GHB: What You Need to Know

Robert Cole Pueringer, MD
Medical Toxicology, Addiction Medicine, Internal Medicine
Essentia Health - Duluth
Volunteer Staff - Minnesota Poison Control System
Adjunct faculty – University of Minnesota

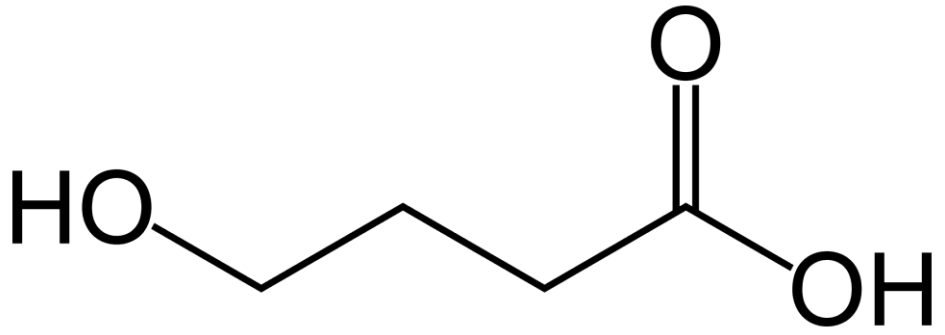
Objectives

- Describe the pharmacology of γ-hydroxybutyric acid (GHB) and its analogues
- Summarize the clinical manifestations of GHB intoxication/toxicity
- Characterize the presentation and management of the GHB withdrawal syndrome

Outline

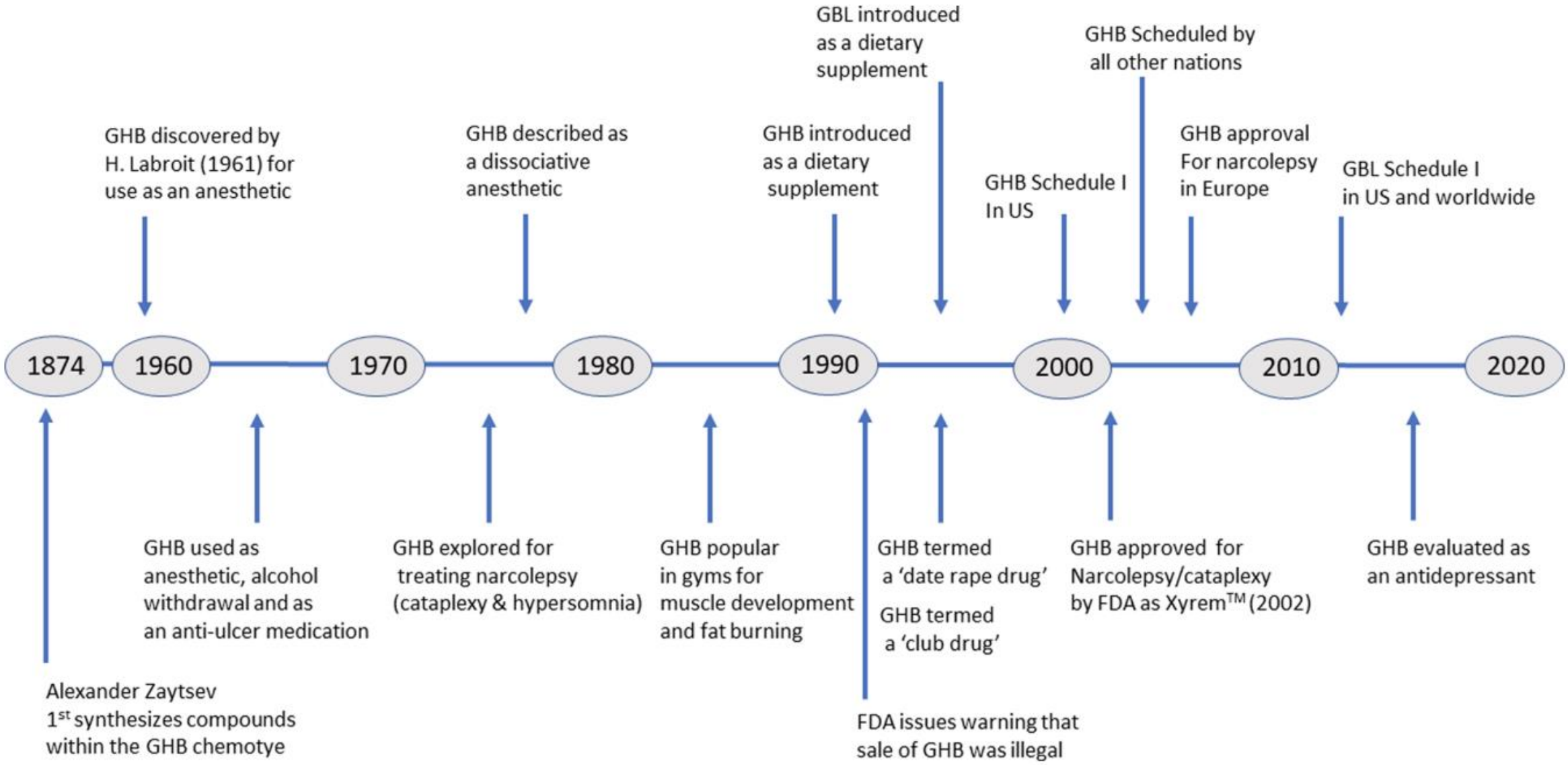
- Introduction
- Epidemiology
- Pharmacology
- Toxicity/Clinical Effects
- Addiction
- Withdrawal
- Management

GHB overview



- γ-hydroxybutyric acid (GHB)
  - CNS depressant
  - Used/misused recreationally as "party drug" or "club drug”
  - Gained notoriety as “date rape” drug
- Street names:
  - GHB, G, Gina, Liquid Ecstasy, Liquid X, Liquid G, Goop, Georgia Home Boy, Easy Lay
- Uses:
  - Sedation, euphoria, disinhibition, increased sexual awareness, strength enhancer
- Common component of “Chemsex” cocktail

ghb.pdf. https://www.deadiversion.usdoj.gov/drug_chem_info/ghb.pdf



Trombley TA, Capstick RA, Lindsley CW. DARK Classics in Chemical Neuroscience: Gamma-Hydroxybutyrate (GHB). *ACS Chem Neurosci*. Published online July 23, 2019. doi:10.1021/acschemneuro.9b00336

Epidemiology (US)

- Low prevalence of use in general population, ↑ in certain subpopulations (nightclub attendees)

- Peak prevalence in early 2000s
  - MTF survey:
    - 1.4-2.0% (2000-2004) → <1% since 2015
  - ED visits involving GHB peaked in 2000 (4,969) → 2011 (2,406)

- NPDS data (GHB/analogues)
  - 2002 = 1,386
  - 2008 = 448
  - 2020 = 776

- Treatment admissions → Unknown in US; increasing in the UK (in addition to overdose deaths)

Palamar JJ. Prevalence and Correlates of GHB Use among Adults in the United States. *J Psychoactive Drugs*. Published online May 26, 2022:1-6.
Gummin DD, Mowry JB, Beuhler MC, Spyker DA, Bronstein AC, Rivers LJ, Pham NPT, Weber J. 2020 Annual Report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 38th Annual Report. *Clin Toxicol* . 2021;59(12):1282-1501.

	Full Sample % (95% CI) N = 241,675	No GHB Use % (95% CI) N = 241,534	GHB Use % (95% CI) N = 141	aOR (95% CI)
Age				
18–25	13.8 (13.6–14.0)	13.8 (13.6–14.0)	20.2 (13.1–29.8)[c]	1.00
26–34	16.0 (15.8–16.2)	16.0 (15.8–16.2)	24.5 (15.9–35.9)	1.06 (0.53–2.14)
35–49	24.6 (24.4–24.9)	24.6 (24.4–24.9)	47.1 (33.6–61.1)	2.28 (1.02–5.10)[a]
≥50	45.6 (45.1–46.0)	45.6 (45.1–46.0)	8.2 (2.6–23.2)	0.40 (0.08–1.95)
Sex/Sexual Orientation				
Heterosexual Male	46.4 (46.1–46.8)	46.4 (46.1–46.8)	28.3 (17.0-43.1)[c]	1.00
Heterosexual Female	48.3 (47.9–48.6)	48.3 (47.9–48.6)	25.3 (15.2–39.1)	1.56 (0.71–3.43)
Gay Male	1.1 (1.1–1.2)	1.1 (1.1–1.2)	32.7 (20.9–47.1)	27.82 (11.09–69.80)[c]
Lesbian/Bisexual Female	3.3 (3.1–3.4)	3.2 (3.1–3.4)	10.5 (5.4–19.6)	3.37 (1.44–7.90)[b]
Bisexual Male	0.9 (0.9–1.0)	0.9 (0.9–1.0)	3.2 (1.3–7.8)	3.39 (1.17–9.82)[a]
Race/ethnicity				
Non-Hispanic White	63.7 (63.1–64.2)	63.7 (63.1–64.2)	61.9 (49.9–72.6)[b]	1.00
Non-Hispanic Black	11.9 (11.5–12.3)	11.9 (11.5–12.3)	5.2 (2.6–10.4)	0.40 (0.16–1.00)
Hispanic	16.2 (15.7–16.6)	16.1 (15.7–16.6)	27.1 (17.4–39.7)	1.61 (0.84–3.10)
Other/Mixed	8.3 (8.1–8.5)	8.3 (8.1–8.5)	5.7 (2.9–11.1)	0.68 (0.33–1.41)
Education				
College Degree or Higher	31.4 (31.0–31.9)	31.4 (31.0–31.9)	33.5 (21.9–47.6)	1.00
Less than High School	12.5 (12.2–12.7)	12.5 (12.2–12.8)	6.1 (3.3–11.0)	0.39 (0.13–1.23)
High School	25.3 (25.0–25.6)	25.3 (25.0–25.6)	32.3 (21.8–44.8)	1.45 (0.64–3.31)
Some College	30.8 (30.5–31.1)	30.8 (30.5–31.1)	28.1 (19.5–38.7)	0.78 (0.35–1.73)
Past-Year Other Drug Use				
Cannabis	15.9 (15.7–16.1)	15.9 (15.7–16.1)	64.4 (51.7–75.4)[c]	1.71 (0.69–4.23)
Cocaine	2.1 (2.0–2.2)	2.1 (2.0–2.1)	42.2 (30.2–55.3)[c]	1.46 (0.41–5.16)
Ecstasy	1.0 (0.9–1.0)	1.0 (0.9–1.0)	37.8 (25.8–51.4)[c]	4.41 (1.80–10.75)[b]
LSD	0.8 (0.7–0.8)	0.8 (0.7–0.8)	25.2 (16.4–36.8)[c]	1.13 (0.32–3.94)
Methamphetamine	0.7 (0.7–0.8)	0.7 (0.7–0.8)	43.1 (32.7–54.3)[c]	15.68 (7.40–33.25)[c]
Heroin	0.3 (0.3–0.4)	0.3 (0.3–0.4)	14.9 (7.7–27.0)[c]	1.43 (0.47–4.32)
Ketamine	0.2 (0.1–0.2)	0.2 (0.1–0.2)	25.8 (16.4–38.2)[c]	8.52 (2.67–27.20)[b]
Prescription Opioids	4.0 (3.9–4.1)	4.0 (3.9–4.1)	31.2 (21.3–43.1)[c]	1.23 (0.50–3.01)
Tranquilizers/Sedatives	2.5 (2.4–2.6)	2.5 (2.4–2.6)	34.4 (23.9–46.6)[c]	1.81 (0.82–3.98)
Prescription Stimulants	2.0 (1.9–2.1)	2.0 (1.9–2.0)	29.7 (19.4–42.5)[c]	(1.33 (0.68–2.60)

aOR = adjusted odds ratio; CI: confidence interval. [a] $p < .05$, [b] $p < .01$, [c] $p < .001$

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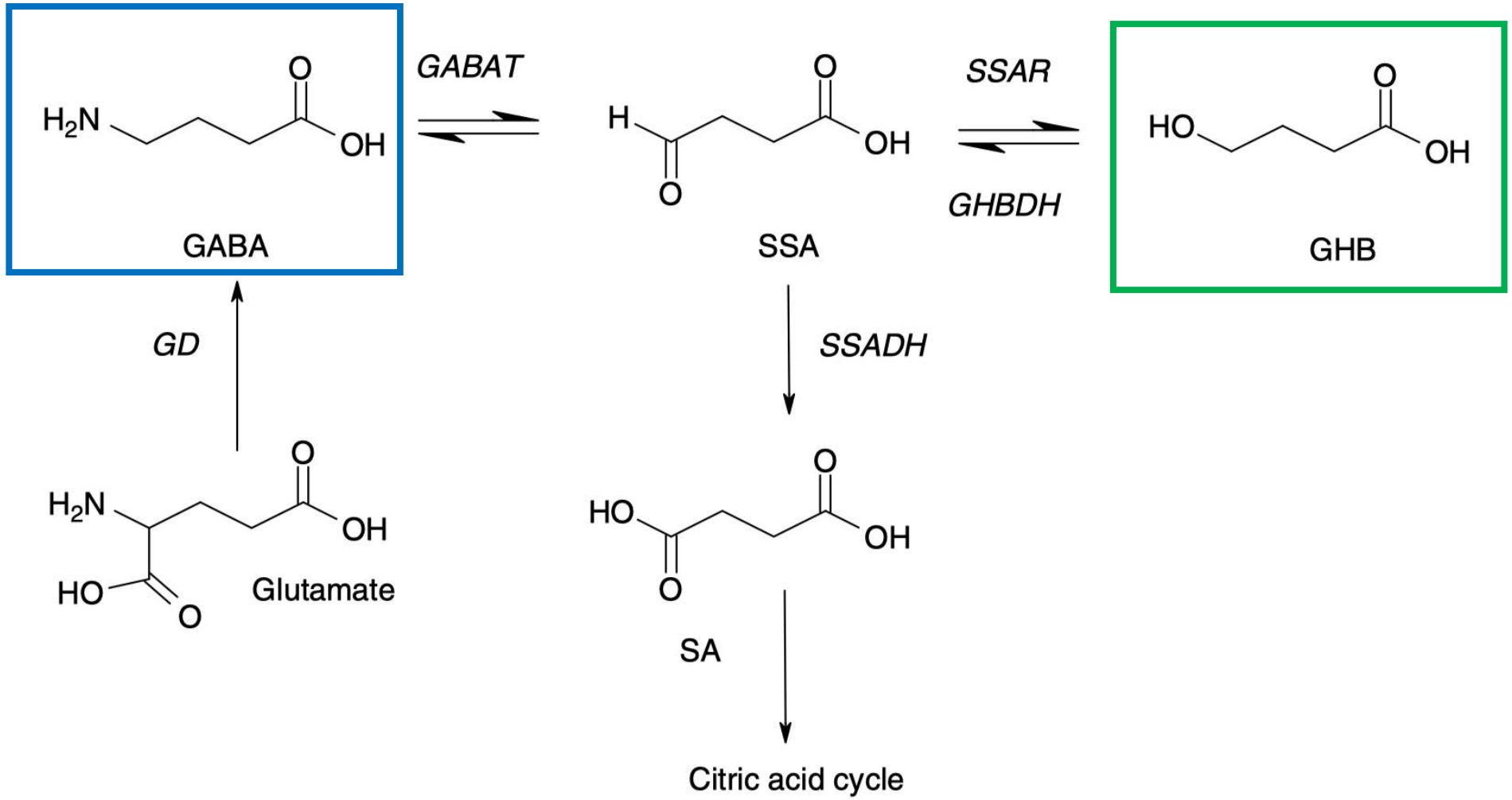
No party, no drugs? Use of stimulants, dissociative drugs, and GHB/GBL during the early COVID-19 pandemic

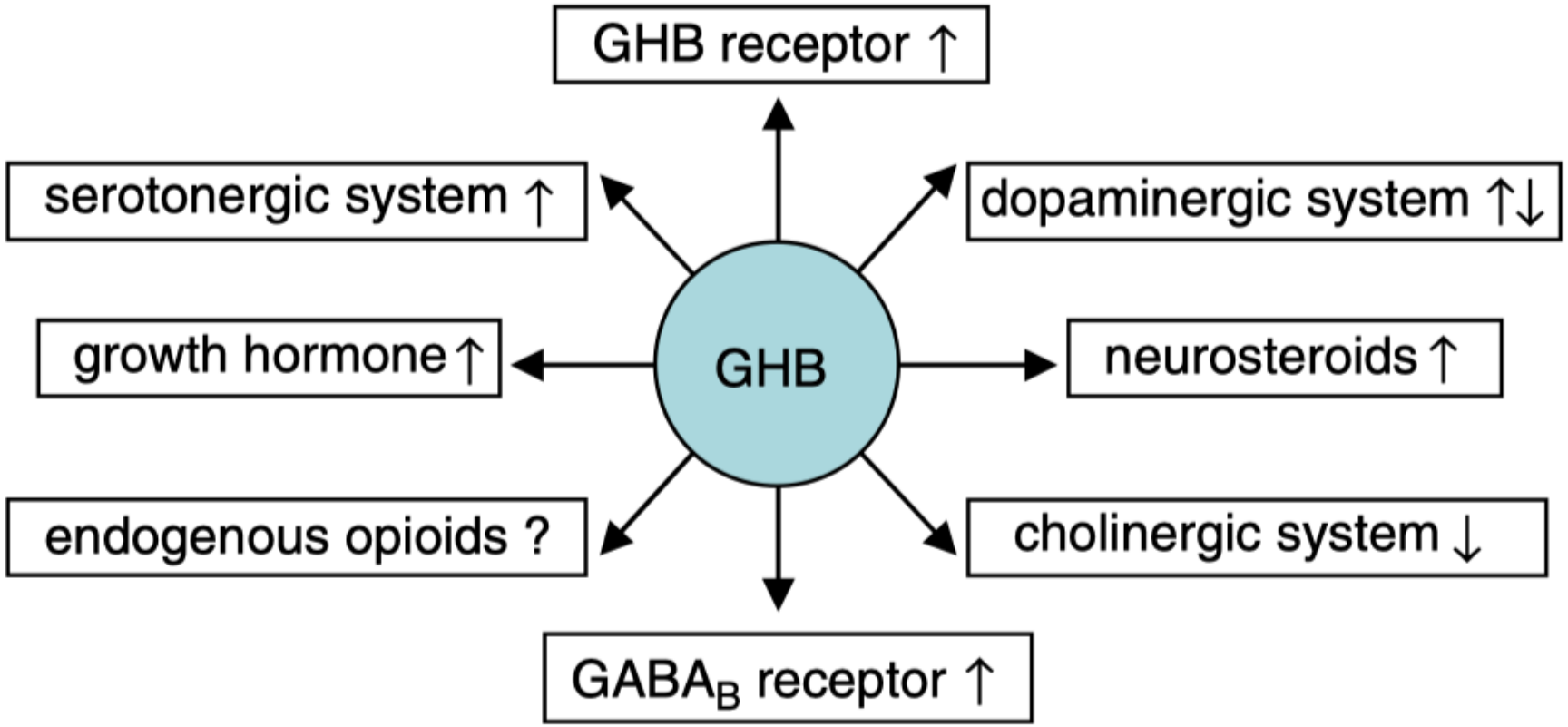
Antonia Bendau[a], Leonard Viohl[a], Moritz Bruno Petzold[a], Jonas Helbig[a], Simon Reiche[a,b], Roman Marek[b,c], Amy Romanello[a,b,d], Daa Un Moon[a], Rosa Elisa Gross[a], Dario Jalilzadeh Masah[a], Stefan Gutwinski[a,b], Inge Mick[a], Christiane Montag[a], Ricarda Evens[a,b], Tomislav Majić[a,b], Felix Betzler[a,*]

- Trends
  - Decreased → 48.0–64.8%
  - Maintained → 11.9–25.5%
  - Increased → 23.6–29.1%
- Biggest Changes
  - MDMA/ecstasy = ↓
  - GHB/GBL + dissociative = ↑
- Motivations → mood-related factors
  - Exhilaration
  - Euphoric
  - High or Buzzed
- Use for pandemic-related stressors
  - 16.4–35.6%
  - → Increased consumption frequency

Pharmacology



Pharmacodynamics



Pharmacodynamics

- **GHB-R agonist**
  - Excitatory GPCR → ↑ glutamate and ↑ DA
    - *Downstream → suppress NMDA components of excitatory transmission*
  - Presynaptic R → ↓ GABA release

      - → Sympathetic/stimulant effects, myoclonus, seizures
      - → Prolactin/GH release

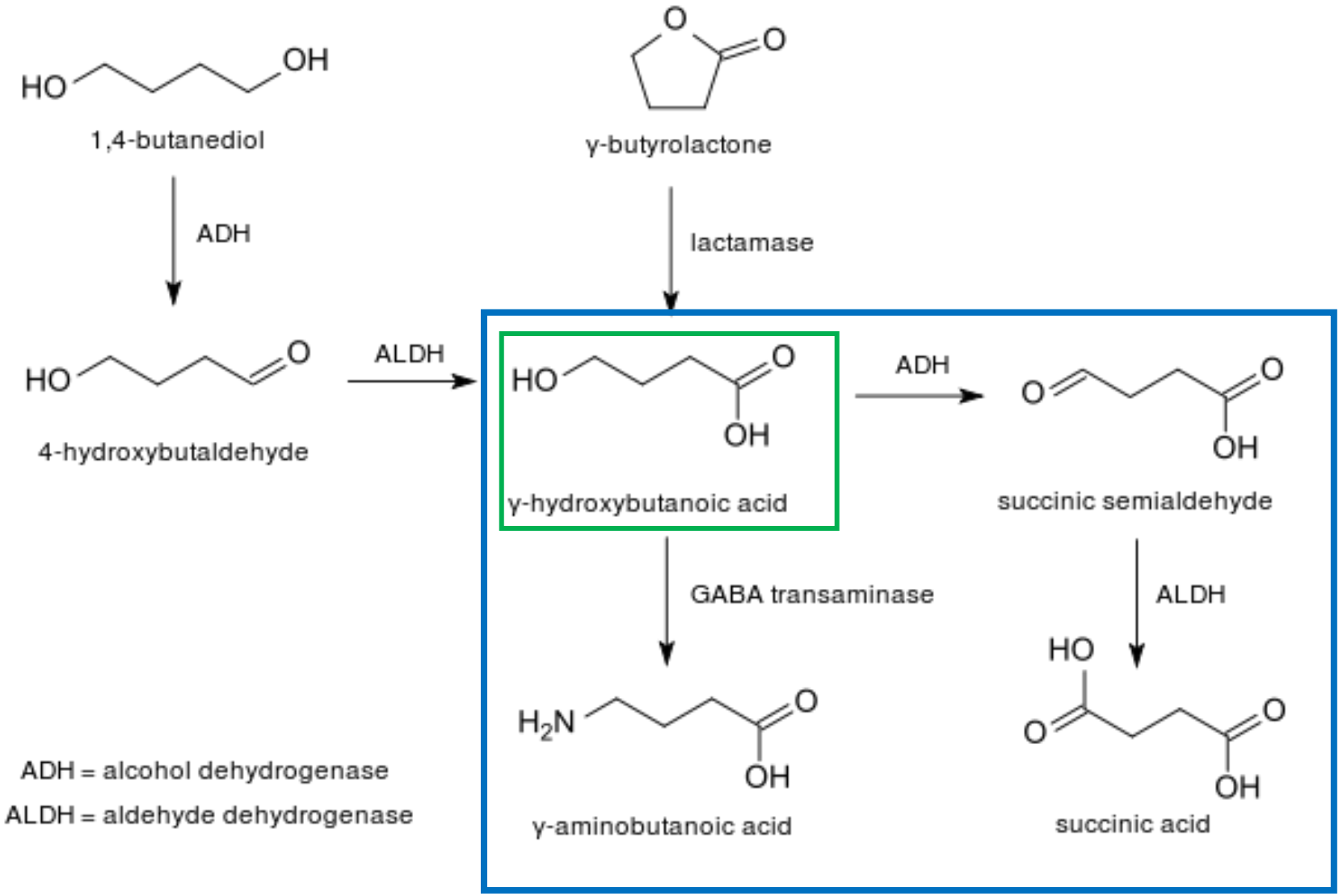
- **GABA-B agonist**
  - Inhibitory GPCR

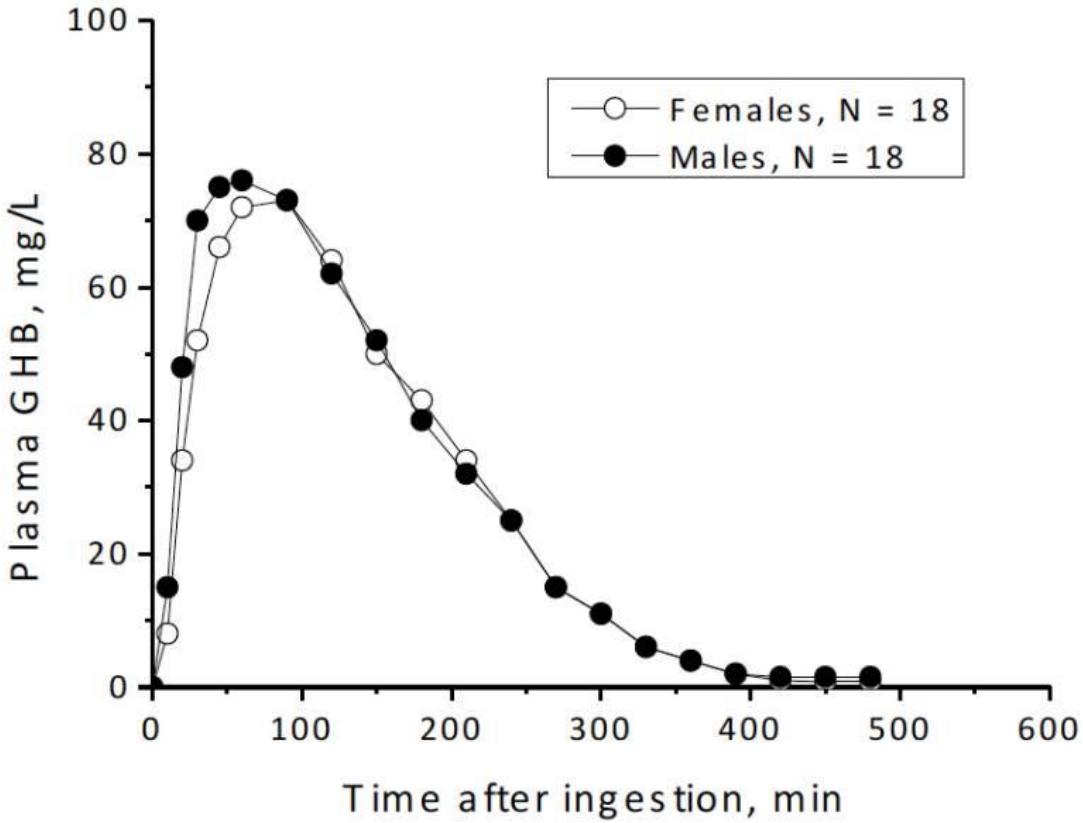
      - → CNS depression, confusion, psychosis, psychomotor impairment, amnesia

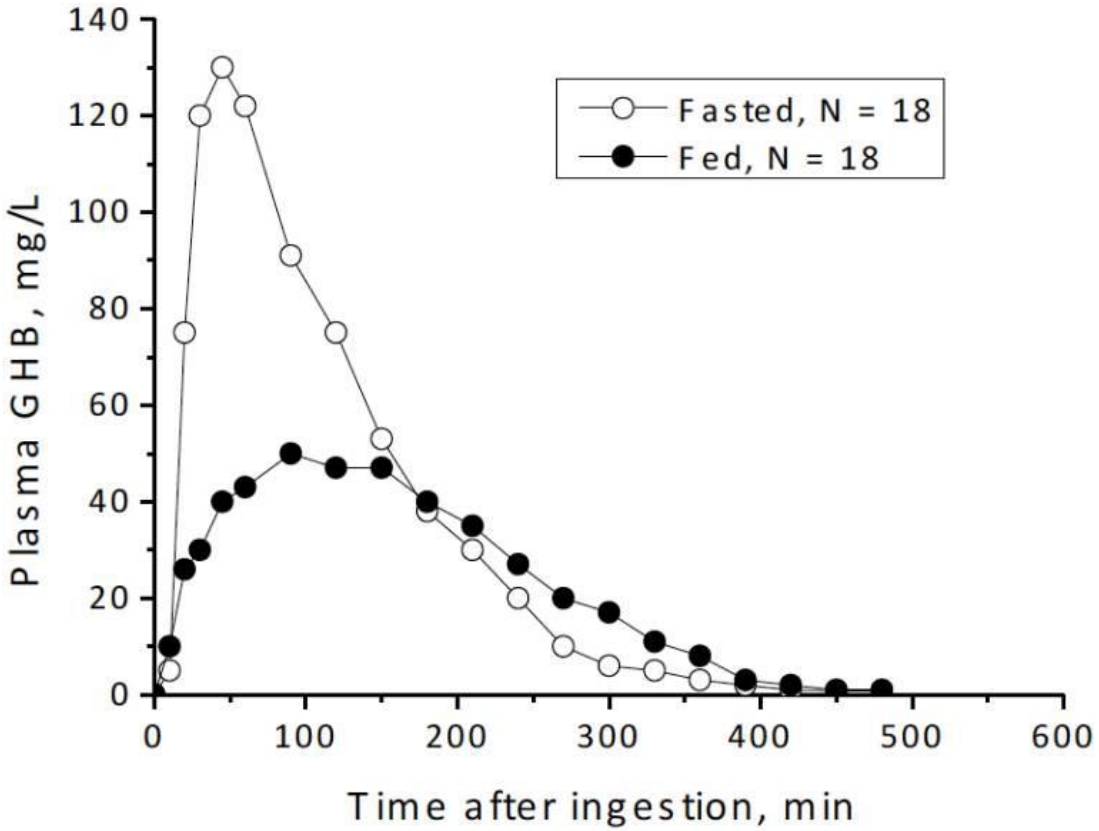
- High doses
  - ↑ GABA → **GABA-A agonist** + **GABA-B agonist**

Pharmacokinetics

- Rapid absorption and elimination
- PO bioavailability ~25-30%
- Low Vd and P.B.
- Urine GHB = 1.2-5 %







Mean (Range) of GHB Concentration, mg/L	Clinical Observations/Hypnotic Effects1
311 (244-395)	Deep sleep (no response to stimuli)
224 (151-293)	Medium sleep (blinking)
135 (63-162)	Light sleep (occasioanl eye opening)
47 (0-99)	Awake

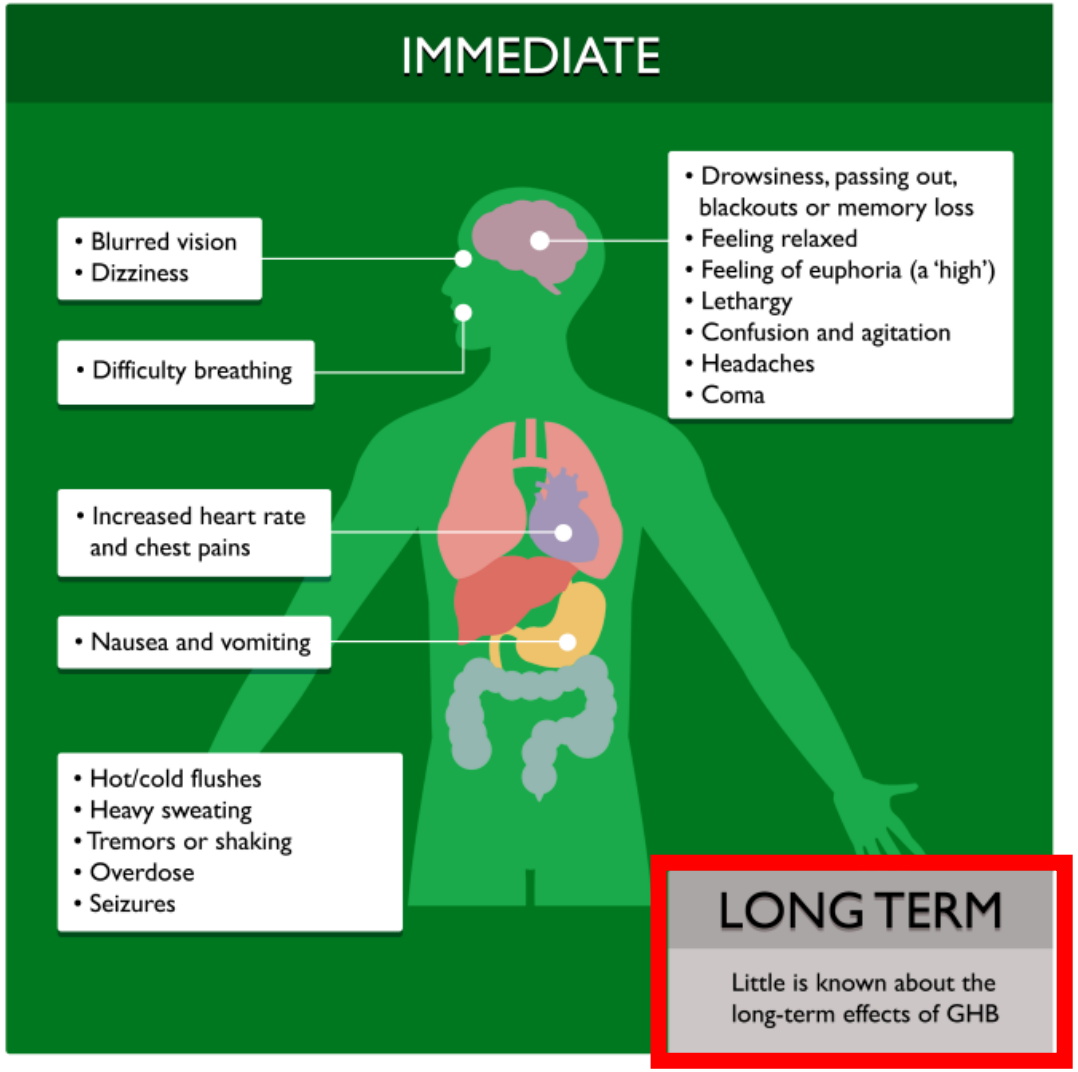
Busardò FP, Jones AW. GHB pharmacology and toxicology: acute intoxication, concentrations in blood and urine in forensic cases and treatment of the withdrawal syndrome. *Curr Neuropharmacol*. 2015;13(1):47-70.

Acute GHB toxicity

- Dose-related CNS depression → coma
  - Myoclonus
  - Hypoventilation (worse with EtOH)
  - Hypothermia (mild)
  - Bradycardia
  - Miosis
  - Amnesia

- Psychomotor agitation common
- Abrupt onset → sudden awakening/resolution
- Co-intoxicants common

- Treatment:
  - Supportive: IVF, rarely peripheral pressors



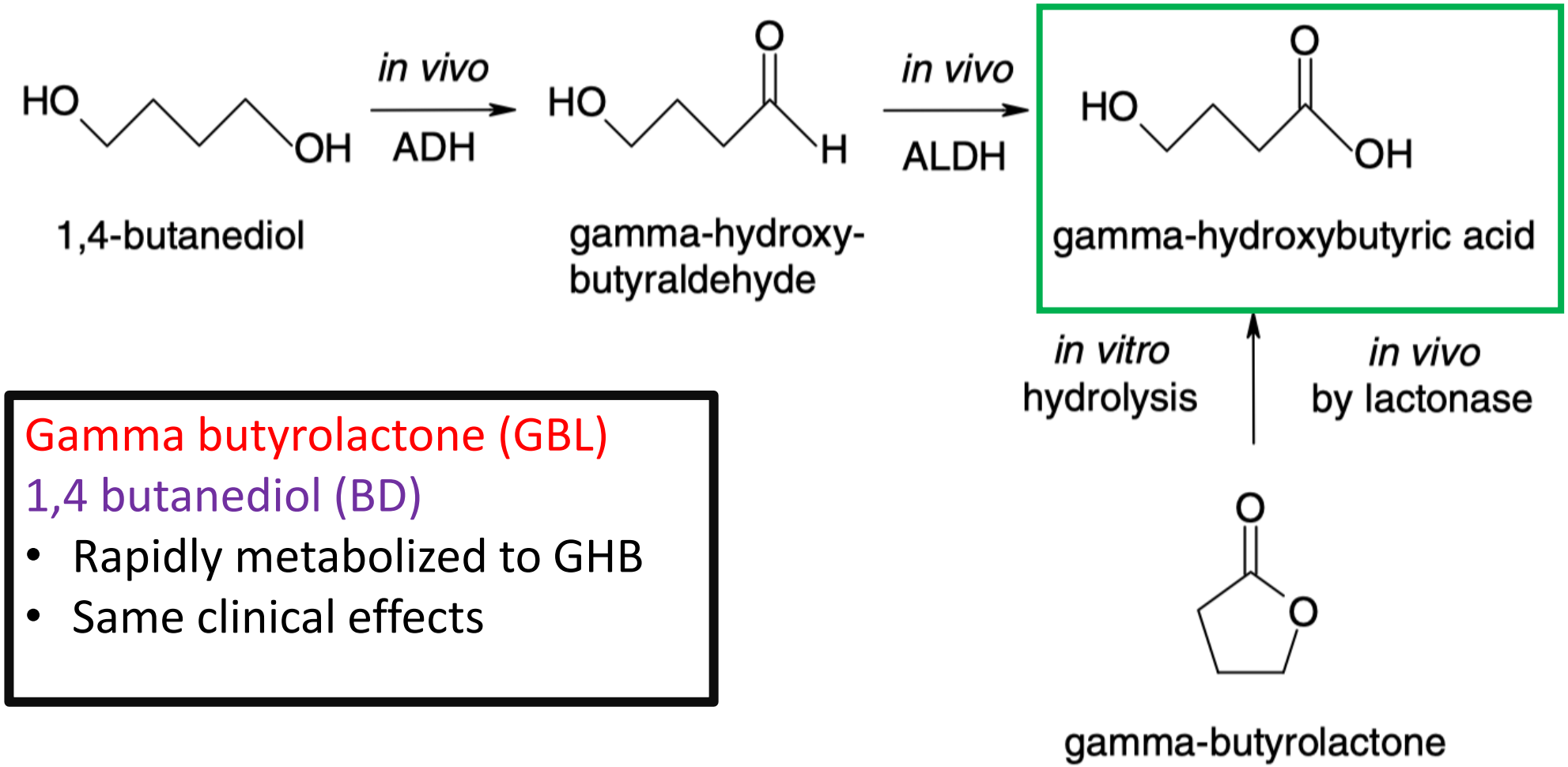
Diagnostic testing

- Difficult diagnosis…
  - Nonspecific symptoms
  - Produced endogenously + short $t_{1/2}$
    - → rapid clearance from urine/blood
  - GHB not detected on a routine hospital immunoassays

- Definitive confirmation
  - GC/MS

- Suspicion of drug-facilitated sexual assault
  - First-catch urine, if possible

GHB analogs: GBL and BD



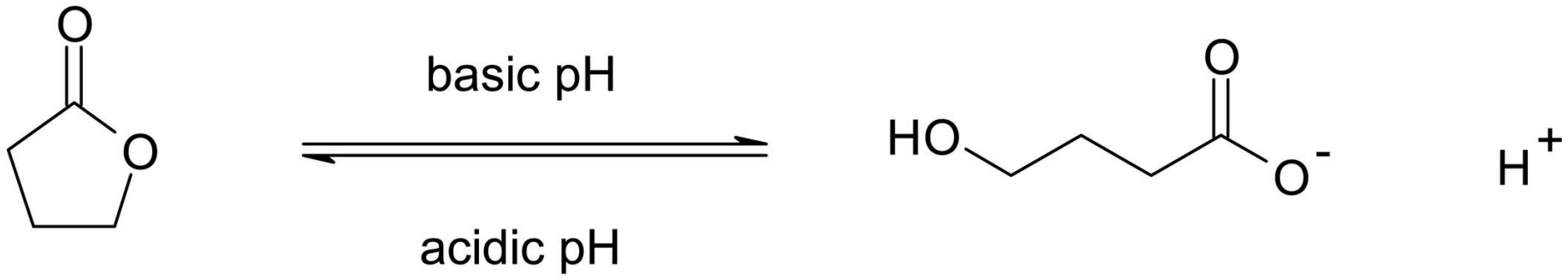
Gamma butyrolactone (GBL)

1,4 butanediol (BD)

- Rapidly metabolized to GHB
- Same clinical effects

GBL (gamma-butyrolactone)

- Endogenous lactone of GHB → ↑ lipophilicity
- In animals: more rapid absorption and prolonged hypnosis



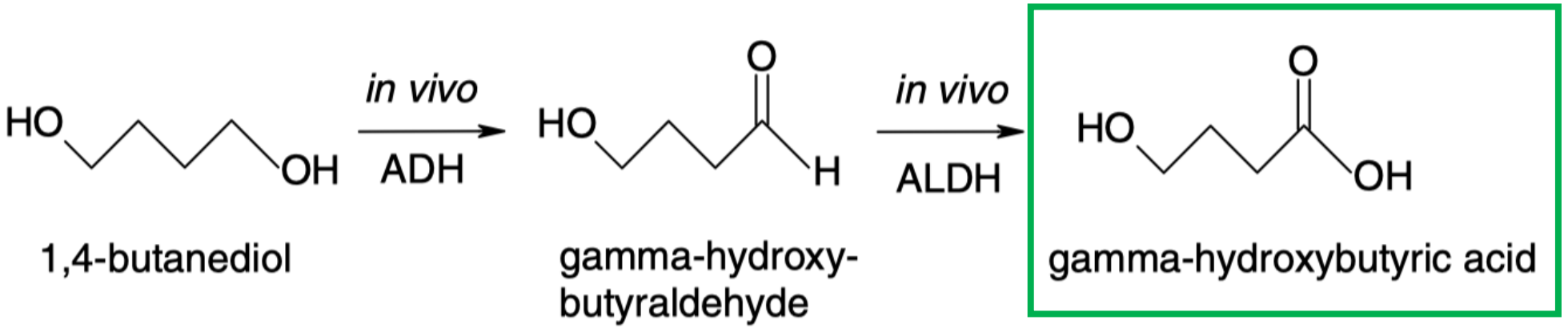
pH < 2

pK_a = 4.72

K_a = pH dependent!

BD (1,4 butanediol)

- Aliphatic alcohol
- Ethanol may alter the pharmacokinetics of BD
  - → Delayed and/or prolonged clinical course



GHB and SUD

- GHB is highly addictive

- What leads to a SUD?
  - Occasional use → unlikely
  - High doses, increased frequency, strong environmental stimuli → more likely

- Repeated doses/use often in the setting of insomnia
  - GHB → rebound insomnia or alertness after 2-3 hours of sleep
    - Complicated effects on sleep cycle

Lapierre O, Montplaisir J, Lamarre M, Bedard MA. The effect of gamma-hydroxybutyrate on nocturnal and diurnal sleep of normal subjects: further considerations on REM sleep-triggering mechanisms. *Sleep*. 1990;13(1):24-30.

GHB withdrawal syndrome

GHB withdrawal

- Chronic GHB use → tolerance
  - Downregulation of inhibitory GABA and GHB receptors
- Abrupt cessation
  - ↓ GABA/GHB-mediated neuroinhibition → unopposed excitatory neurotransmission
- GHB withdrawal is generally like alcohol or benzodiazepine withdrawal…
  - More rapid and abrupt onset
  - Severe/prolonged neuropsychiatric symptoms (delirium, psychosis)
  - Less severe autonomic disturbances

GHB withdrawal

- Symptom onset = 1-6H
- **Early/mild**
  - Anxiety
  - Tremor
  - Diaphoresis
  - Insomnia
  - Tachycardia
- Can rapidly progress to severe agitation, delirium, and seizures

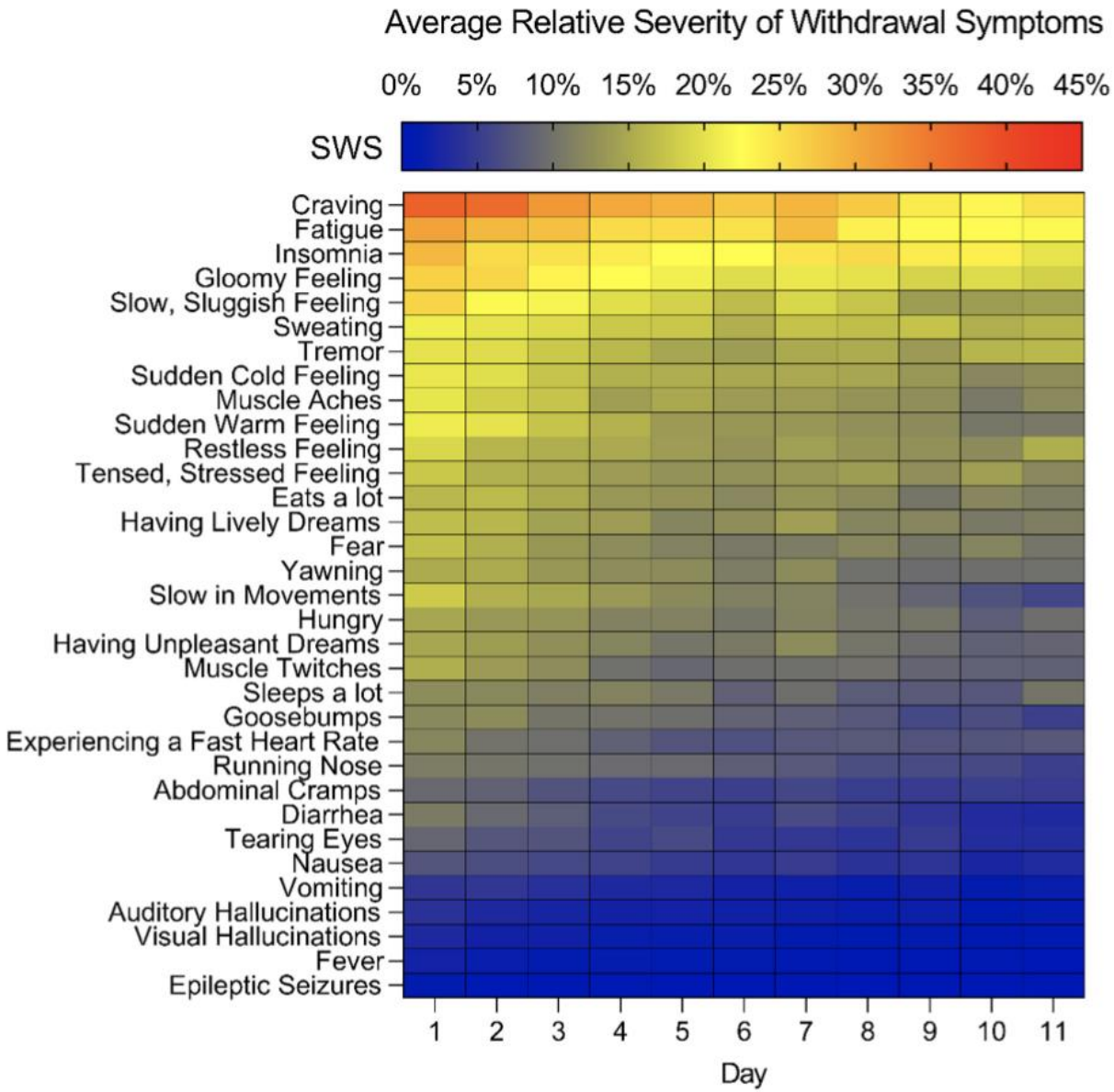
Kamal RM, van Noorden MS, Franzek E, Dijkstra BAG, Loonen AJM, De Jong CAJ. The Neurobiological Mechanisms of Gamma-Hydroxybutyrate Dependence and Withdrawal and Their Clinical Relevance: A Review. *Neuropsychobiology*. 2016;73(2):65-80.

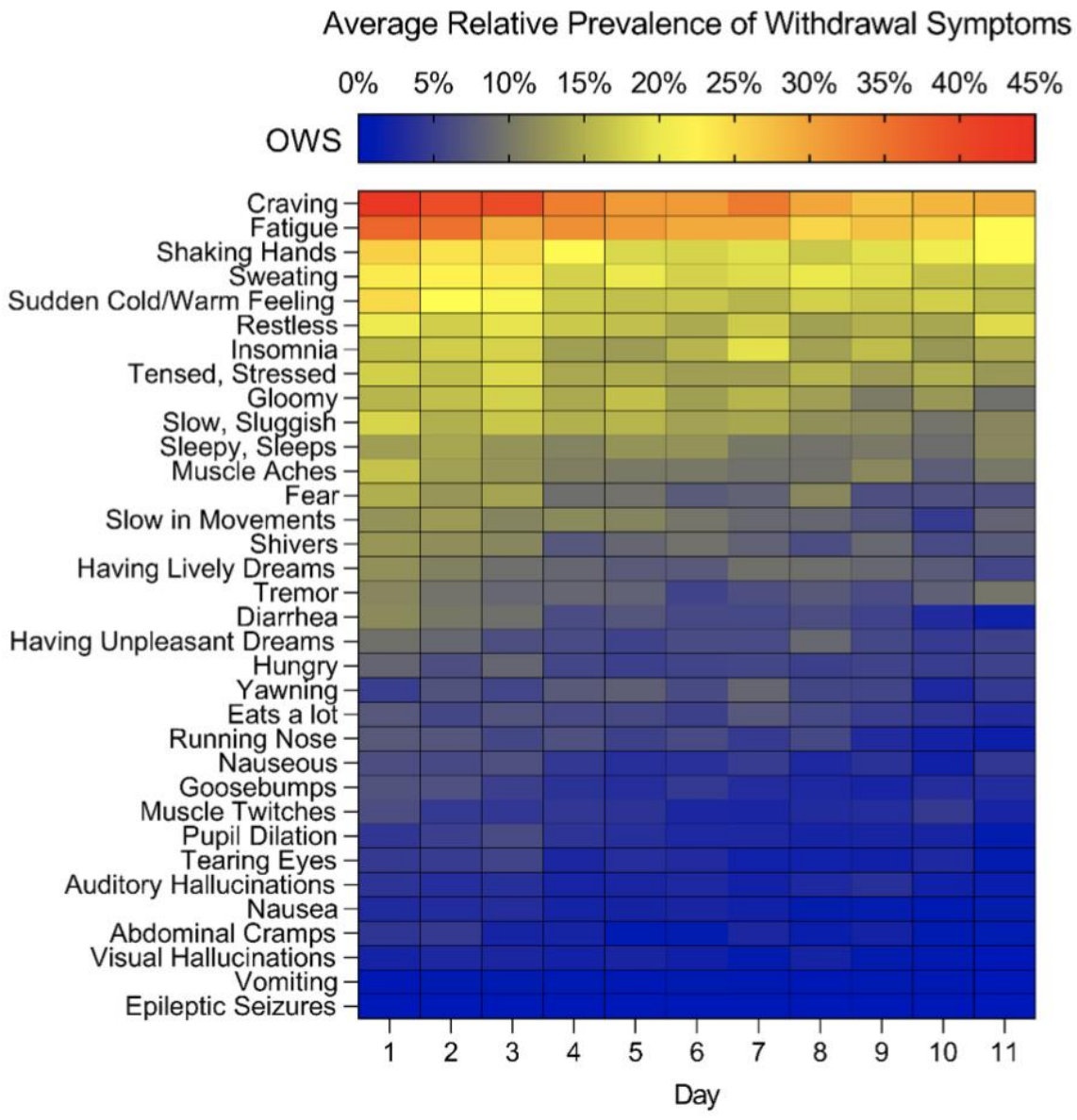
Characterization of the GHB Withdrawal Syndrome

Casper J. H. Wolf [1,2,3,*], Harmen Beurmanjer [3,4], Boukje A. G. Dijkstra [3,4], Alexander C. Geerlings [1], Marcia Spoelder [2], Judith R. Homberg [2] and Arnt F. A. Schellekens [1,3]

- Subjective
  - Cravings, fatigue, insomnia, sweating and feeling gloomy
- Objective
  - **Cravings**, **fatigue**, tremors, **sweating**, and sudden cold/warm feelings
- No association between vital signs and withdrawal symptoms
- Do not strongly differ from withdrawal syndromes of other sedatives

Wolf CJH, Beurmanjer H, Dijkstra BAG, Geerlings AC, Spoelder M, Homberg JR, Schellekens AFA. Characterization of the GHB Withdrawal Syndrome. *J Clin Med Res*. 2021;10(11). doi:10.3390/jcm10112333





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GHB withdrawal

- Unpredictable course
  - Apparent initial improvement → dramatic deterioration
- Profound insomnia common
  - Role in ongoing use, withdrawal severity, decision to seek treatment, relapse
  - Exacerbates psychosis and delirium
- Who develops withdrawal?
  - Higher daily dose, increased dosing frequency
    - Often >30g GHB or >15g GBL daily; 3+ times daily, or doses 2-3H doses
    - GHB ρ = 1.13g/mL

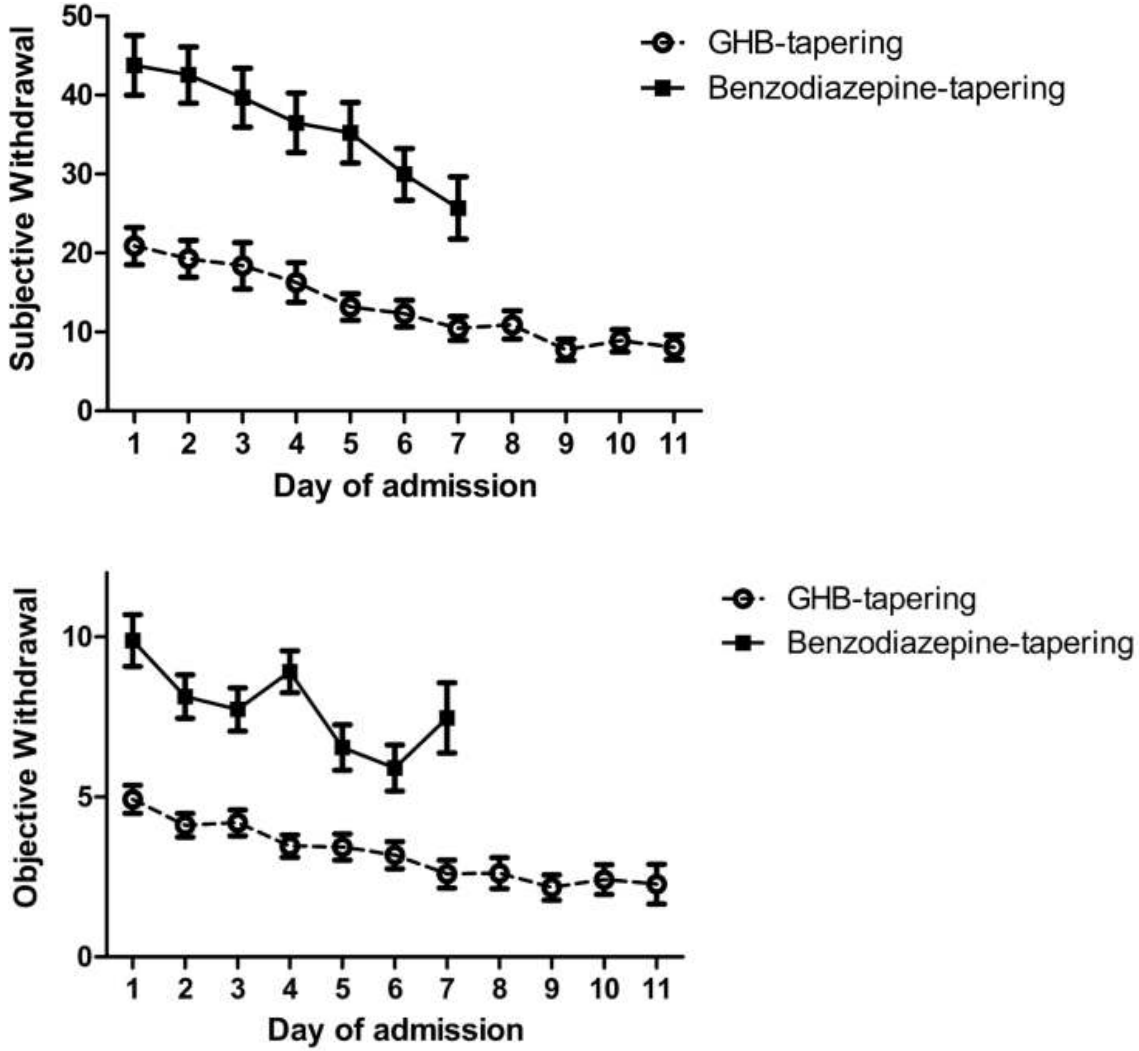
Lapierre O, Montplaisir J, Lamarre M, Bedard MA. The effect of gamma-hydroxybutyrate on nocturnal and diurnal sleep of normal subjects: further considerations on REM sleep-triggering mechanisms. *Sleep*. 1990;13(1):24-30.
Kamal RM, van Noorden MS, Franzek E, Dijkstra BAG, Loonen AJM, De Jong CAJ. The Neurobiological Mechanisms of Gamma-Hydroxybutyrate Dependence and Withdrawal and Their Clinical Relevance: A Review. *Neuropsychobiology*. 2016;73(2):65-80.

Withdrawal management

- Supportive care is bedrock of treatment
- Pharmacotherapy?

Pharmacotherapy for GHB withdrawal

- GHB
  - Robust inpatient studies in Europe
  - Pharmaceutical GHB titration and taper protocol
- Benzodiazepines
  - Low rates of psychosis, delirium, and other complications (outpatient)
  - BZD refractory cases reported
- Baclofen
  - Decrease cravings
  - Often used in conjunction with BZD



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Baclofen + Diazepam

- Multiple case reports/series
- Baclofen 10mg TID + diazepam (variable dose)
  - Diazepam 10-20mg TID, sometimes up to 35mg TID
- Baclofen preloading?
  - Start baclofen 2 days prior to detoxification
    - Lower BZD dose, improved symptom control, shortens overall course
- Baclofen withdrawal?
  - Something to consider but has not been described in this setting

My approach to GHB withdrawal

- Baclofen + diazepam
  - If possible, start baclofen 10mg TID 2 days prior to stopping GHB
- Diazepam dose and level of care depend on severity of SUD
  - High GHB dose and dosing frequency
  - Co-intoxicants (sedatives), reliable follow up, Unwilling to be admitted?
- Starting dose:
  - Diazepam 10-20mg TID + baclofen 10mg TID
  - Low threshold to increase diazepam for persistent symptoms
- Once dosing has been established, plan to begin slow taper on diazepam and baclofen over 1-3 weeks

Take home points

- GHB and analogues are commonly used in Chemsex (often meth) by the MSM community and cause sedation, euphoria, disinhibition, and increased sexual awareness
- GHB toxicity is characterized by CNS depression/coma, amnesia, myoclonus, and sometimes psychomotor agitation; it has rapid onset followed by abrupt resolution and is difficult to detect
- BD and GBL are industrial solvents and GHB analogues metabolized to GHB *in vivo*
- GHB withdrawal syndrome is like those of other sedative-hypnotics but with less autonomic disturbances + more severe insomnia and neuropsychiatric manifestations
- GHB withdrawal can be treated with BZD and/or baclofen

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