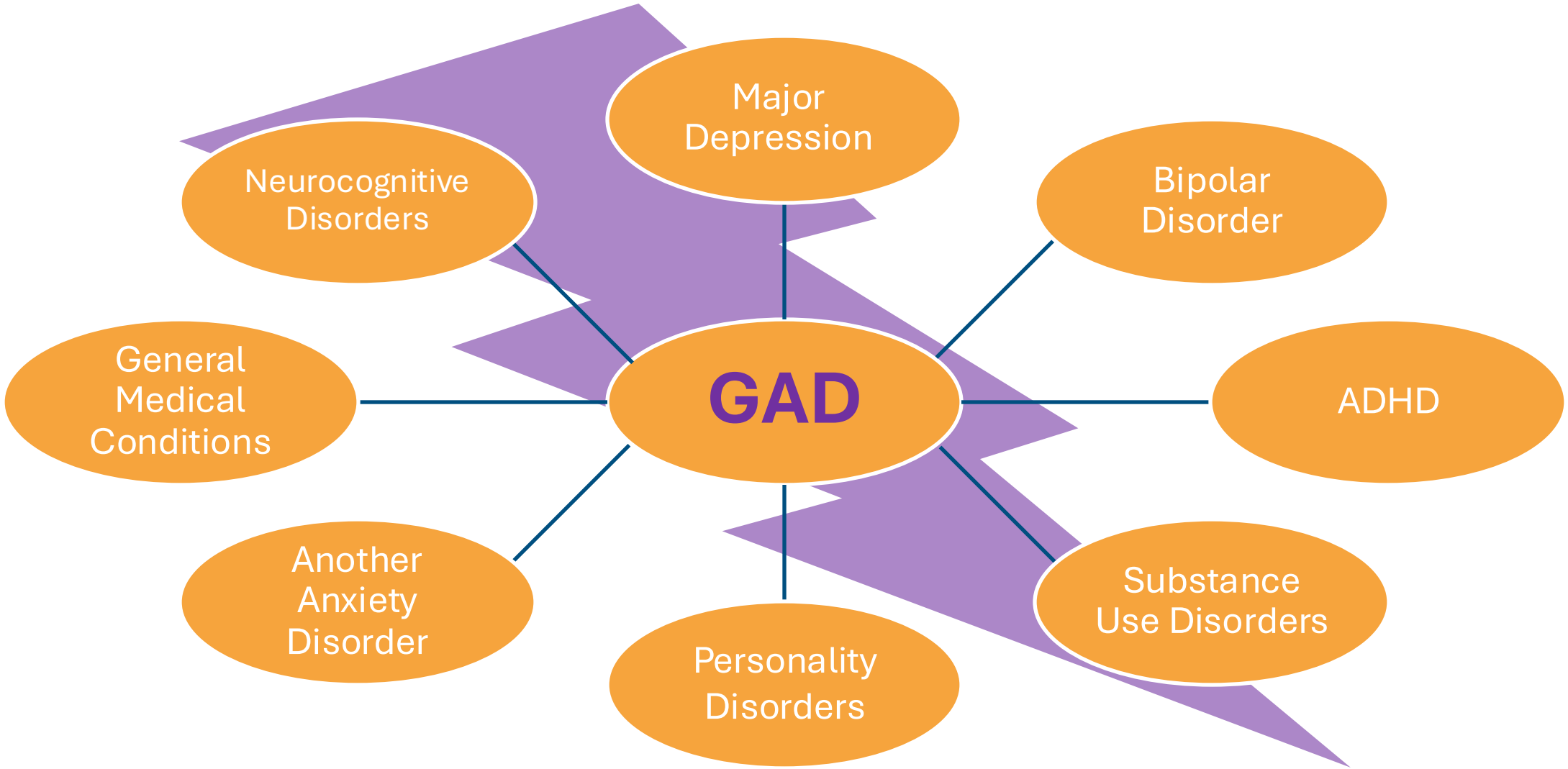


Somatic symptoms are common!



Szuhany KL & Simon NM. JAMA. 2022;328;(24):2431-2445.

Common Comorbidities with GAD



Kalin NH. *Am J Psychiatry*. 2020;177(5):365-367. Meuret AE, et al. *Adv Exp Med Biol*. 2020;1191:237-261. Quenneville AF, et al. *Psychiatry Res*. 2022;310:114423. Marmorstein NR. *J Anxiety Disord*. 2012;26(1):88-94. Pavlova B, et al. *Lancet Psychiatry*. 2015;2(8):710-717.

Diagnostic Assessment: Anxiety

Context:
When did anxiety start?

Duration:
How long does it last?

Triggers:
What exacerbates it?

Pattern of avoidance or anticipatory anxiety

Impact:
how is it changing your life?

Archer, J., Bower, P., Gilbody, S., Lovell, K., Richards, D., Gask, L., Dickens, C., & Coventry, P. (2012). Collaborative care for depression and anxiety problems. *The Cochrane database of systematic reviews*, *10*(10), CD006525. https://doi.org/10.1002/14651858.CD006525.pub2

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)?

MDD = major depressive disorder. SAD = social anxiety disorder. OCD = obsessive compulsive disorder

American Psychiatric Association. DSM-5-TR. 2022. Kessler RC, et al. Epidemiol Psychiatr Sci. 2015;24(3):210-226.

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

TSH = Thyroid-Stimulating Hormone; CBC = Complete Blood Count; CMP = Comprehensive Metabolic Panel; UDS = Urine Drug Screen; ECG = Electrocardiogram (EKG). American Psychiatric Association. DSM-5-TR. 2022.

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

Current Therapies for GAD

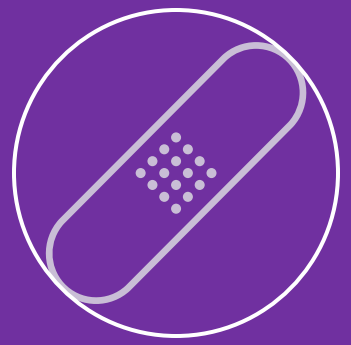
GAD Treatment Guidelines: APA, NICE, CANMAT, WFSBP

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

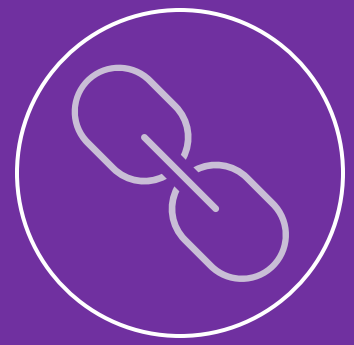


Benzodiazepines:

- 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:

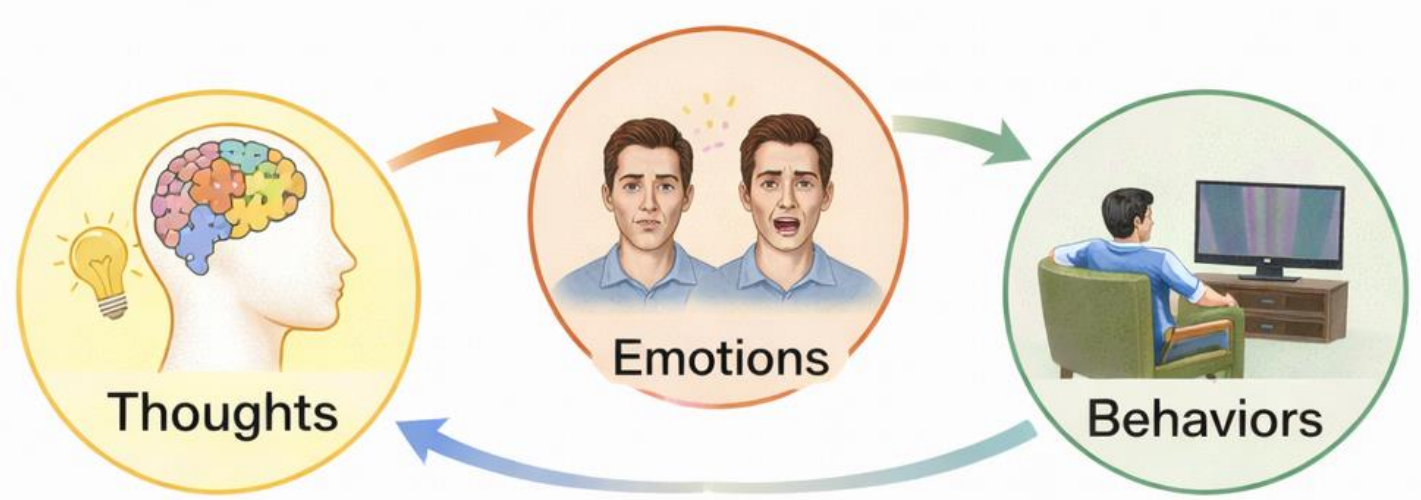
- offers superior outcomes for patients with moderate-to-severe GAD or significant comorbidity

CANMAT = Canadian Network for Mood and Anxiety Treatments; CBT = cognitive behavioral therapy; NICE = National Institute for Health and Care Excellence; WFSBP = World Federation of Societies of Biological Psychiatry.

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

Bennett R, Nelson D. *Nat Clin Pract Rheumatol*. 2006;2(8):416-424.

Medication Treatment Algorithm for GAD

Treatment for Acute Transient Anxiety

BZDs

Short-term, intermittent course of anxiolytic therapy, particularly for patients with episodic anxiety

Prolonged Treatment Indicated

SSRIs | *SNRI* | *CBT*

Evaluate after 6-8 weeks of treatment

Responsive

6 months to 1 year of treatment for medication and booster sessions for CBT

Nonresponsive

- Reassess diagnosis
- Examine for comorbidity
- Assess for treatment compliance
- Assess for adequate dose
- Side effects intolerable

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, buproprion, pregabalin, gabapentin, propranolol, or an antipsychotic

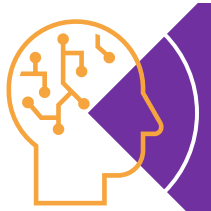
BZD = benzodiazepines; SSRI = selective serotonin reuptake inhibitor; SNRI = serotonin norepinephrine reuptake inhibitor; CBT = cognitive behavioral therapy.

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

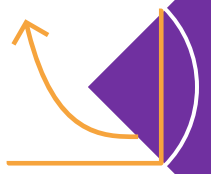


SSRIs and SNRIs demonstrated superior efficacy over placebo for response + remission in GAD

- 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

Slee A, et al. Lancet. 2019;393(10173):768-777. Gosmann NP, et al. PLoS Medicine. 2021;18(6):e1003664. Gommoll C, et al. Depress Anxiety. 2015;32:451-459.

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

Beard JIL, Delgadillo J. *Depress Anxiety*. 2019;36(9):866-878. Ho FYY, et al. *Sci Rep*. 2016;6:29281. Jha MK, et al. *Am J Psychiatry*. 2018;175(12):1176-1184. Jha MK, et al. *Int J Neuropsychopharmacol*. 2017;21(4):325-332.

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*

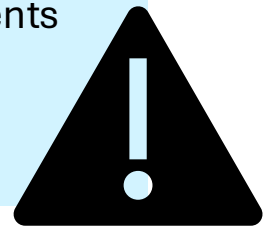
Not recommended as first line for GAD

Appropriate for short-term adjunctive use when:

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

Use with caution:

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



Risks include:

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

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

Brandt. EClinicalMedicine. 2024;70:102507.
Table: Adapted from https://www.thecarlatreport.com/articles/4518-benzodiazepines-the-basics-and-beyond

Second-Line & Adjunctive Pharmacotherapy for GAD

Buspirone (FDA approved)

- Non-habit-forming anxiolytic with delayed onset (~2–4 weeks); no sedation or dependence risk
- Effective for generalized anxiety; less effective for patients with prior benzodiazepine use or comorbid depression
- Start 10mg in divided doses, target up to 60mg daily

Hydroxyzine (off-label)

- Antihistamine with rapid anxiolytic effect; useful for acute anxiety or as adjunct in patients avoiding benzodiazepines
- No dependence risk; sedation is main adverse effect; limited evidence for long-term use

Pregabalin (off-label)

- FDA-approved for epilepsy and neuropathic pain; approved for GAD in Europe
- Risk of misuse and abuse, somnolence, dizziness

Antipsychotics (off-label)

- Quetiapine XR 50-150mg daily is effective as monotherapy in GAD (response rate 62%, remission 35.3%)

Beta-blockers (off-label)

- 2025 meta-analysis of use of any beta blockers in anxiety disorders found no evidence of efficacy compared to placebo
- Adverse effects include dizziness, fatigue, sexual dysfunction, hypotension, bradycardia; contraindicated in asthma

FDA = US Food and Drug Administration; SUD = substance use disorder.

Slee A, et al. Lancet. 2019;393(10173):768-777. Kong W, et al. Front Pharmacol. 2020;11:580858. Maneeton N, et al.. Drug Des Devel Ther. 2016 Jan 12;10:259-76. Archer et al, J Affective Disorders 2025;368: 90-99.

Recommendations for Medication Initiation

Provide education to your patient. Utilize shared decision making to elicit treatment preferences & side effect deal breakers

Start medications at low doses, titrate up slowly, and follow up frequently

Encourage patients to report side effects and validate their experience

Consider medication adjustments / switches / augmentation if needed for side effect management

Always ask about sex, weight, and emotional blunting!

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

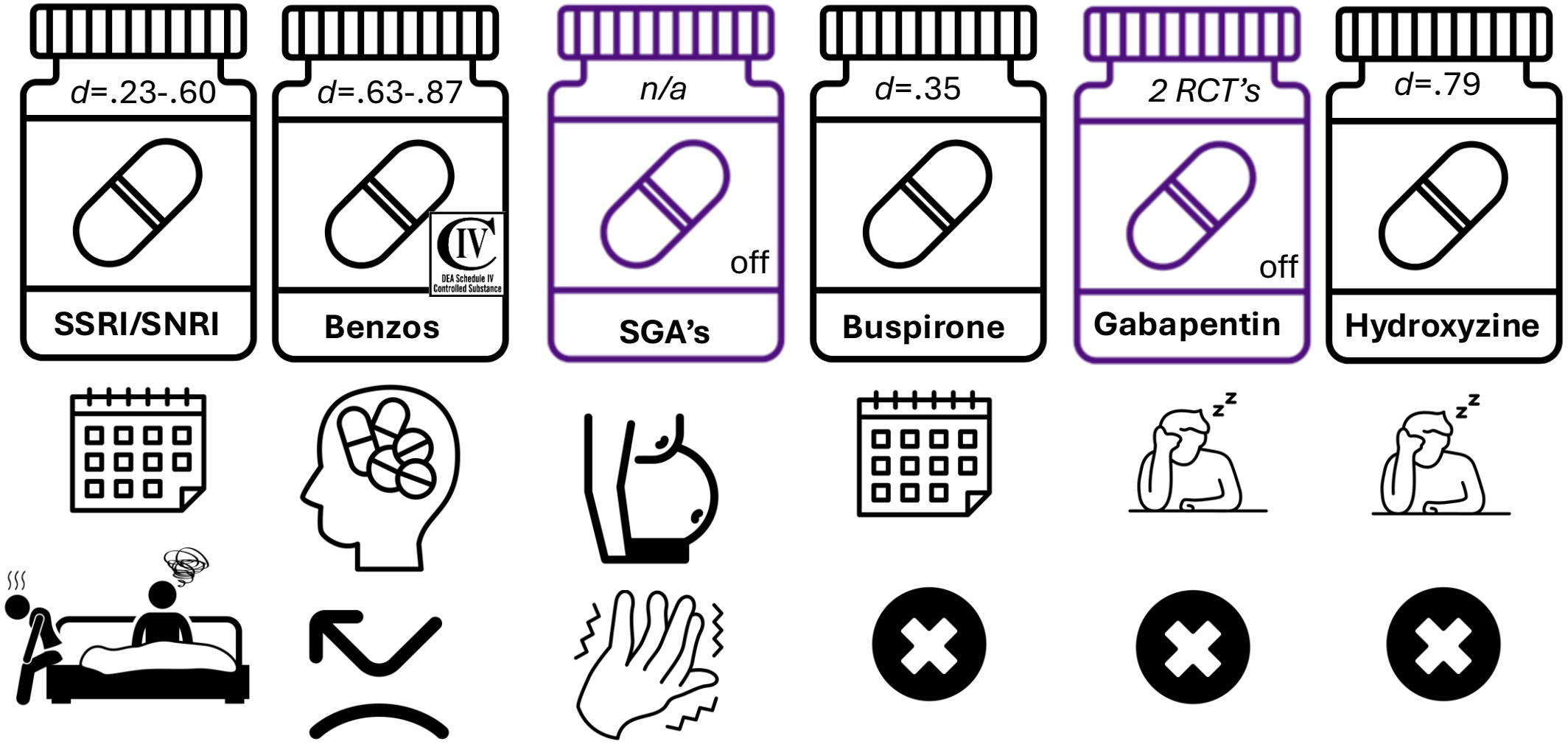
For patients who respond to medication without significant adverse effects, the drug should be continued for at least 1 year after response to reduce relapse.

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, boostering sessions to reinforce previously learned skills or troubleshooting obstacles can be effective.

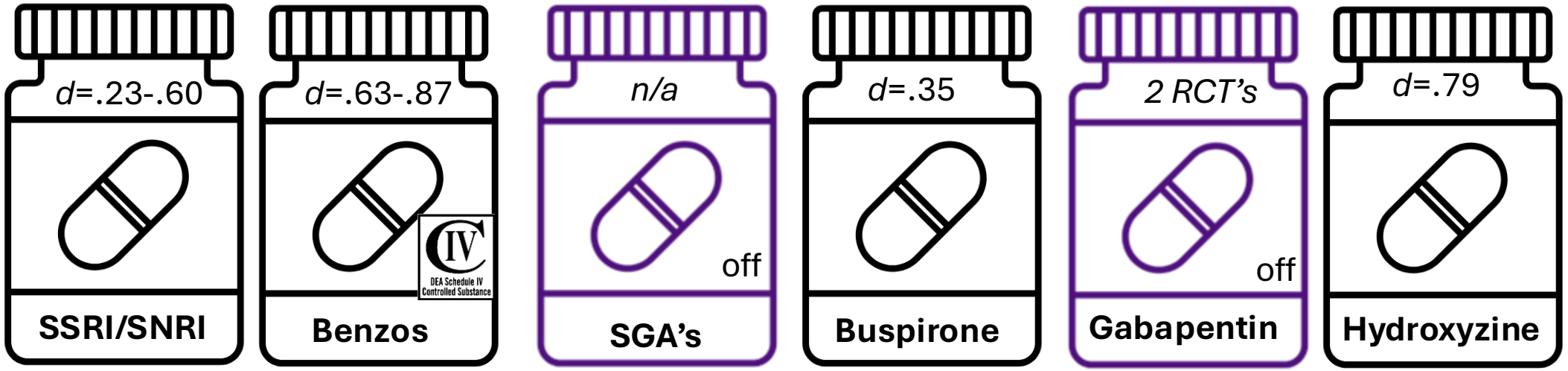
Szuhany KL, Simon NM. *JAMA*. 2022;328;(24):2431-2445.

Current GAD Pharmacopeia and Their Shortcomings



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.

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.

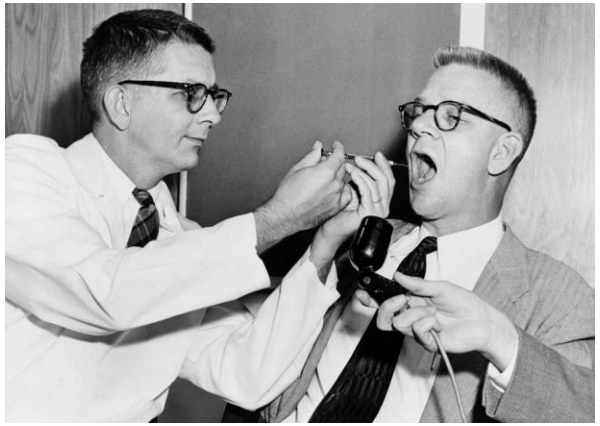
Slee A, et al. Lancet. 2019;393(10173):768-777. Kong W, et al. Front Pharmacol. 2020;11:580858. Szuhany, K. L., & Simon, N. M. (2022). Anxiety Disorders: A Review. *JAMA*, *328*(24), 2431–2445. Slee A, et al. Lancet. 2019;393(10173):768-777. Kong W, et al. Front Pharmacol. 2020;11:580858. Gosmann NP,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

Key Learning Points

- Major treatment guidelines (APA, NICE, CANMAT, WFSBP) converge on SSRIs/SNRIs and CBT as first-line treatments
- SSRIs/SNRIs offer dual efficacy for comorbid GAD+MDD, making them the preferred pharmacotherapy when both disorders are present; SNRIs may offer a modest advantage at higher doses
- 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

Investigational Psychedelics for 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

Phase 3 Psilocybin MDD, TRD
FDA NDA Q3/4 2026

Phase 3 LSD MDD, GAD
FDA NDA Q3/4 2026

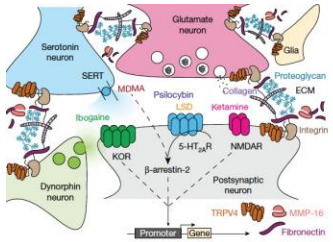
Phase 3 Deuterated DMT/MDD
TBD

Industry Sponsored studies
2010-preset

***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

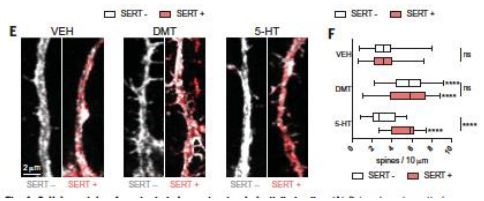
How can psychedelics be therapeutic?



Leading to release of neurotransmitters or activation of receptors

A drug is ingested

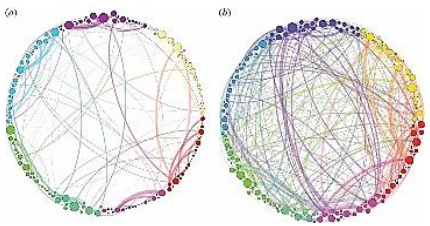
Changing our story/ Emotional Breakthrough
Feeling connected to a larger whole
Finding meaning/spirituality



Growing new brain connections (psychoplastinogen)

Therapeutic Response

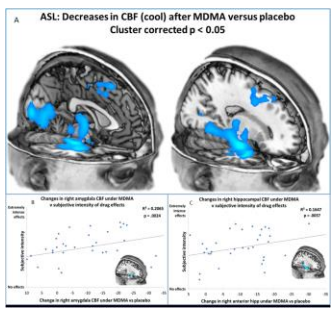
Increased tolerance of difficult emotions



Placebo Psilocybin

Changing the way the brain
talks to itself and predicts events

Re-opening of critical
learning periods

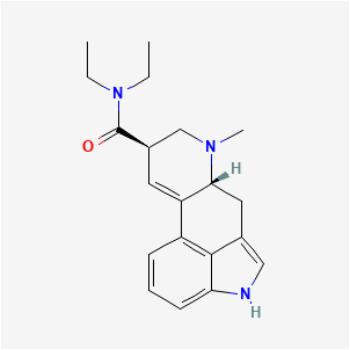


Reduction in limbic activation

Nardou R, et al. *Nature*. 2023;618(7966):790-798. Carhart-Harris RL, et al. *Proc Natl Acad Sci U S A*. 2012 ;109(6):2138-2143. Petri G, et al. *J R Soc Interface*. 2014;11(101):20140873. Zeifman RJ, et al. *J Affect Disord*. 2023;334:100-112. Hartogsohn I. *BioSocieties*. 2026 [Epub ahead of print].

2025: Phase 2/3 MM120 (Lysergide)

- **Drug**: MM120 (LSD)
- **Indication**: GAD
- **Primary outcome**: HAM-A Δ at 4 weeks
- **Size**: N=198 (22 sites)
- **Type:** DB RCT, LSD (single dose 200, 100, 50, 25mcg) or placebo with support, but not therapy



LAD (LSD)

$5HT_{1A,1B,\ 1D,2A,2C,}$ $DA_{1,2,\ 3,}$ $\alpha_{1A,2A,2B,2C}$ partial agonist

JAMA | Preliminary Communication

Single Treatment With MM120 (Lysergide) in Generalized Anxiety Disorder
A Randomized Clinical Trial

Reid Robison, MD; Robert Barrow, MS; Craig Conant, BA; Eric Foster, PhD; Jamie M. Freedman, BS; Paula L. Jacobsen, PhD; Jamileh Jemison, MD, MS; Sarah M. Karas, PsyD; Daniel R. Karlin, MD, MA; Todd M. Solomon, PhD; Miri Halperin Wernli, PhD; Maurizio Fava, MD

IMPORTANCE Effective and well-tolerated pharmacotherapies for generalized anxiety disorder (GAD), which is one of the most common psychiatric disorders, are needed.

OBJECTIVE To determine the dose-response relationship of MM120 (lysergide D-tartrate) in adults with moderate to severe GAD.

DESIGN, SETTINGS, AND PARTICIPANTS This phase 2b, multicenter, randomized, double-blind, placebo-controlled study enrolled 198 adults aged 18 to 74 years with a primary GAD diagnosis who presented with moderate to severe symptoms (defined by a Hamilton Anxiety Rating Scale [HAM-A] score ≥20) and was conducted at 22 outpatient psychiatric research sites in the US from August 2022 to August 2023. The anxiety and depression end point assessments were conducted by independent central raters who were blinded to the trial protocol, treatment allocation, and study visit date. The last date of follow-up was November 27, 2023.

INTERVENTIONS Participants were randomized to receive a single (freebase equivalent) treatment dose with 25 µg (n = 39), 50 µg (n = 40), 100 µg (n = 40), or 200 µg (n = 40) of MM120 or placebo (n = 39).

MAIN OUTCOME AND MEASURES The primary outcome was a dose-response relationship assessed using the multiple comparison procedure modeling (MCP-Mod) method for change in HAM-A score at 4 weeks (score range, 0-56; higher scores indicate greater severity; ≤7 indicates no or minimal anxiety; 8-14, mild; 15-23, moderate; and ≥24, severe). The minimal clinically important difference was 2.5 points.

RESULTS Of the 198 participants randomized, 194 were included in the full analysis set (mean age, 41.3 [SD, 13.6] years; 56.7% were female; and 3.6% were Asian, 7.7% were Black

Editorial

Supplemental content

Robison, R., et al . (2025). Single Treatment With MM120 (Lysergide) in Generalized Anxiety Disorder: A Randomized Clinical Trial. *JAMA*, e2513481. Advance online publication. https://doi.org/10.1001/jama.2025.13481. Wacker, D., et al (2017). Crystal Structure of an LSD-Bound Human Serotonin Receptor. *Cell*, *168*(3), 377–389.e12. https://doi.org/10.1016/j.cell.2016.12.033

DT120 (MM120): Phase 2b Trial Design

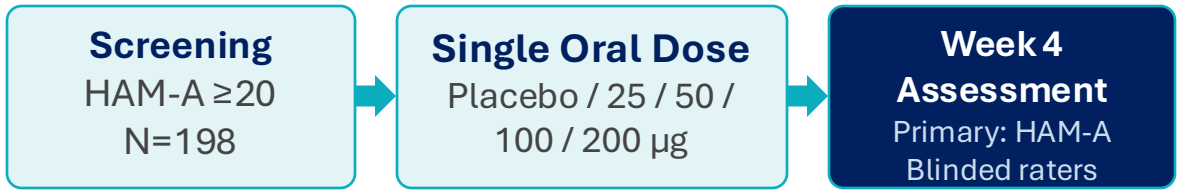
Key Findings: Clinical **response** (≥50% HAM-A reduction): **65% at Week 12**, sustained from Week 4

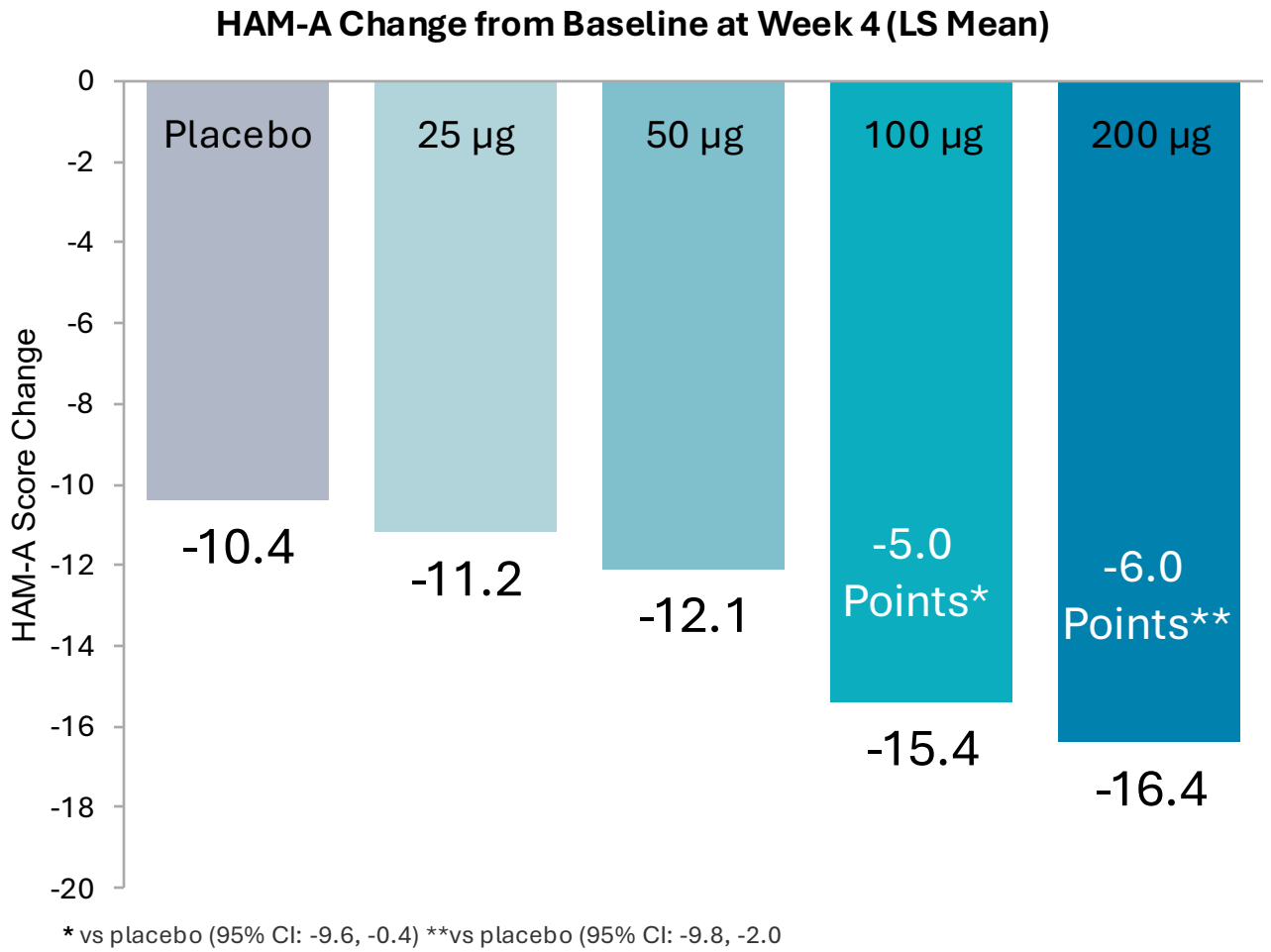
Clinical **remission** (HAM-A ≤7): **48%** at Week 12

Clinical activity was rapid, observed as early as Day 2 post-dose, and durable, with continued improvement from Week 4 to Week 12

Visual perceptual changes were dose-dependent (46% at 25 µg, 93% at 100 µg, 100% at 200 µg); nausea and headache also reported. No SAE.

Forthcoming: Phase 3 MDD, PTSD, GAD studies





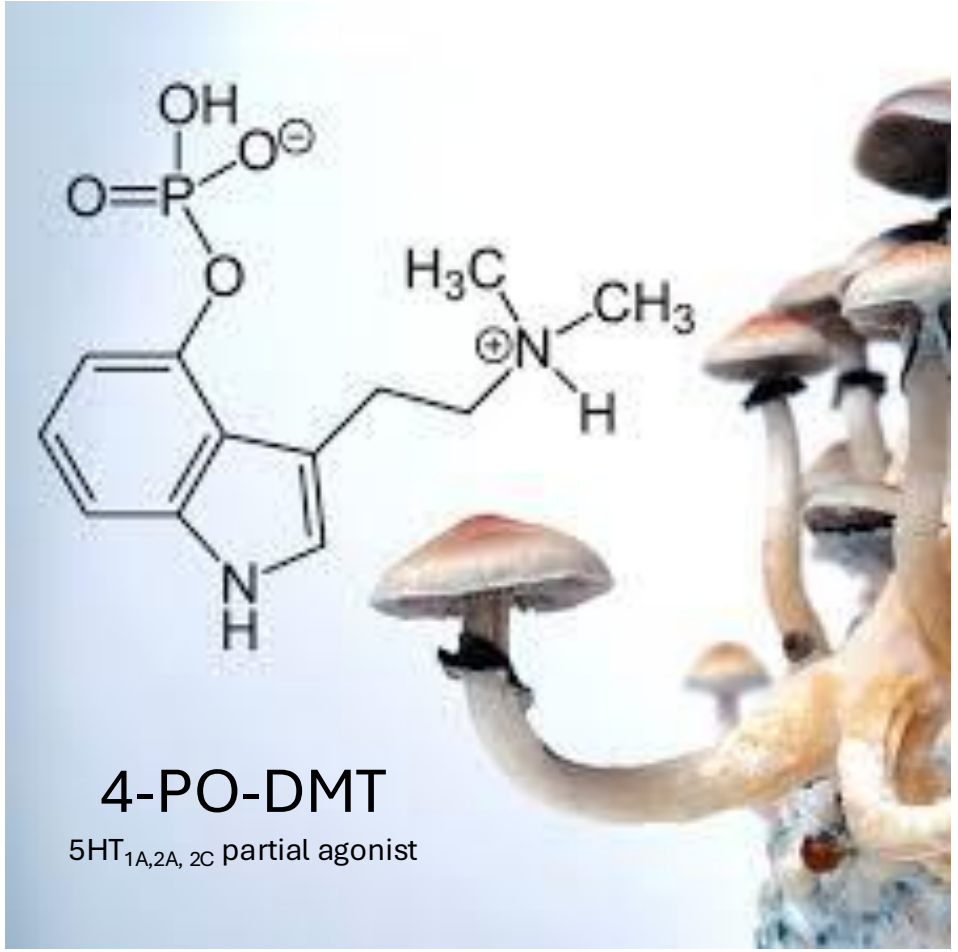
* vs placebo (95% CI: -9.6, -0.4) **vs placebo (95% CI: -9.8, -2.0

CI = confidence interval; GAD = generalized anxiety disorder; HAM-A = Hamilton Anxiety Rating Scale; MCP-Mod = multiple comparison procedure–modeling; MM120 = lysergide D-tartrate.

Robison R, et al. JAMA. 2025;334(15):1358-1372.

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



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

Screening
Mod-severe GAD, N=73

2 Dosing Sessions
PSX-001 25mg or placebo

Primary
HAM-A multiple timepoints

11-Week Follow-up
Durability confirmed

Primary Endpoint Result

-12.8 pts
PSX-001 HAM-A reduction

-3.6 pts
Placebo HAM-A reduction

9.2 pts
treatment difference
($p<0.0001$)

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)

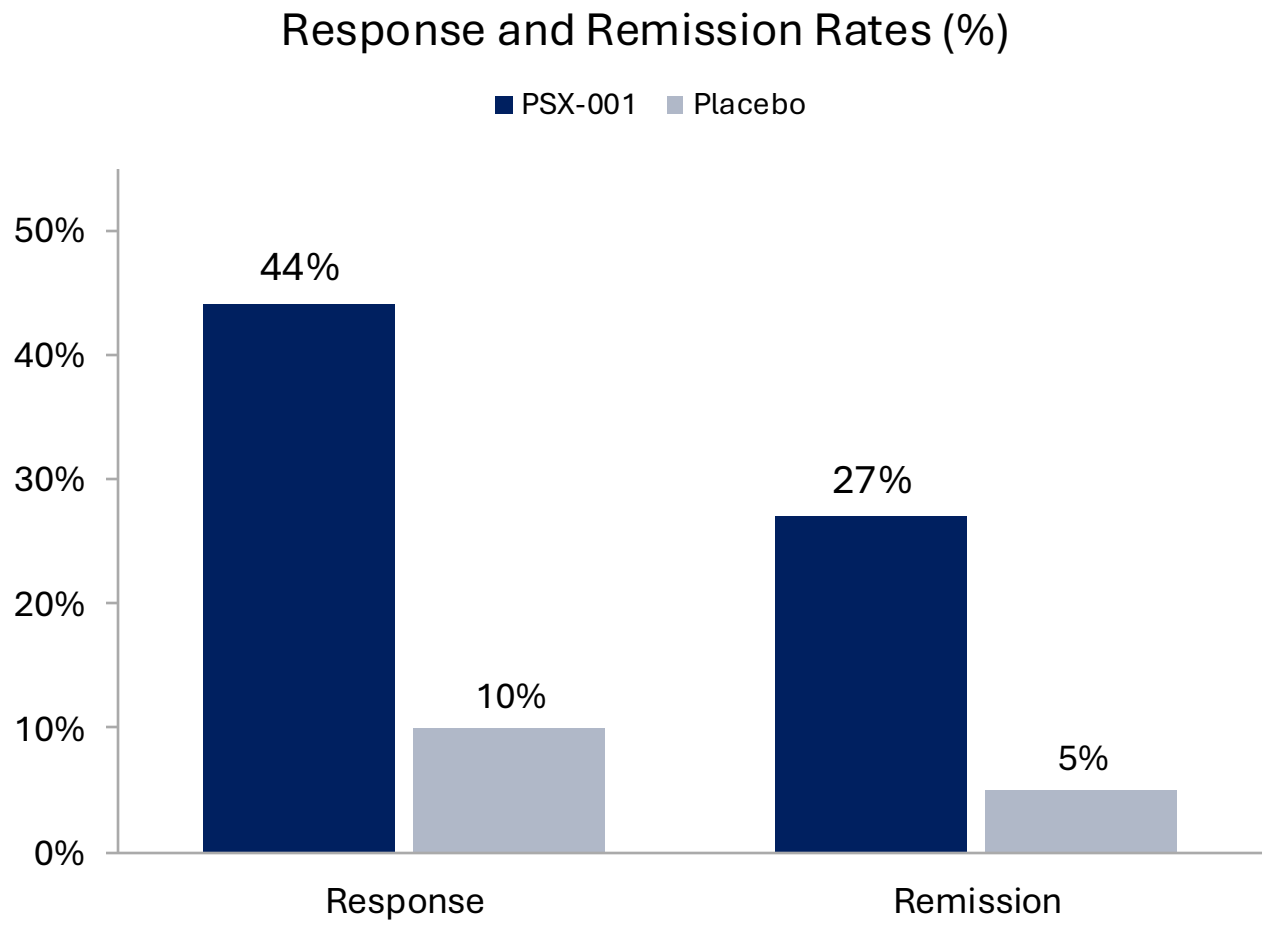
GAD-7
-7.4 vs -3.5 pts
($p<0.0004$)

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



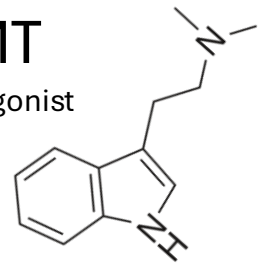
Incannex Healthcare Inc. Incannex Reports Positive Results from Phase 2 Clinical Trial of PSX-001 (Psi-GAD) for Generalised Anxiety Disorder. August 26, 2025. https://ir.incannex.com/news-releases/news-release-details/incannex-reports-positive-results-phase-2-clinical-trial-psx-001

2026: Phase 2a deuterated N,N- DMT

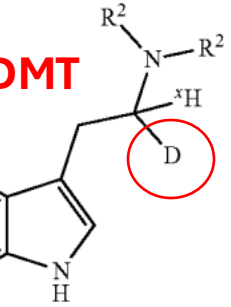
- **Drug**: HLP004 (Deuterated N,N-DMT)
- **Indication**: Moderate – Severe GAD (HAM-A average 22, GAD-7 ≦ 10)
- **Size**: N=36
- **Type:** DB RCT or placebo (IM 20mg vs 2mg HLP004), 2 doses, 2 weeks apart,12-week endpoint on HAM-A. Manualized psychotherapy (EMBARK)
- **Key Findings:** (Topline, not yet published) -10.4-points ($p<0.0001$) HAM-A in 20mg group at 6 weeks. At 6 months, 67% responding, 39% remitting. Effects about 1 hour, d/c in 90 min. Awaiting publication

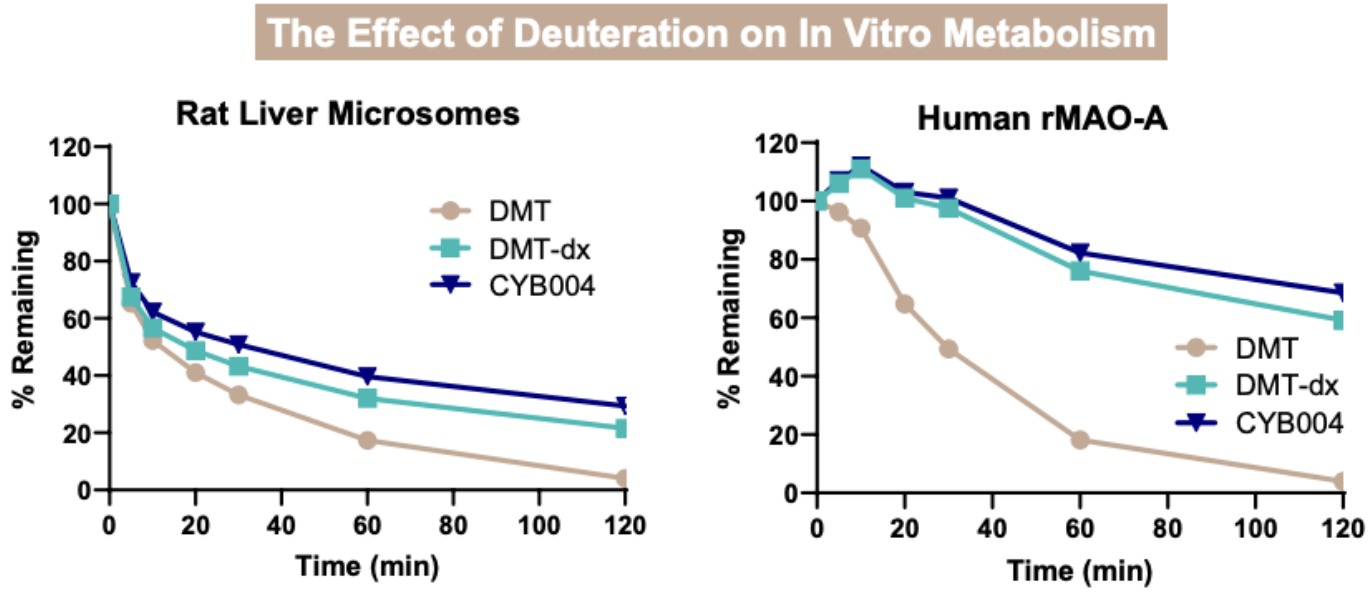
N,N-DMT

$5HT_{1,2,6,7}$ partial agonist



Deuterated DMT





https://ir.helus.com/news-releases/news-release-details

dimethyltryptamine

Varty GB et al (2023) PRECLINICAL CHARACTERIZATION OF CYB004: A NOVEL, DEUTERATED N,N-DIMETHYLTRYPTAMINE (DMT) ANALOG FOR THE POTENTIAL TREATMENT OF GENERALIZED ANXIETY DISORDER (GAD) Poster presentation ACNP accessed 5/22/26 from https://www.helus.com/wp-content/uploads/2025/04/M32-ACNP-2023-CYB004-Varty-Preclinical-Characterization-of-CYB004.pdf

HLP004: Phase 2 Signal Detection Trial Design

HLP004 is Novel Serotonergic Agonist (NSA)

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

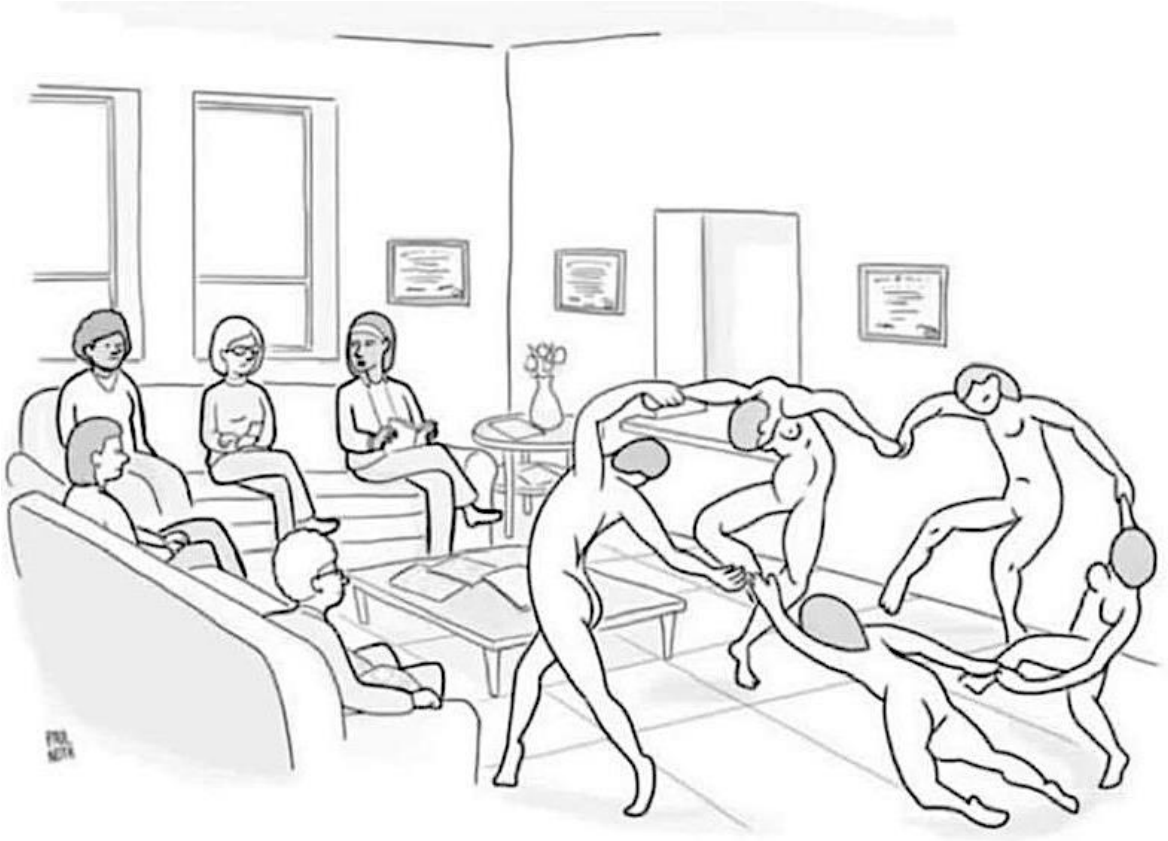
Helus Pharma. Topline Results: Phase 2 Signal Detection Study for HLP004 in GAD. March 5, 2026.

Investigator Initiated Studies

- **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

ClinicalTrials.gov

Psychedelic-Assisted Therapy Studies:
The Problem with Blinding



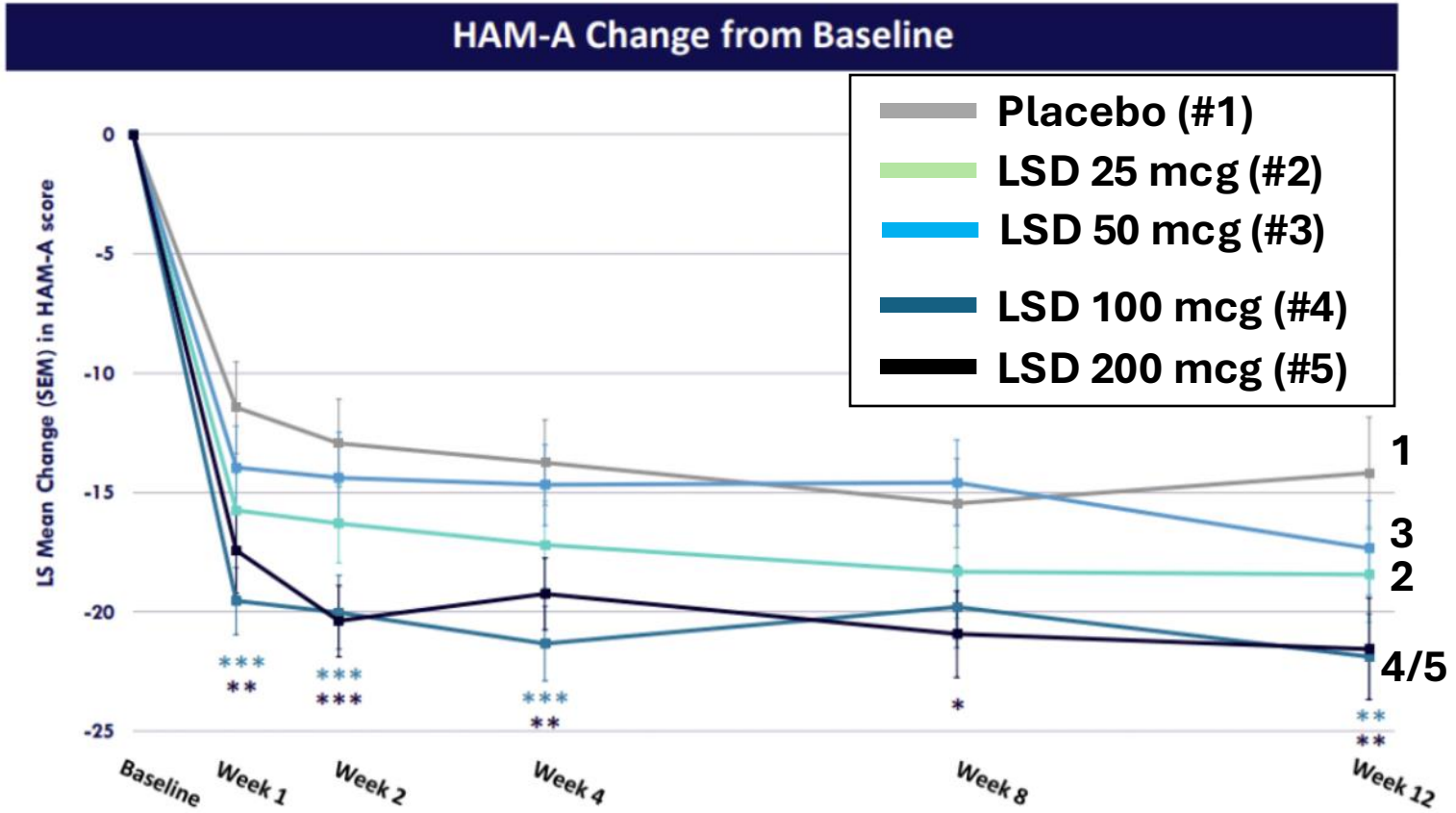
"So I'm guessing we're in the placebo group."

"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**."

Nayak SM, et al. *J Clin Psychiatry*. 2023;84(3):22r14518.

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: *unlikely therapeutic benefit derives exclusively from unblinding*

Robison, R.,et al (2025). Single Treatment With MM120 (Lysergide) in Generalized Anxiety Disorder: A Randomized Clinical Trial. *JAMA*, e2513481. Advance online publication. https://doi.org/10.1001/jama.2025.13481

Key Learning Points

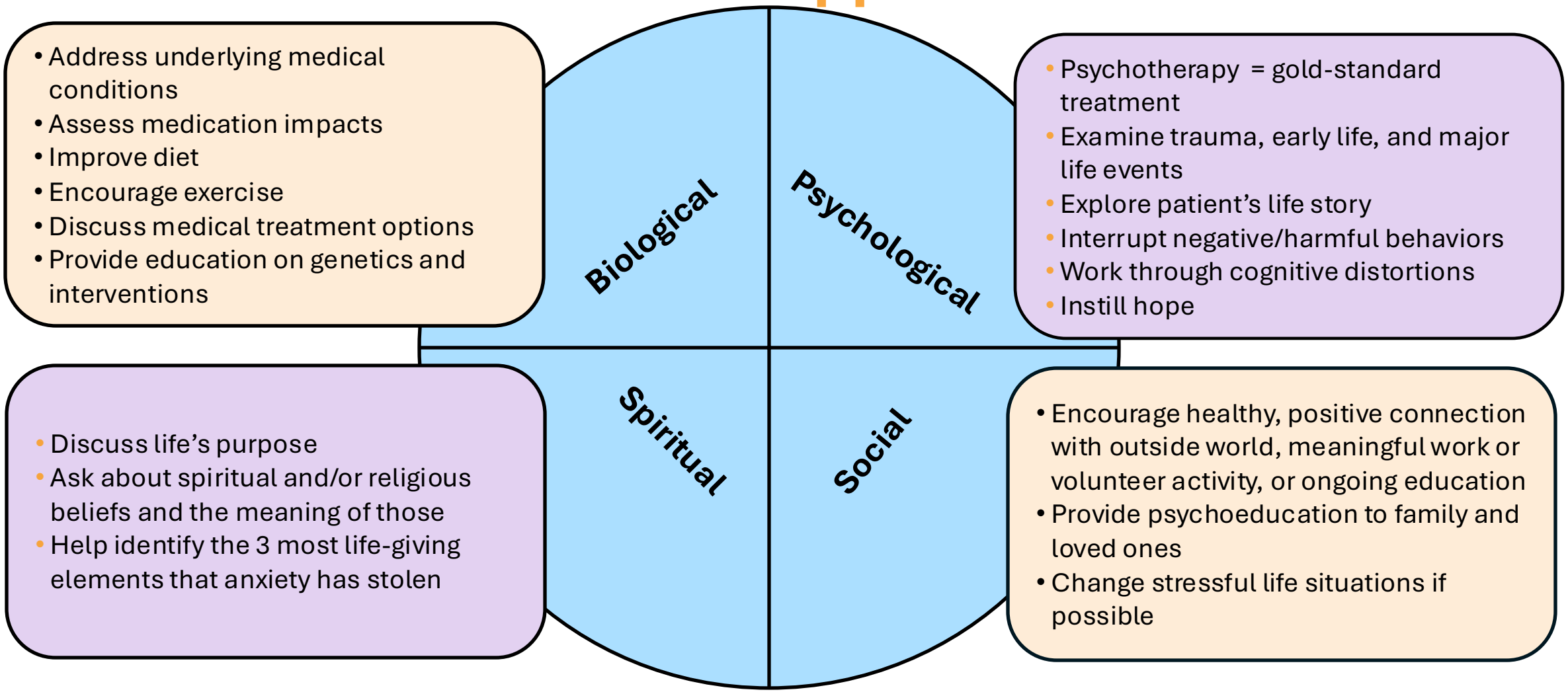
- Three distinct psychedelic mechanistic classes (LSD-based: DT120; psilocybin-based: PSX-001; DMT-based: HLP004) are in active clinical development for GAD, each with phase 2/3 data showing promise
  - Statistically significant HAM-A reductions vs placebo at the 100 and 200 mcg doses of DT120

- Psychedelics may address key unmet needs in GAD (speed of onset, durability, and treatment-resistant populations) through 5-HT2A-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

Faculty Panel Discussion

Patient-Centered Approach to GAD



Robinson WD, Taylor N. "Assessment, Biopsychosocial". In: *The SAGE Encyclopedia of Marriage, Family, and Couples Counseling*. SAGE Publications; 2016.

PRACTICAL TAKEAWAYS

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

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-HT2A-mediated neuroplasticity mechanisms and brain network activity changes

Q & A