Withdrawal, Discontinuation Syndromes, or Nil for Atypical Substances of Misuse

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    - No disclosures
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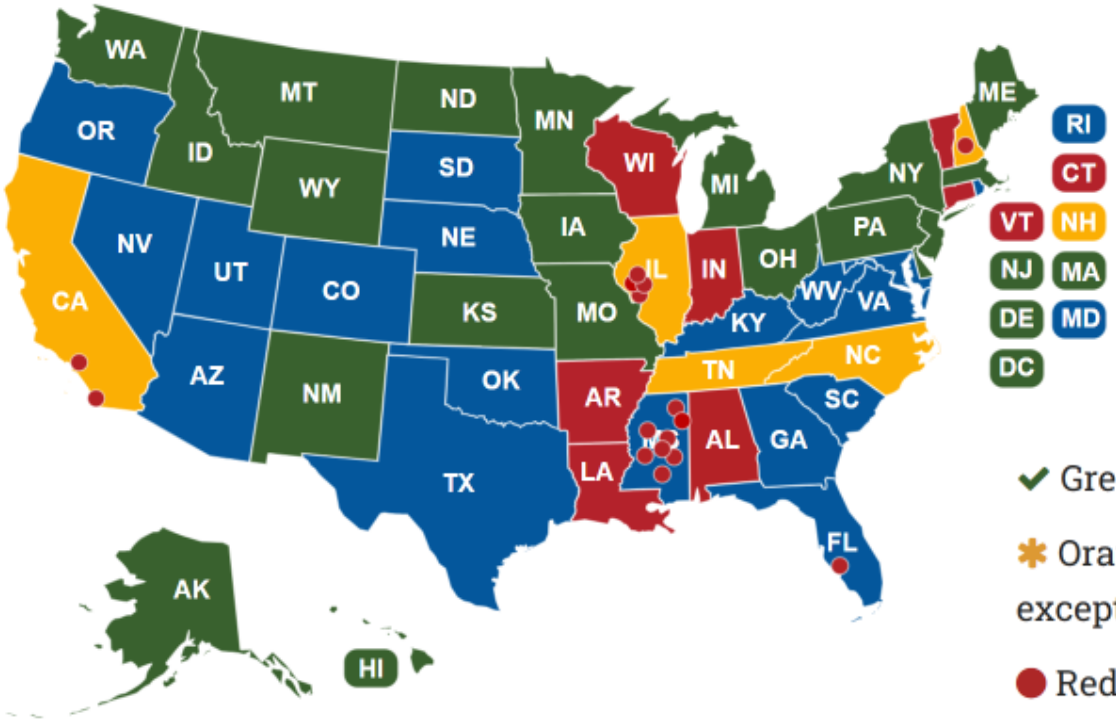
Learning Objectives

- Describe intoxication and withdrawal physiology and phenotypes for dextromethorphan, kratom, cannabinoids, ketamine, gamma-hydroxybutyrate (GHB), and phenibut.
- Compare evidence-informed pharmacologic and supportive strategies for acute withdrawal management, including established and emerging protocols.
- Describe risk stratification and practical order sets with monitoring (vital sign triggers, adjuncts, test-ordering) tailored to detox-unit resources.
- Identify health equity considerations (access to testing, misinformation about safe supply, cost, and medication availability) that influence protocol selection and aftercare.

Kratom

Legality



✔ Green: Kratom is legal in the state

✱ Orange: States legal but with some known local bans or with exceptions.

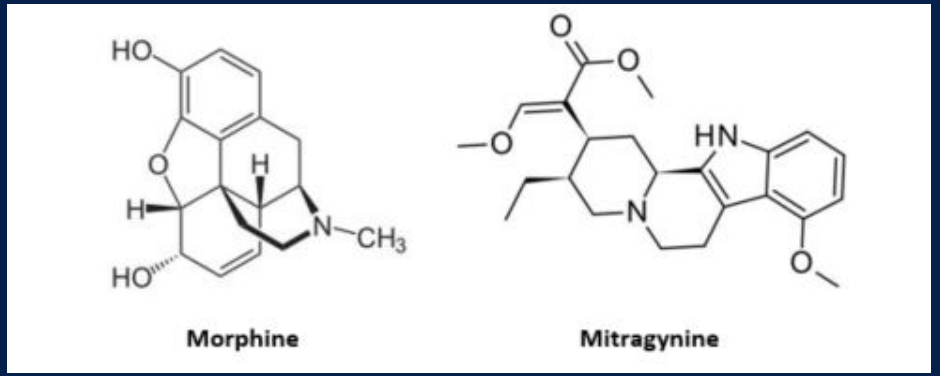
● Red Dot: banned city for Kratom

⊘ Red: Kratom is illegal and banned in the state

♥ Blue: These states have adopted the Kratom Consumer Protection Act bill

https://asam.org/home/kratom-legality-map/

Kratom



- Kratom → contains up to 60 different alkaloids
  - Alkaloid ratio/makeup vary between plants
- Mitragynine
  - Partial mu opioid receptor (MOR) agonist
  - Probable antagonism at KOR and DOR
  - Interactions with adrenergic, dopaminergic, and serotonergic pathways
- Clinical effects short-lived
  - Frequent dosing, typically 5-7x daily; effects: 2-4 hours
  - Sold as a supplement, doses/formulations are unreliable
- Does not cause life-threatening opioid toxicity, but can lead to a use disorder

Hassan et al, 2013; Prozialeck et al, 2021

Kratom Use in the West: Improve Health

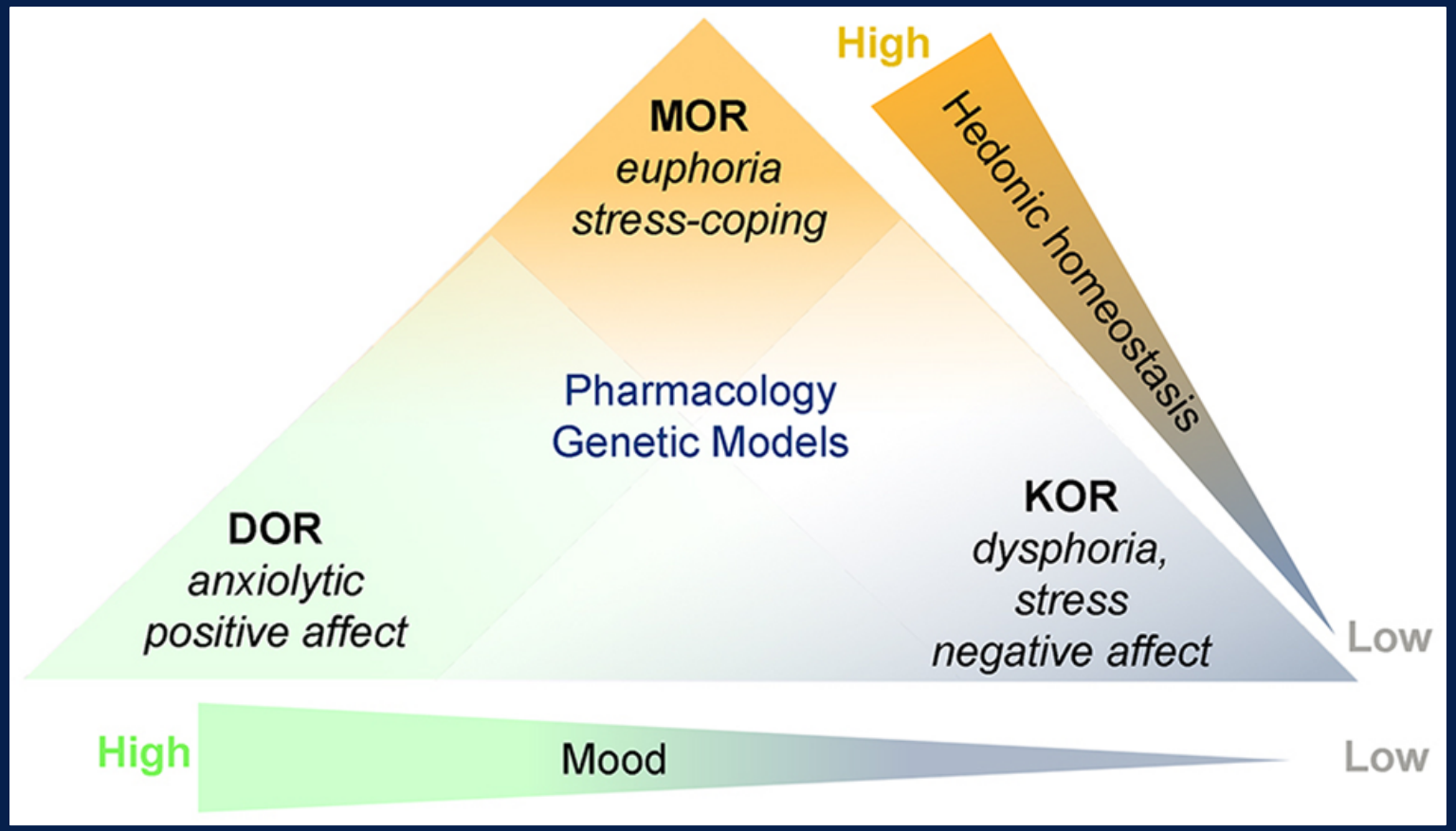
White Vein	Green Vein	Red Vein
Young Leaves		Mature Leaves
High energy **Better productivity** **Help with depression**	**Gentle stimulation** **Better concentration** **Mood lifting**	**Pain killing** **Sedating/relaxing** **Insomnia**

Images from Pixabay. Image 1 &3 credit Anucha Muphasa; Image 2 credit Nelson Hasibaun

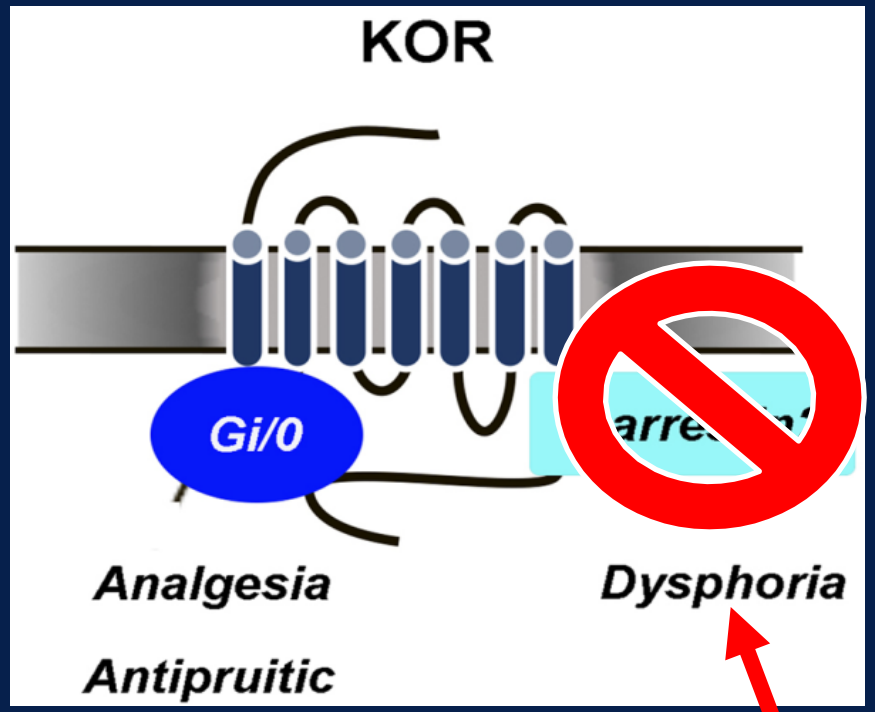
Kratom-Associated Toxicity and Deaths

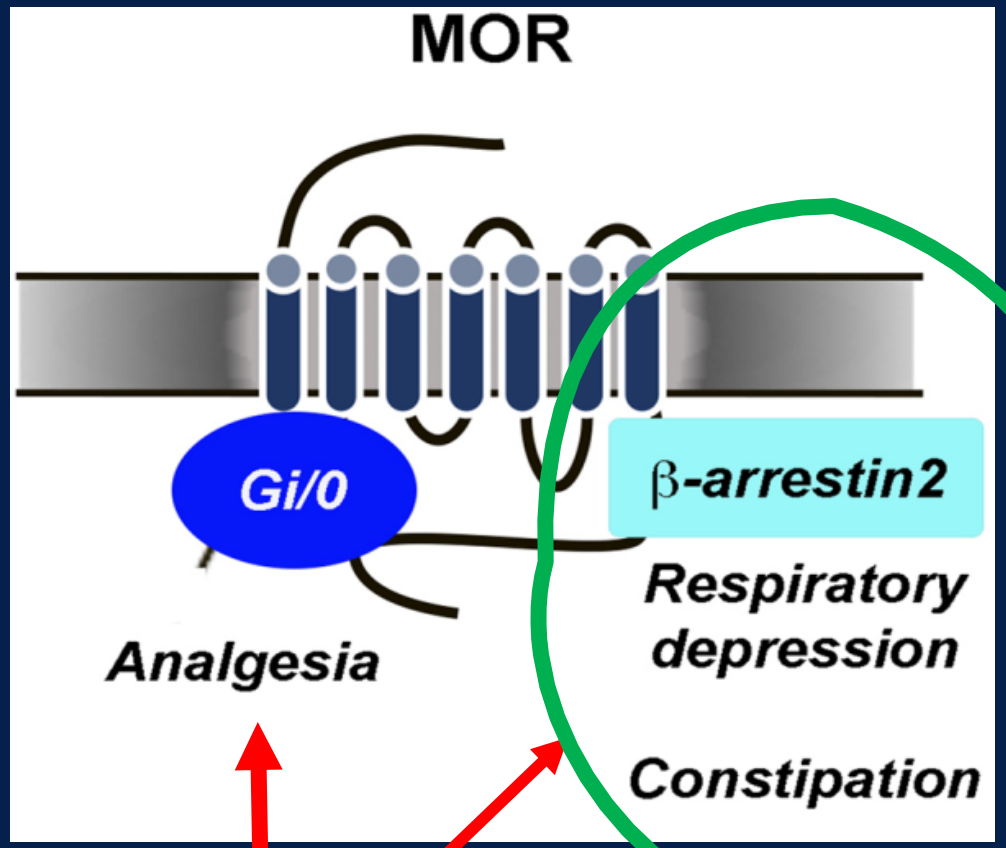
	Southeast Asia	West (US and Europe)
Side Effects	Weight loss, dehydration, constipation, skin hyperpigmentation	N/V, stomach pain, chills and sweats, dizziness, unsteadiness, visual sx
Toxicity	No literature reports of serious toxicity or death	Seizures, hepatotoxicity, coma, multiple deaths, psychosis potential
Where Obtained	Locally	Internet, head shops
How Used	Usually used alone (but not always)	Often combined with other drugs
Legal Status	Illegal in Thailand, Malaysia	Legal in most of US and Europe

Opioid receptor complexity



Valentino RJ, Volkow ND, 2018





Antagonist

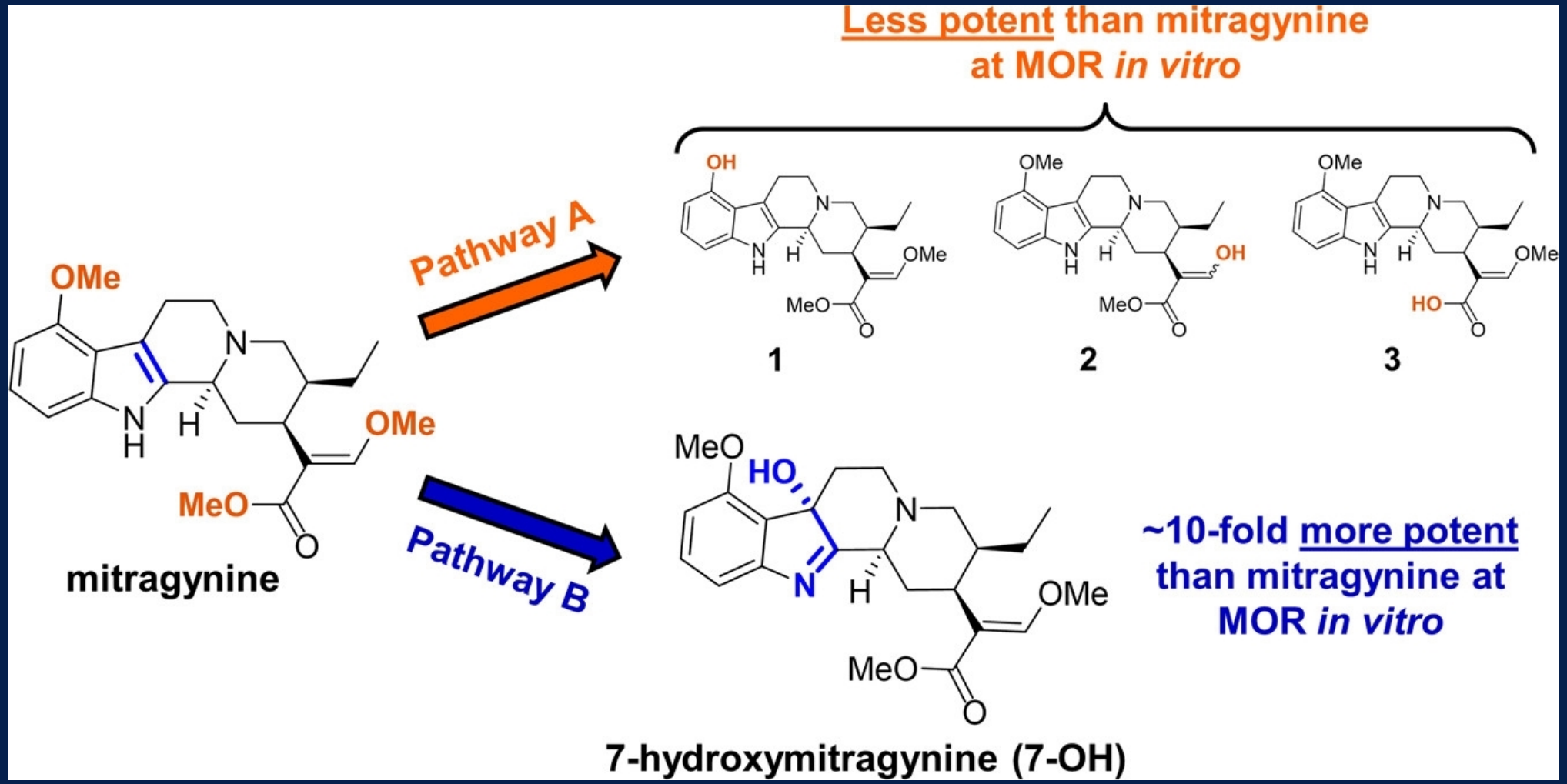
Full agonist

Partial agonist

Buprenorphine
Mitragynine

Valentino RJ, Volkow ND, 2018

7-hydroxymitragynine



Kruegel et al, 2019; Tanna et al, 2023

MoA: Kratom Withdrawal

- Chronic kratom exposure → neuroadaptations
  - MOR downregulation/desensitization
  - Adrenergic receptor upregulation/activation
  - Mitragynine withdrawal involves epigenetic mechanisms distinct from traditional opioids
- Tolerance + abrupt cessation
  - Decrease in downstream signaling from the MOR
- Process mirrors opioid withdrawal but may have some distinct features that depend on the alkaloid variation/composition and formulation/preparation.

Singh et al, 2020; Yunusa et al, 2024

Clinical Features of Kratom Withdrawal Syndrome

Common withdrawal symptoms:

- Anxiety and irritability
- Insomnia
- Rhinorrhea/lacrimation
- Myalgias
- GI symptoms
- Autonomic activation (diaphoresis, palpitations, HTN)

Onset: 12-24 hours after last kratom use; peaks at 24-72 hours

Gradual resolution over 5-7 days; protracted withdrawal has been reported

Alsbrook et al, 2020

Treatment: Kratom Withdrawal Syndrome

- Complicated withdrawal syndrome
  - Treatment: buprenorphine + several days of diazepam or gabapentin
- Management of kratom use disorder
  - Buprenorphine forms backbone of treatment
  - Variable dosing; TDD of 2-16mg SL buprenorphine daily
- **7-OH withdrawal**
  - Likely more severe/intense (the OWS components)
  - May have fewer effects attributable to other alkaloids found in kratom
  - Likely requires higher doses of buprenorphine and several days of adjuncts
    - BZD, odansetron, gabapentinoids, loperamide, clonidine, mirtazapine

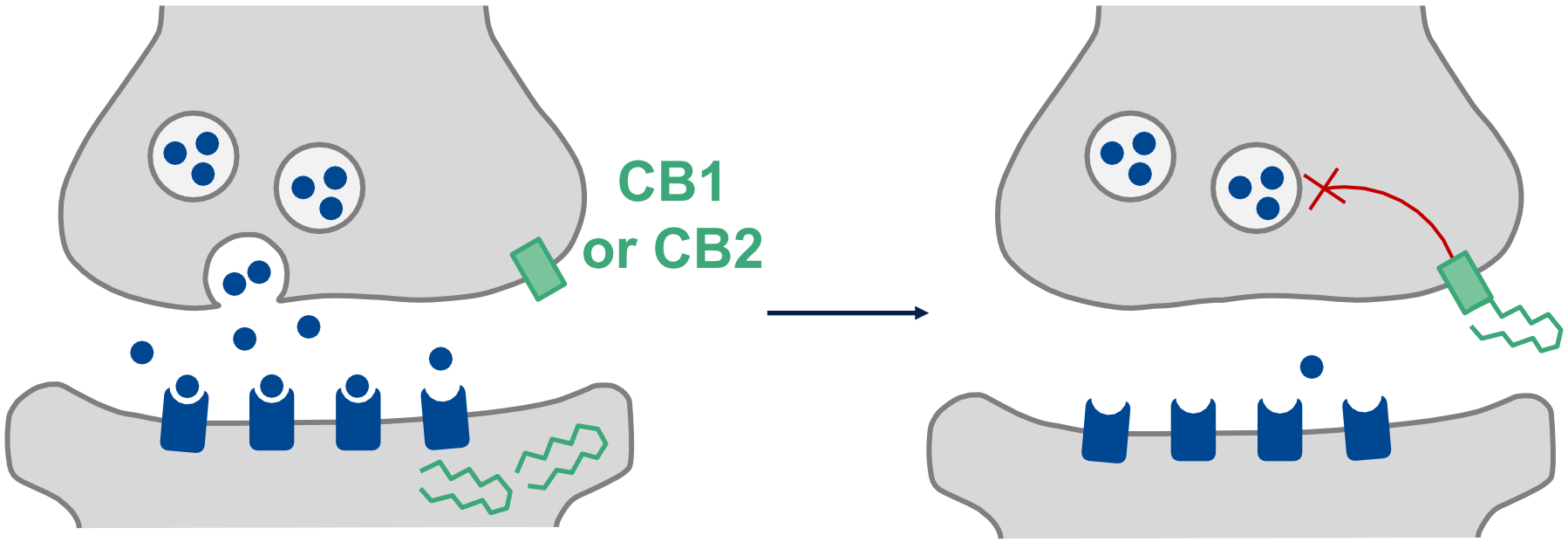
Prozialeck et al, 2021, Demick et al, 2020; Hartley et al, 2022

Questions

- What has been your experience with kratom withdrawal?
- How does kratom withdrawal differ from typical opioid withdrawal syndrome?
- What variables go into the risk assessment of kratom withdrawal?
- Does 7-OH withdrawal differ from kratom withdrawal? If so, how do does management change.

Cannabis/cannabinoids

Endogenous Cannabinoids: MoA

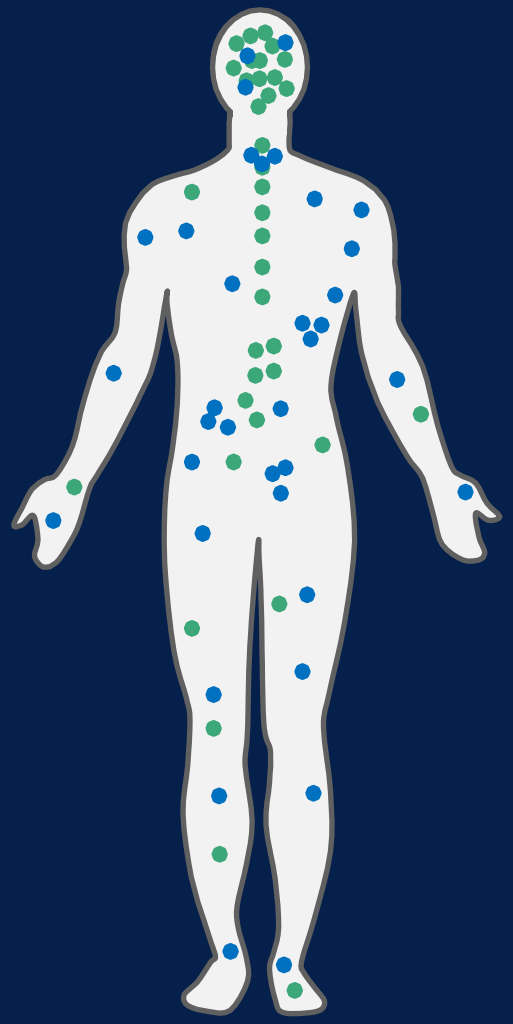


Anandamide (AEA)
2-arachidonoylglycerol (2-AG)

CB1 and CB2 Receptor Distribution

CB1: CNS

- Cortex: Cognition, ***psychoactive effects***
- Hippocampus: Memory
- Basal ganglia, cerebellum: motor function
- Ascending/descending SC: nociception
- Medulla: nausea / vomiting
- Nucleus accumbens: reward



CB2: periphery

- **Thymus, spleen**: ?
- **NK and B cells**: ? inflammatory response, ? chronic pain processes
- Gut: ?
- Kidney: ?
- Pancreas: ?
- Adipose: ?
- Eye: ?

Udoh M, et al. (Brit J Pharmacol 2019)

Cannabinoid Withdrawal Syndrome (CWS)

- Chronic cannabinoid use + ↓ downstream signaling from CB1 receptor
- Extensive supporting literature, basic and clinical
  - Can be precipitated by centrally acting CB1-R antagonists (Rimonabant and AM4113)
- Psychological + physical signs/symptoms
  - Behavioral/emotional manifestations often predominate
- CWS severity is proportional to the intensity of cannabis use (frequency/duration)
- CWS occurs in 47% of chronic cannabis users

Bahji et al, 2020; Kesner et al, 2021; Gorelick, 2023

CWS: MoA

- Cellular/physiologic changes from chronic cannabis use
  - CB1 receptors
    - Cortical/subcortical regions
    - Downregulation ***and*** desensitization
  - Endogenous cannabinoid (EC)
    - EC system is altered
    - Regional-specific changes in EC levels in CNS
  - DA receptors (NAcc)
    - Downregulation ***and*** decreased release of DA
  - Withdrawal state → increased the release of CRF (stress hormone from amygdala)
  - Other neural pathways likely involved…

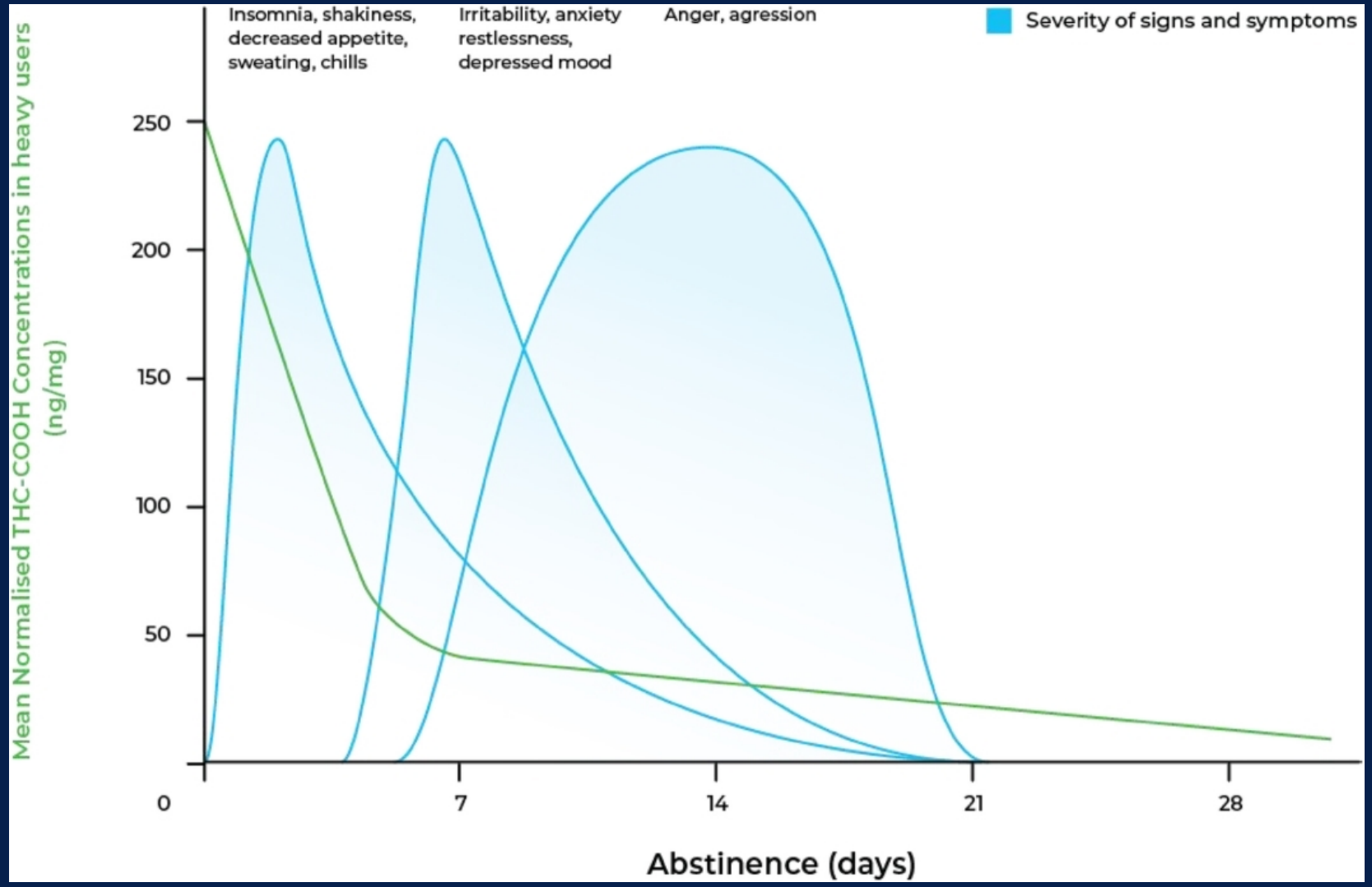
Kesner et al, 2021, Gorelick, 2023

Clinical manifestations

- Psychological
  - Decreased mood, anxiety, irritability
  - Restlessness, sleep disturbance
  - Decreased appetite
- Physical
  - Less common
  - Abdominal cramps, muscle aches, tremor, headache, sweating, chills
- Begin within 1-2 days, peaks in 2-6 days, lasts for up to 4 weeks
  - Mirrors the time it takes for reversal of receptor adaptations
- CWS substantially overlaps with those of other withdrawal syndromes, like tobacco (nicotine) withdrawal

Gorelick, 2023, Kesner et al, 2021,

CWS Time Course



Conner et al, 2022

Why CWS matters…

- Clinically significant as a **negative reinforcer for returning to cannabis use**
  - Worse CWS → ↑ functional impairment → ↑ risk of relapse
- CWS symptoms substantially overlap with those of other withdrawal syndromes
  - States of relative neuroexcitation
- Insomnia is most strongly associated with a return to cannabis use
- No great treatment options for CUD; CWS treatment can be targeted to increase success rates
  - Many pharmacotherapies for CUD help temper CWS symptoms

CWS Management

- Insomnia and mood disturbances → most important variables

1. Psychosocial treatments
   - Supportive counseling
   - Cognitive behavioral therapy (CBT)

2. Pharmacotherapy

CWS: Pharmacotherapy

- No FDA-approved medications; limited experimental evidence
- Cannabinoid agonists
  - Most supporting evidence
  - Promising in small RCTs
  - Dronabinol, nabilone, nabiximols
- Gabapentinoids
  - Promising, needs more research
- Symptom-targeted
  - Anxiety → gabapentinoids, BZD
  - Sleep → Z-drugs, BZD > mirtazapine
- Consider starting and maintaining on NAC or a cannabinoid agonist

Treat co-occurring withdrawal symptoms separately and sufficiently

Shah et al, 2023; Mason et al, 2012; Gorelick, 2023; Brezing et al, 2018

Pharmacotherapies for the Management of CWS

Medication	Dosing	Efficacy for CWS	Treatment Retention / Abstinence	Safety Profile	Key Limitations	References
Dronabinol	20-40 mg BID (up to 120 mg/day studied)	Dose-dependently reduces withdrawal symptoms; improved treatment retention (77% vs 61% placebo)	No significant difference vs placebo (RR 1.04, 95% CI 0.71-1.52)	Well-tolerated; few adverse effects; minimal cognitive impairment at doses up to 120 mg/day	Not FDA-approved for CUD; failed to reduce cannabis use in 12-week trial	[1-4]
Nabilone	Variable dosing	Attenuated withdrawal and relapse in experimental studies	Limited data	Well-tolerated; low abuse potential	Very limited clinical trial data; not FDA-approved for CUD	[5-6]
Nabiximols	Self-titrated up to 113.4 mg THC/105 mg CBD daily	Reduced withdrawal symptoms and craving in short-term studies	No significant difference vs placebo in 12-week trial	Well-tolerated; no serious adverse events; low intoxication potential	Not available in US; mixed results in longer trials	[7-9]
Gabapentin	1200 mg/day	Significantly reduced withdrawal symptoms (p0.001); improved executive function	Significantly reduced cannabis use by urine toxicology (p=0.001) and self-report (p=0.004)	Well-tolerated	Single positive RCT (n=50); needs replication in larger trials	[4, 10-11]
N-acetylcysteine	1200 mg BID (2400 mg/day)	May reduce withdrawal intensity and craving	No significant difference vs placebo (RR 1.17, 95% CI 0.73-1.88)	Well-tolerated; gastrointestinal AEs more common (63% vs 37% placebo); few serious AEs	Efficacy particularly when combined with CM; failed in recent trial without robust behavioral platform	[4, 12-14]
Anticonvulsants / Mood Stabilizers	Variable	May reduce withdrawal symptoms	Uncertain efficacy (very low-certainty evidence)	Higher withdrawal due to adverse effects (RR 2.88, 95% CI 1.05-7.86)	Poor tolerability limits therapeutic value	[4]

Questions

- What has been your experience with CWS? Why does it often go unrecognized?
- How do you approach treatment, specifically pharmacotherapy? Any methods of risk assessment?
- How do you differentiate CWS from other withdrawal syndromes?
- Why start NAC? Do you regularly use cannabinoid agonists?

GHB

Phenibut

Kava

Gamma Hydroxybutyric Acid

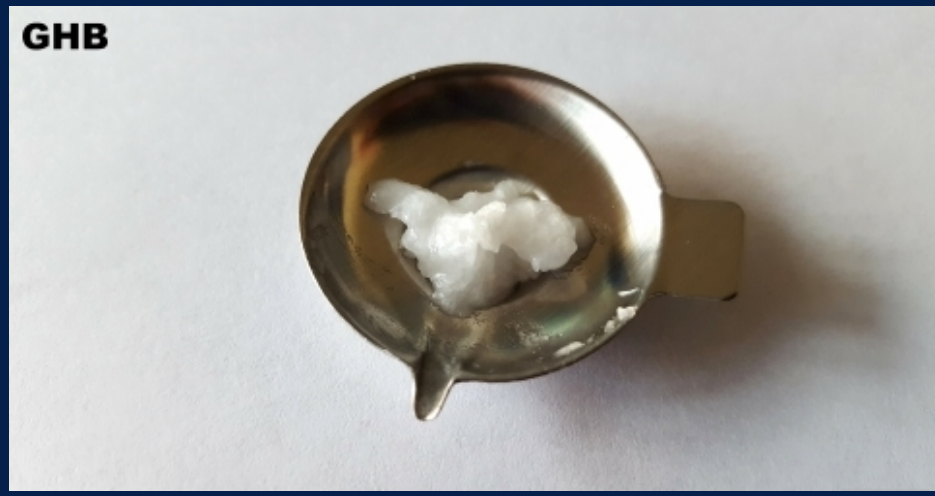
- GABA precursor
- Acts primarily on GHB-specific receptors and on GABA-B receptors, possibly some GABA-A effects

GHB

GABA

Gamma Hydroxybutyric Acid

- Emerged early 2000s in body builders due to steroidogenesis effects
- Also for euphoria, anxiolysis, stimulant, sedative effects
- Use prominent in males 27-34 years
- May be seen in those who practice "chemsex"
- Co-ingestants are common



DMTrott - Own work. Originally published in *The Honest Drug Book* [ISBN: 978-0995593602]

Beurmanjer et al. A qualitative approcah in understanding illness perception and treatment needs in patient with gamma hydoryxbutyrate use disorder. Eur Addict Res 2019

Gamma Hydroxybutyric Acid

- Withdrawal is similar to alcohol/benzodiazepines:
  - Tremor
  - Diaphoresis
  - Anxiety
  - Agitation
  - Confusion
  - Seizures
  - Tachycardia and HTN
  - Profound Insomnia is a common feature
  - Hyperthermia is a severe feature that may be associated with rhabdomyolysis and AKI


Adobe stock image, open access.

- Withdrawal is rapid onset with more prominent neuropsychiatric features (ie delirium,psychosis)
- May be lethal

Dyer et al. Gamma-hydroxybutyrate withdrawal syndrome. Ann Emerg Med 2001.

Gamma Hydroxybutyric Acid

- Features predicting severe withdrawal:
  - Daily doses of 30 grams or more
  - Dosing 3 or more times per day
  - Around the clock use with nocturnal dosing for sleep or to control symptoms
  - Use of alcohol or other sedatives for sleep or self-treatment of withdrawal
  - Previously failed attempts at detoxification
  - History of prior GHB withdrawal with psychosis or delirium
  - Significant medical or psychiatric co-morbid conditions

- Withdrawal often within 24 hours but can be as early as 30 minutes and may last 2-15 days

Wolf et al. Characterization of the GHB Withdrawal Syndrome. J Clin Med. 2021.

GHB Withdrawal Management

- No randomized controlled trials exist and management is primarily supportive
- Benzodiazepines primarily used, typically intravenous
  - Long-acting often preferred such as diazepam
  - Diazepam 10 mg IV every 5-10 minutes for those with severe features and titrated to provide sedation
  - For mild withdrawal, Diazepam 20 mg po every 1-2 hours, up to 60 mg initially with up to 120 mg in 24 hours
- Severe withdrawal should be managed in an intensive care unit
- CIWA-Ar, OWS, SWS not validated but has been used

GHB Withdrawal Management

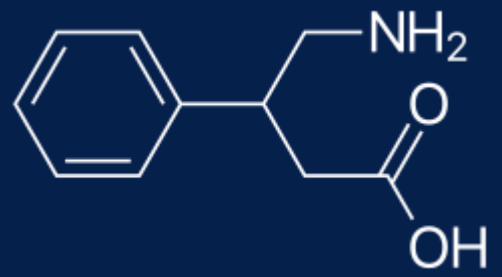
- Barbiturates:
  - Phenobarbtial 250 mg IV, then titrated in increments of 125-250 mg every 15-30 minutes (500 mg may be needed for initial symptom control)
- Propofol
  - Described in refractor agitation in severe cases
  - Will need intubation
  - Initial infusion 20 mcg/kg/min titrated up to 80 mcg/kg/min
- Baclofen
  - Acts at GABA-B and GHB receptors
  - 10 mg TID added to diazepam in cases of refractory symptoms
  - Early administration was associated with better treatment completion rates

GHB withdrawal adjuncts

- Sodium oxybate (sodium-GHB pharmaceutical was used in a Dutch treatment protocol with success in 85% but high relapse rates
  - First dose within 2.5 hours
  - 70% of the calculated street dose, dosed every 2-3 hours, and tapered 0.3 g per/dose/day
- Dexmedetomidine should be considered and adjunct and not used without other GABA-ergic agents
- Antipsychotics are not routinely recommended
- Hypertension should be managed with sedation and beta-blockers are considered by some to be contraindicated
- IV fluids and vitamin repletion

Dijkstra et al. Dtoxification with titration and tapering in gamma-hydroxybutyrate dependent patients: the Dutch GHB monitor project. 2016.

Phenibut (beta-phenyl-gamma-aminobutyric acid)

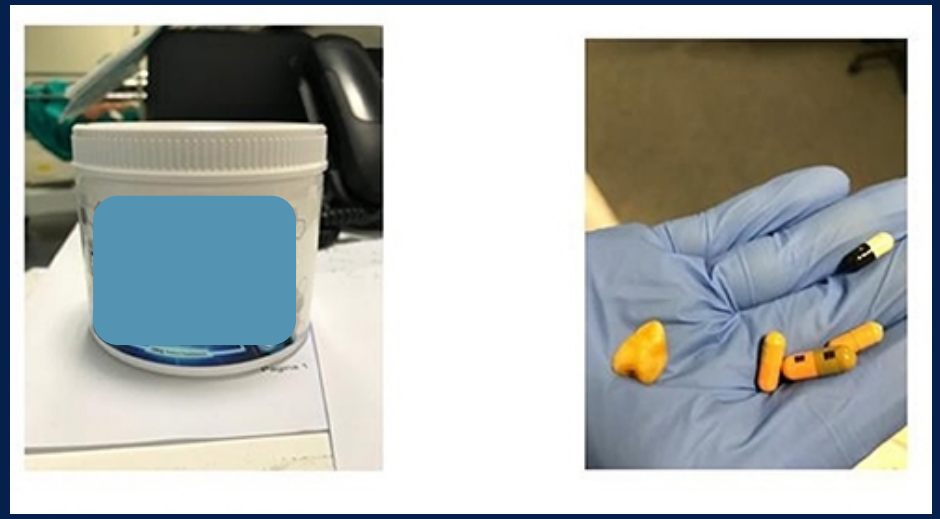


- Developed 1960s
- "cognitive enhancement" supplements

- GABA-B receptor agonist
- May bind alapha-2-delta subunit of voltage-dependent calcium channel (gabapentin-like mechanism)
- Very small GABA-A effect

- Dose-dependent effects of wakefulness, euphoria at low doses; sedation, anxiolysis, muscle relaxation at higher doses

Phenibut



Esposito et al. Psychomotor agitation non-responsive to treatment: a case of phenibut withdrawal. Front Psychiatry. 2021.

Phenibut Withdrawal

- Similar to baclofen withdrawal
- Anxiety, insomnia, Nausea, common
- Psychomotor agitation
- Psychosis: auditory/visual hallucinations, delusions, paranoia, catatonia
- Neurologic effects: tremor, myoclonus, rigidity, seizure
- Rhabdomyolysis, hyperthermia

- Dependence described with as little as 10 days of use

Hardman et al. Acute phenibut withdrawal: a comprehensive literature review and illustrative case report. Bosn J Basic Med Sci. 2019.

Phenibut Withdrawal

- Baclofen
  - Case report: 10 mg of baclofen for each gram phenibut daily, followed by taper
- Benzodiazepines – often refractory when used alone and often combined with baclofen
- Phenobarbital
- Gabapentinoids

Samokhvalov et al. Phenibut dependence. BMJ case rep. 2013.

Difiore & Pittman. A case of phenibut withdrawal management and detoxification using baclofen in the outpatient setting. Case Rep Psychiatry. 2024.

Kava

- Kratom and Kava Tonic
- *All the problems with Kratom . . . And more!*

Kava

- Kava = *Piper methysticum*
  - Pacific islands
  - Makes kavalactones
  - Traditional beverage made from ground roots
  - For anxiety and sleep
  - Associated with hepatotoxicity
- Withdrawal:
  - GABA-ergic agents (benzo/barb)

- MOA:
- $GABA_A$ potentiation
- dopamine, norepinephrine and serotonin reuptake inhibition
- voltage-gated calcium and sodium channel blockade
- monoamine oxidase B inhibition
- Histaminergic, μ and δ-opioid receptor interactions have also been suggested

Bleifess et al. Severe kava withdrawal managed with phenobarbital. *Am J EM*. June 2025.

Questions

- How do you differentiate phenibut or GHB withdrawal from toxicity?
- What are the distinguishing features of phenibut, GHB, and kava withdrawal syndromes?
- What is your treatment approach to phenibut, GHB, and kava withdrawal syndromes?

NMDA Antagonists:
Ketamine
Dextromethorphan (DXM)

Ketamine Pharmacology

Mechanism Cascade: From Receptor to Clinical Effect

NMDA Antagonism

Blockade of glutamate receptors (primary mechanism)

Dopamine Release

Striatal & cortical release (reinforcement)

Opioid Modulation

Weak Mu and Kappa opioid binding & endogenous potentiation

Disinhibition Hypothesis

Blockade on **GABAergic interneurons** reduces inhibition → glutamate surge & AMPA throughput.

Direct Inhibition Hypothesis

NMDA Blockade on **pyramidal neurons** suppresses burst firing → triggers plasticity, prevent AMPA downregulation

References: Zanos & Gould (2018) *Mol Psychiatry*; Vines et al. (2022) *Intelligent Medicine*

Clinical Convergence: Neuroadaptation

Both pathways increase **synaptic plasticity** (BDNF), mTOR pathway--> antidepressant effects,
Chronic upregulation NMDA and plasticity pathways --> **tolerance, withdrawal, and mood instability**

Dextromethorphan (DXM) Mechanism

Receptor Binding Profile & Pharmacokinetics

Multimodal Mechanism

- **NMDA Antagonism:** Primary dissociative effect: metabolite *dextrorphan* (DXO), (blocks glutamate signaling).
- **Sigma-1 Agonism:** Modulates calcium signaling and neurotransmitter release; contributes to psychotomimetic and antitussive effects.
- **Reuptake Inhibition:** Blocks serotonin (5-HT) and norepinephrine (NE) reuptake: distinct "serotonergic" component

Key Distinction

⚠ Unlike ketamine: significant risk of **Serotonin Syndrome;** risk increased with with SSRIs or MAOIs.

CYP2D6 Metabolic Variability

1. Conversion Pathway

DXM (prodrug) -->hepatic **CYP2D6** --> dextrorphan (DXO).
DXO is a more potent NMDA antagonist

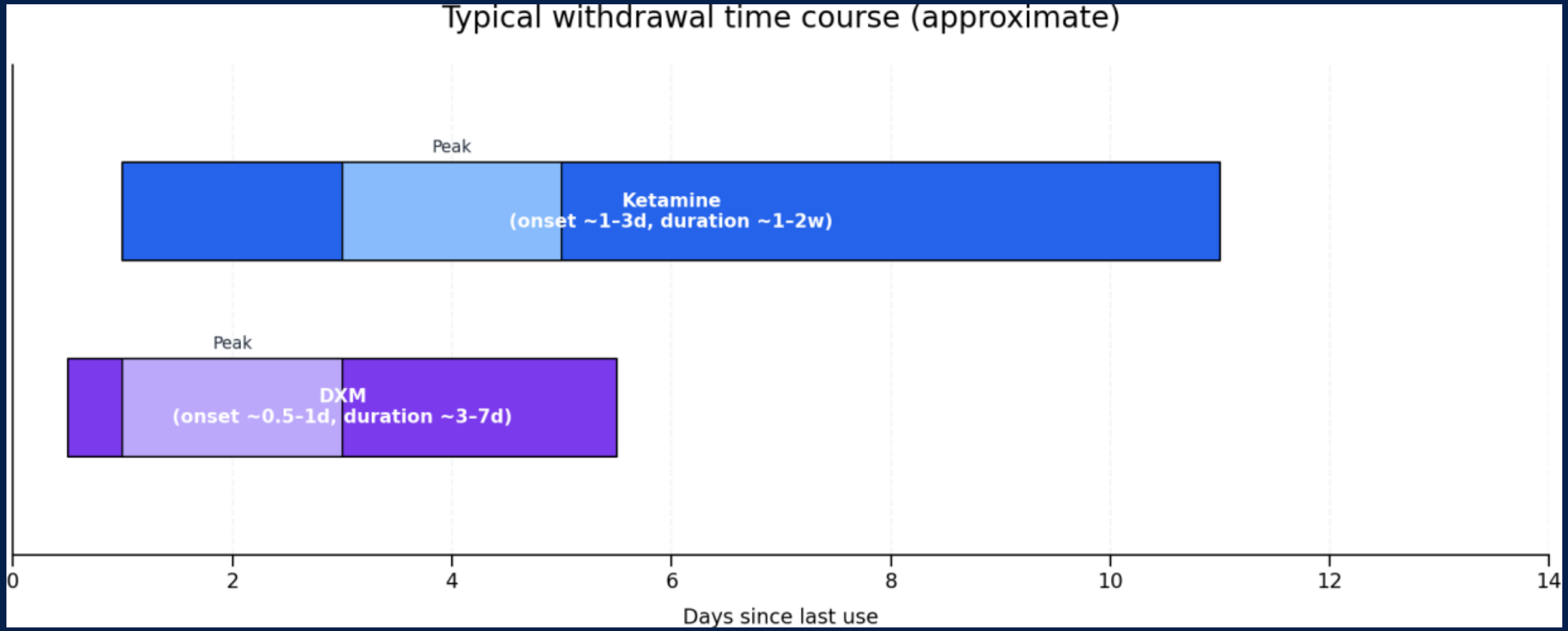
2. Genetic Polymorphism

- **Poor Metabolizers (~10%):** Accumulate parent DXM → higher serotonergic toxicity risk and prolonged duration.
- **Ultra-Rapid Metabolizers:** Rapid increase in DXO → intense, rapid-onset dissociation

DXM is often co-formulated with acetaminophen, chlorpheniramine, or guaifenesin

References: Mutschler et al. (2010) *Dtsch Arztebl Int*; Romanelli & Smith (2009) *J Am Pharm Assoc*

NMDA Antagonist Withdrawal



Pathophysiology

Ketamine Withdrawal: Mechanisms & Timeline

Neurobiological Drivers

Vines, L., Sotelo, D., Johnson, A., Dennis, E., Manza, P., Volkow, N. D., & Wang, G. J. (2022). Ketamine use disorder: preclinical, clinical, and neuroimaging evidence to support proposed mechanisms of actions. *Intelligent medicine*, *2*(02), 61-68.

Glutamatergic Rebound

Chronic NMDA antagonism leads to compensatory receptor upregulation. Cessation causes a surge in glutamatergic sensitivity, driving **hyperarousal, anxiety**.

Reward Dysregulation

Alterations in mesolimbic dopamine pathways result in a "reward deficit" --> **dysphoria, anhedonia, and intense psychological cravings**.

Clinical Course

Onset

24 – 72 Hours

- **Anxiety**
- Tremors
- Diaphoresis
- Restlessness

Peak Intensity

3 – 5 Days

- **Severe Insomnia**
- Dysphoria
- Instability
- Intense Cravings

Protracted / Taper

1 – 2 Weeks

- Mood Labile
- Sleep Normalizing
- Persistent Cravings

Withdrawal Management

Clonidine 0.1 mg q6h PRN for autonomic symptoms

Diazepam 5 mg PRN for severe anxiety/agitation

Trazodone 50 mg nightly for sleep

Additional evaluation:

Referral to urology for suspected **ketamine-associated cystitis**

Ketamine Withdrawal: Management Protocol

Symptom-Directed Pharmacotherapy

Autonomic Hyperactivity First Line

Alpha-2 Agonists (e.g., Clonidine 0.1 mg q6–8h PRN). Monitors BP/HR; mitigates tremors and diaphoresis.

Anxiety & Agitation

Hydroxyzine or short-term **Benzodiazepines** (limited course). Use cautiously to avoid sedation stacking.

Insomnia & Sleep Architecture

Trazodone or **Mirtazapine**. Prioritize sleep restoration as insomnia is a key relapse trigger.

Clinical Pearl

Unlike opioid withdrawal, ketamine withdrawal does not require a tapered substitution. Treatment is **symptomatic and supportive**, focusing on stabilizing the glutamatergic rebound.

Monitoring & Supportive Care

Structured Environment

Low-stimulus setting to reduce anxiety. Monitor Vitals and CK (rhabdomyolysis risk in severe agitation).

Urologic Complications

"Ketamine Cystitis": Monitor for hematuria/dysuria. Ensure hydration. **Refer to Urology** if symptoms are severe or persistent.

Relapse Prevention

Initiate counseling immediately post-detox. Establish follow-up for comorbid depression/mood disorders.

References: Schak et al. (2016) *Am J Psychiatry*; Schwenk et al. (2021); Vines et al. (2022)

Case Presentation

Clinical Case: Dextromethorphan (DXM) Withdrawal

Patient Profile

24-year-old Male

Last Use

~30 hours prior to admission

Substance Use History

Daily DXM use for ~12 months

Dose: 600–900 mg/day

Presenting Symptoms

- Marked anxiety & restlessness
- Severe insomnia
- Dysphoric mood
- Strong cravings for DXM

Vital Signs

HR **104** bpm

BP **148/90**

Mild autonomic hyperactivity

Laboratory Findings

CK Level	210 U/L
UDS	**Positive PCP***

Diagnostic Alert

*False positive result. DXM metabolites cross-react with PCP immunoassays.

Clinical Impression

Presentation is consistent with **Dextromethorphan (DXM) Withdrawal**.

Caution: If patient is taking SSRIs/SNRIs, evaluate for *Serotonin Toxicity* given DXM's serotonin reuptake inhibition properties.

References: Mutschler et al. (2010) *Dtsch Arztebl Int*; Romanelli & Smith (2009) *JAPhA*; Cao et al. (2016) *Clin Tox*

Pathophysiology

DXM Withdrawal: Mechanisms & Timeline

Neurobiological Drivers

NMDA Upregulation

Similar to ketamine, chronic antagonism leads to compensatory upregulation--> relative glutamatergic hyperactivity driving **agitation and insomnia**.

Serotonergic Adaptation

Chronic exposure alters serotonin signaling; discontinuation mimics SSRI discontinuation syndrome **dysphoria and "brain zaps" described**

Sigma-1 Modulation

Sigma-1 receptors regulate stress response. Withdrawal of agonist effects contributes to **heightened stress sensitivity and anxiety**.

Clinical Course

Onset

12 – 24 Hours

Restlessness | Mild Anxiety | Early Cravings | Tremor

Peak Intensity

24 – 72 Hours

Dysphoria | Severe Insomnia | Irritability | Autonomic Signs

Resolution

3 – 7 Days

Improving Mood | Sleep Normalizing | Lingering Anxiety

References: Mutschler et al. (2010) *Dtsch Arztebl Int*; Romanelli & Smith (2009) *JAPhA*; Cao et al. (2016)

DXM Withdrawal: Management Protocol

Symptom-Directed Pharmacotherapy

Autonomic Hyperactivity

Alpha-2 Agonists (e.g., Clonidine). Useful for managing hypertension, tachycardia, and diaphoresis common in early withdrawal.

Agitation & Anxiety

Benzodiazepines (PRN). Consider acute agitation. **Avoid typical** antipsychotics if possible (seizure threshold concerns).

Sleep Support

Trazodone or **Mirtazapine**. Addressing severe insomnia is critical. Monitor for additive serotonergic effects.

Important Note

There are currently **no FDA-approved pharmacotherapies** specifically for Dextromethorphan Use Disorder. Treatment relies on supportive care and behavioral interventions.

Monitoring & Supportive Care

Supportive Care

Hydration, electrolyte repletion, and a low-stimulus environment to manage sensory hypersensitivity and irritability.

Behavioral Therapy

Cognitive Behavioral Therapy (CBT) and Motivational Interviewing (MI). Essential for long-term recovery and relapse prevention.

References: Romanelli & Smith (2009) *J Am Pharm Assoc*; Cao et al. (2016) *Clin Toxicol*

Ketamine Versus Dextromethorphan Withdrawal

Feature	**Ketamine**	**Dextromethorphan (DXM)**
Primary pharmacology	NMDA antagonist	NMDA antagonist + **serotonergic activity**
Withdrawal type	Mainly **psychological**	Psychological + mild autonomic
Onset	~24–72 hr	~12–24 hr
Peak	3–5 days	1–3 days
Duration	~1–2 weeks	~3–7 days
Craving severity	Often prominent	Moderate
Autonomic symptoms	Mild	Mild–moderate
Medical complications of Intoxication	**Ketamine cystitis**	**Serotonergic interactions**
Detox focus	Sleep, anxiety, craving	Anxiety, dysphoria, sleep

Questions

- Have you seen physiologic symptoms with ketamine/dextromethorphan withdrawal?
- Would someone experience withdrawal if they are receiving regular ketamine from a medical provider on a typical schedule?
- Withdrawal symptoms from low-dose ketamine?
- Any other pharmacological treatments you would use?

Summary Table

Substance	Primary Mechanism	Withdrawal Phenotype	Onset / Duration	Key Risks	Management Focus
Kratom / 7-OH	Partial μ-opioid agonism	Opioid-like + autonomic	12–24 h / ~5–7 d	Severe symptoms with 7-OH	**Buprenorphine**, adjuncts
Cannabis	CB1 downregulation	Psychological > physical	1–2 d / weeks	Insomnia-driven relapse	Sleep, mood, support
GHB	GABA-B agonism	Sedative-hypnotic	Minutes–24 h / 2–15 d	Delirium, seizures, death	**High-dose BZDs, ICU**
Phenibut	GABA-B agonism	Agitation, psychosis	Hours–1 d / days	Psychosis, seizures	**Baclofen ± BZDs**
Ketamine	NMDA antagonism	Psychological, insomnia	24–72 h / 1–2 wks	Cravings, cystitis	Sleep, anxiety control
DXM	NMDA + serotonergic	Psych + mild autonomic	12–24 h / ~3–7 d	Serotonin toxicity	Supportive, avoid SSRIs

Final Questions????

Final Takeaways

- **Atypical withdrawals are common—and don't follow classic rules** (often neuroadaptation-driven, not GABA or opioid failure)
- **Treat the phenotype, not the drug** (insomnia, anxiety, autonomic symptoms, craving)
- **Kratom (especially 7-OH) can cause true opioid-like withdrawal** (buprenorphine is often effective)
- **Cannabis withdrawal is real and relapse-driving** (insomnia is the key target; no FDA-approved therapies)
- **GHB and phenibut are the dangerous exceptions** (can be life-threatening; manage like severe sedative withdrawal)
- **Ketamine and DXM withdrawal are mainly psychological** (glutamatergic rebound; focus on sleep, anxiety, and safety)