SEDATIVES

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Financial Disclosures

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Outline

1. Historical View
2. Neurobiology
3. Epidemiology
4. Risk and Benefits of Benzodiazepines
5. Phases of Sedative-Hypnotic Treatment and related Syndromes

6. Selective nonbenzodiazepine hypnotic agents
7. Barbiturates
8. GHB
9. Conclusions

Historical View

- First half of XX century Barbiturates (starting with Barbital)
- 1950 Meprobomate
- 1950s Benzodiazepine were introduced as substitute for barbiturates (starting with Chlordiazepoxide)
- 1960s Benzodiazepines widely available and prescribed
- 1970s Benzodiazepines became the most commonly prescribed of all medications around the world

Historical View

- 1980s Identification of medication losing efficacy over time and became associated with adverse effects
- 1990s Short acting benzodiazepines
- 2000s (drug tolerance and withdrawal) Not sufficient for dependence and nonbenzodiazepine hypnotic agents; elderly population risks
- 2014-present DSM 5 (sedative use disorder); guidelines adopted regarding use

Types of Sedatives

- BZ- receptor agonist (BZRA)

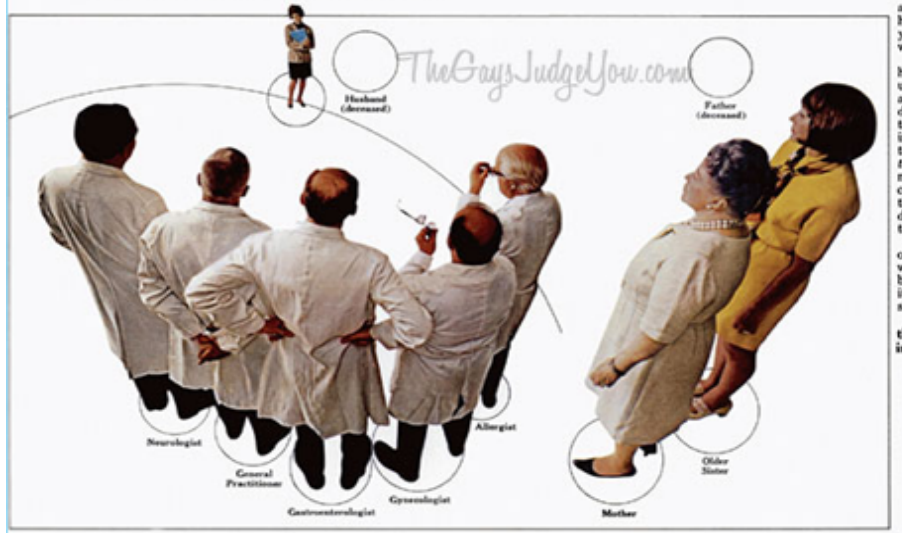
  - Benzodiazepines

  - Selective non-benzodiazepine hypnotics (Z-drugs)

- Barbiturates

- Others: GHB and Paraldehyde, chloral hydrate, meprobomate

Her world orbits around doctors. Psychic tension rules her universe.



This childless widow's interpersonal relationships, sociometrically diagrammed, reveal the patterns of dominance, closeness, absence, and loss created by the principal people in her life.

Her mother's obvious preferenc for her older sister has always rankled this patient. The deaths of her father an husband accentuated her alienation an hostility. Hypochondriasis is the way she disowns her conflicts.

While you gradually turn her away from somatic concerns and guide her through old, hidden problem areas you can ease her undue psychic tension with Valium® (diazepam).

Valium 10-mg tablets *q.i.d.* can help most psychoneurotic patients undergoing severe psychic tension and apprehension with or without associate depressive symptoms. The fourth table taken at bedtime, can combat anxiety-induced sleeplessness. For less severe tension states, Valium 5-mg tablets *t.i.d.* or *q.i.d.* may be adequate. Drowsi ness, fatigue and ataxia are the most commonly reported side effects. Tailor the dosage to the individual—a procedure facilitated by the three convenien tablet strengths.

For hypochondriacs—and many other types of psychoneurotic patients walled in by situational stress—Valium by relieving psychic tension, may prov itself a useful adjunct to your healing skills.

Please see last page of this advertisement for prescribing information.

Valium®
(diazepam)
2-mg, 5-mg, 10-mg tablets

ROCHE Roche Laboratories Division of Hoffmann-La Roche Inc. Nutley, N.J. 07110

Syndromes of the 1960s

The battered parent syndrome

She's the paradox of our age. Compared to her mother, she has more education, more usable income and more labor-saving devices. Yet she is physically and emotionally overworked, overwrought and—by the time you see her—probably overwhelmed.

What went wrong? Is parenthood something other than the rosy fulfillment pictured by the women's magazines? Is anxiety and tension fast becoming the occupational disease of the homemaker?

Some say it's unrealistic to educate a woman and then expect her to be content with the Cub Scouts as an intellectual outlet.

Or to grant that she is socially, politically and culturally equal, while continuing to demand domestic and biological subservience.

Or to expect her to shoulder the guilt burden of this child-centered age without unraveling around the emotional edges.

Or to compete with her husband's job for his time and involvement.

But whatever the cause, the consequences—anxiety, tension, insomnia, functional disorders—fill waiting rooms.

Sometimes it helps to add 'Miltown' to her treatment—to help her relax both emotional *and* muscular tension. It's no substitute for a week in Bermuda, or for emotional readjustment. But it will often make the latter easier for her, as well as for the physician.

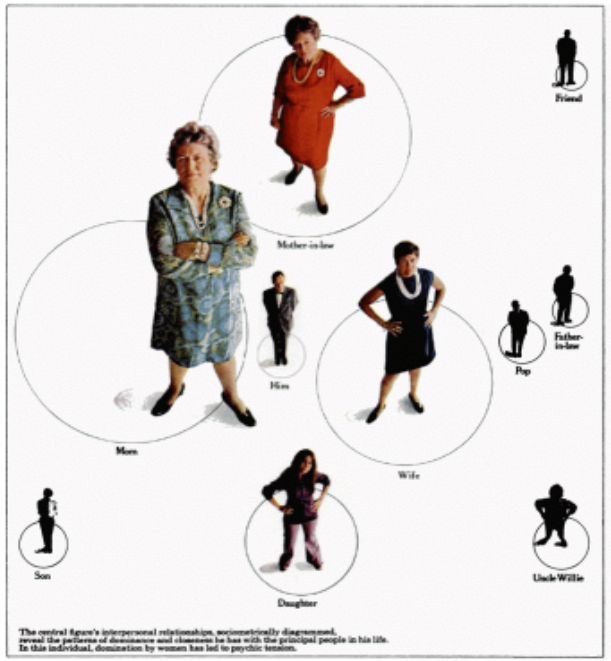
And 'Miltown' has been doing just that—for a dozen years now—with substantial success.

Indications: Effective in relief of anxiety and tension states; adjunctively when anxiety may be a causative or disturbing factor. Fosters normal sleep through anti-anxiety and muscle-relaxant properties.

Contraindications: Previous allergic or idiosyncratic reactions to meprobamate. *(Brief summary of prescribing information is continued on next page.)*

Wallace Pharmaceuticals/ *Cranbury, N.J.*

when reassurance is not enough **MILTOWN®**
(MEPROBAMATE)



The central figure's interpersonal relationships, sociometrically diagrammed, reveal the patterns of dominance and closeness he has with the principal people in his life. In this individual, domination by women has led to psychic tension.

Women dominate his universe

psychic tension can rule his life

He doesn't understand the source of his psychic tension. But you do. He relates well to women with domineering traits. But not to men. Not even his own son.

Whenever psychic tension is a significant component in the clinical profile, consider the use of Valium (diazepam). On proper maintenance dosage, Valium can help reduce the psychoneurotic patient's tension—anxiety, apprehension, agitation, alone or with depressive symptoms—to more comfortable and adaptable levels. The most commonly reported side effects are drowsiness, fatigue and ataxia.

For your passive-dependent, tension-ridden patient dominated by women—and for countless other psychoneurotics—Valium may prove itself a helpful partner to your psychotherapeutic skills.

Please see last page of this advertisement for prescribing information.

for the relief of psychic tension in psychoneurotic states
Valium®
(diazepam)
2-mg, 5-mg, 10-mg tablets
t.i.d.* and *h.s.

Case: RR

A year later, Mr. RR, 59-year-old Latino male with a past history of ETOH use disorder, anxiety, insomnia, and past medical history of HTN, GERD, and pancreatitis, arrives in the emergency department with a friend for confusion and diaphoresis.

Neurobiology ($GABA_A$ Receptor)

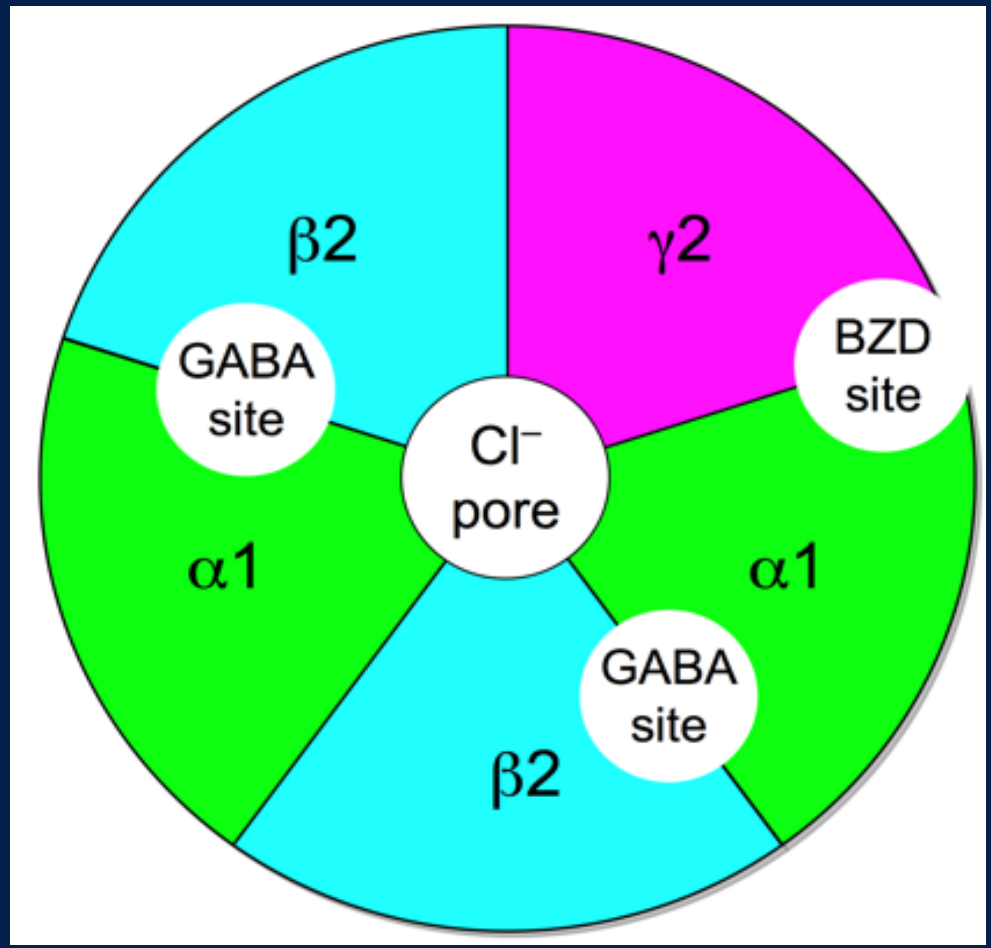
- GABA - the primary inhibitory neurotransmitter system in the CNS

- Transmembrane pentamer composed of:

  2α , 2β

  1γ

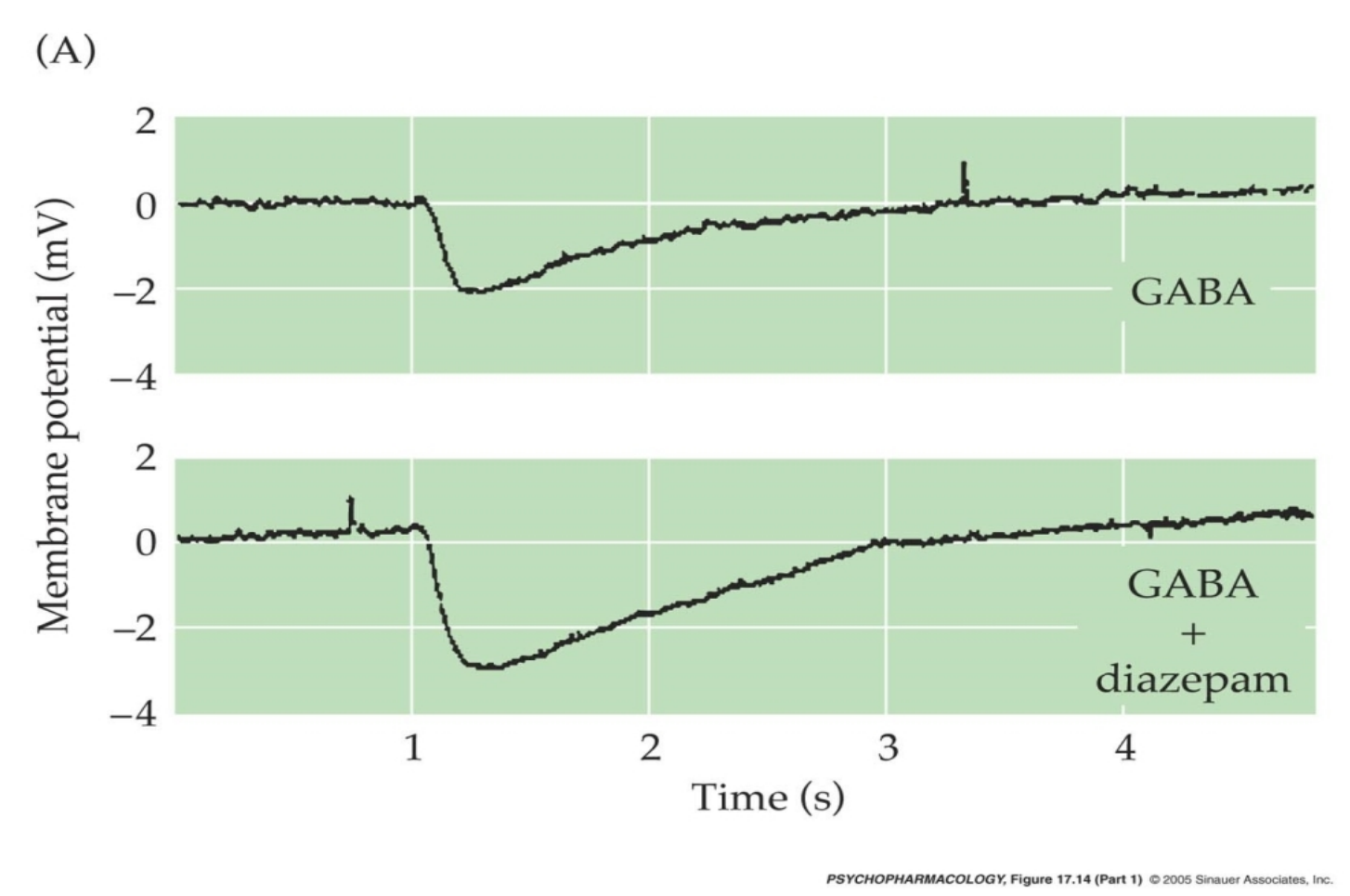
Neurobiology ($GABA_A$ Receptor)



Neurobiology ($GABA_A$ Receptor)

- GABA is estimated to be present in 40% of all synapses in the human brain
- It is an inhibitory neurotransmitter opposed to excitatory neurotransmitters such as glutamate.
- It reduces the excitability of the post synaptic side of the synapse
- 2 types : $GABA_A$ ionotropic (prominent target for drugs) and $GABA_B$ metabotropic
- BZDs increase the number of time the Cl- channel opens (frequency)
- BBTs increase the duration of the opening of the Cl-channel

Effects of GABA and diazepam (benzodiazepine) on membrane potentials and chloride flux



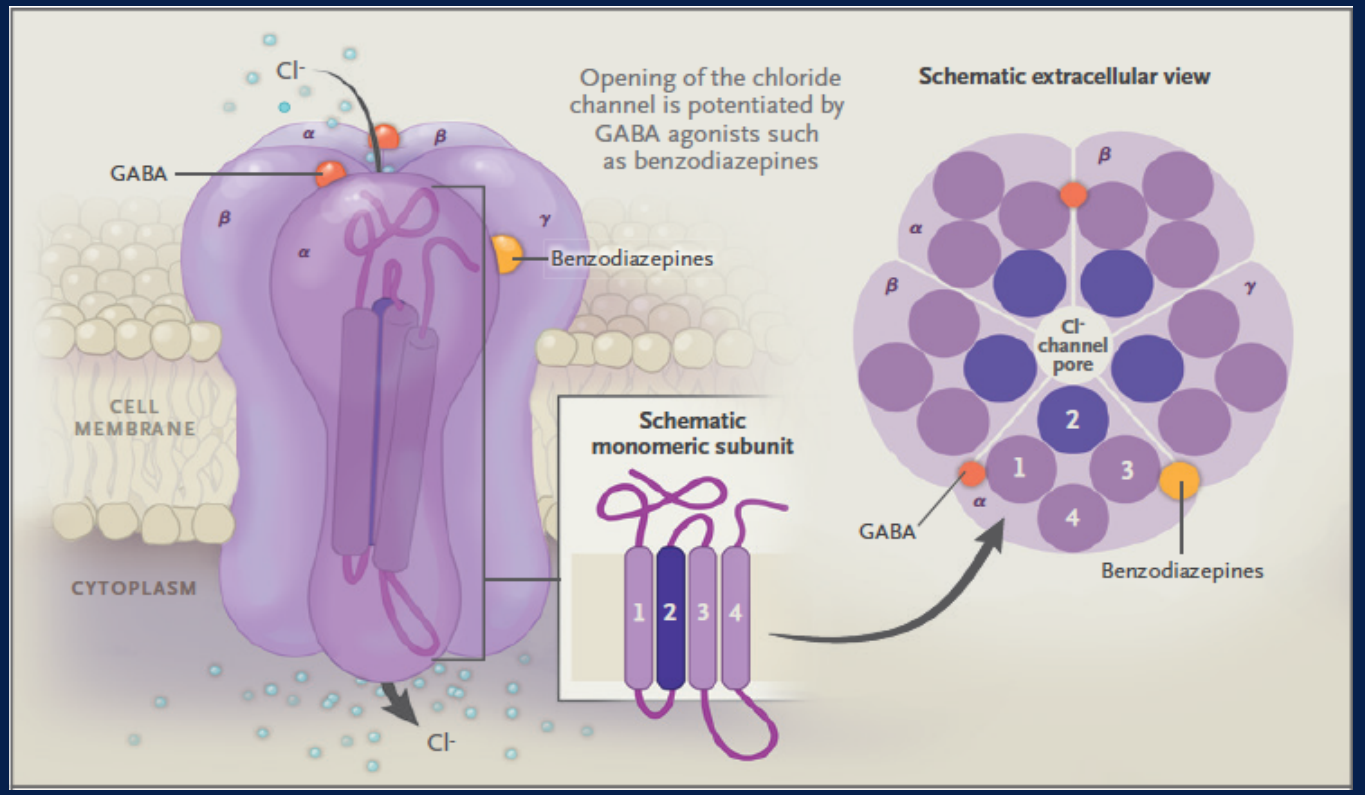
PSYCHOPHARMACOLOGY, Figure 17.14 (Part 1) © 2005 Sinauer Associates, Inc.

Neurobiology ($GABA_A$ Receptor)

Benzodiazepines require the presence of GABA

Barbiturates do not require the presence of GABA

Flumazenil blocks effects of benzodiazepine and zolpidem but not Barbiturates



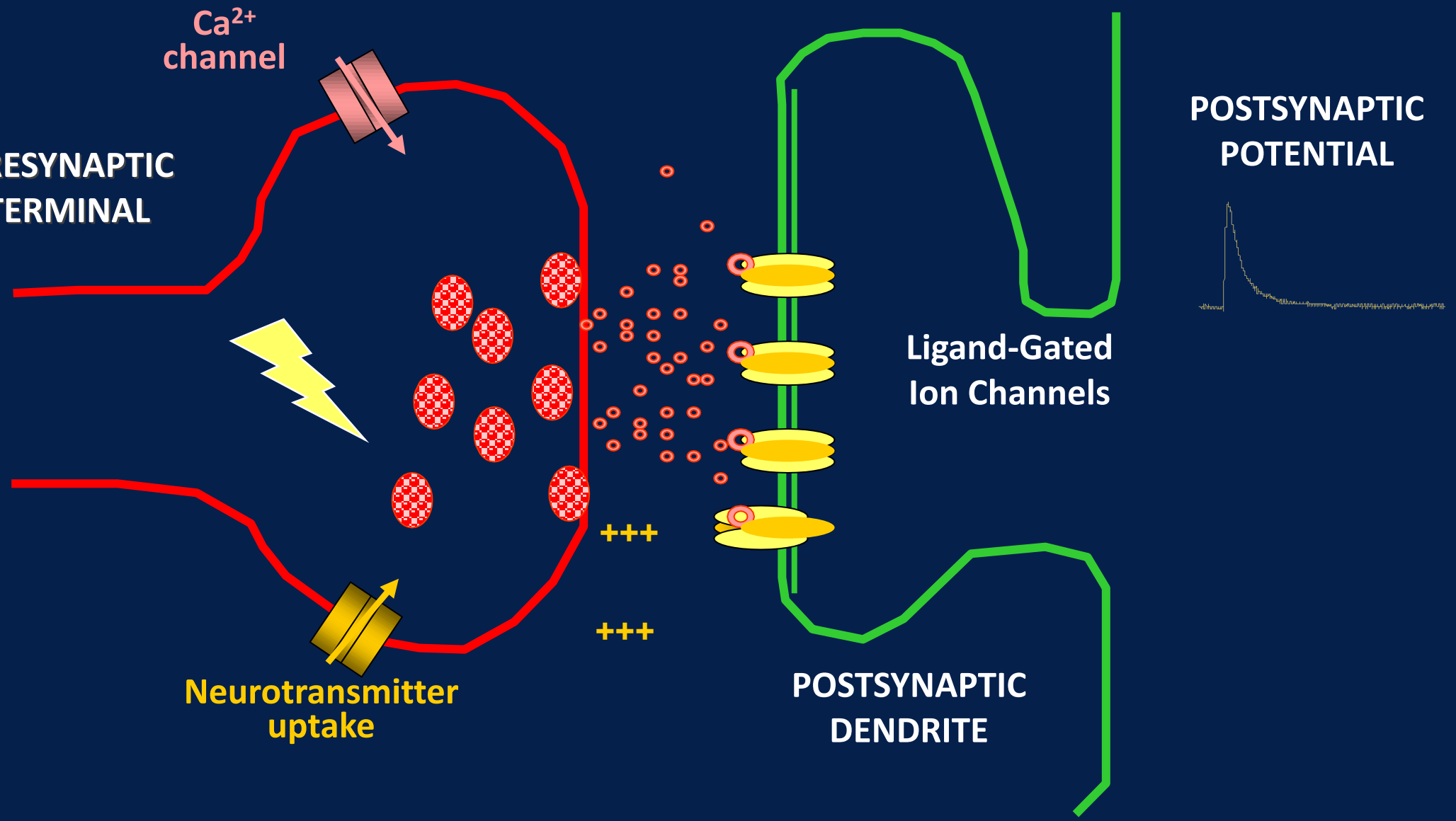
Soyka, N Engl J Med 2017; 376:1147-1157

Neurobiology ($GABA_A$ Receptor)

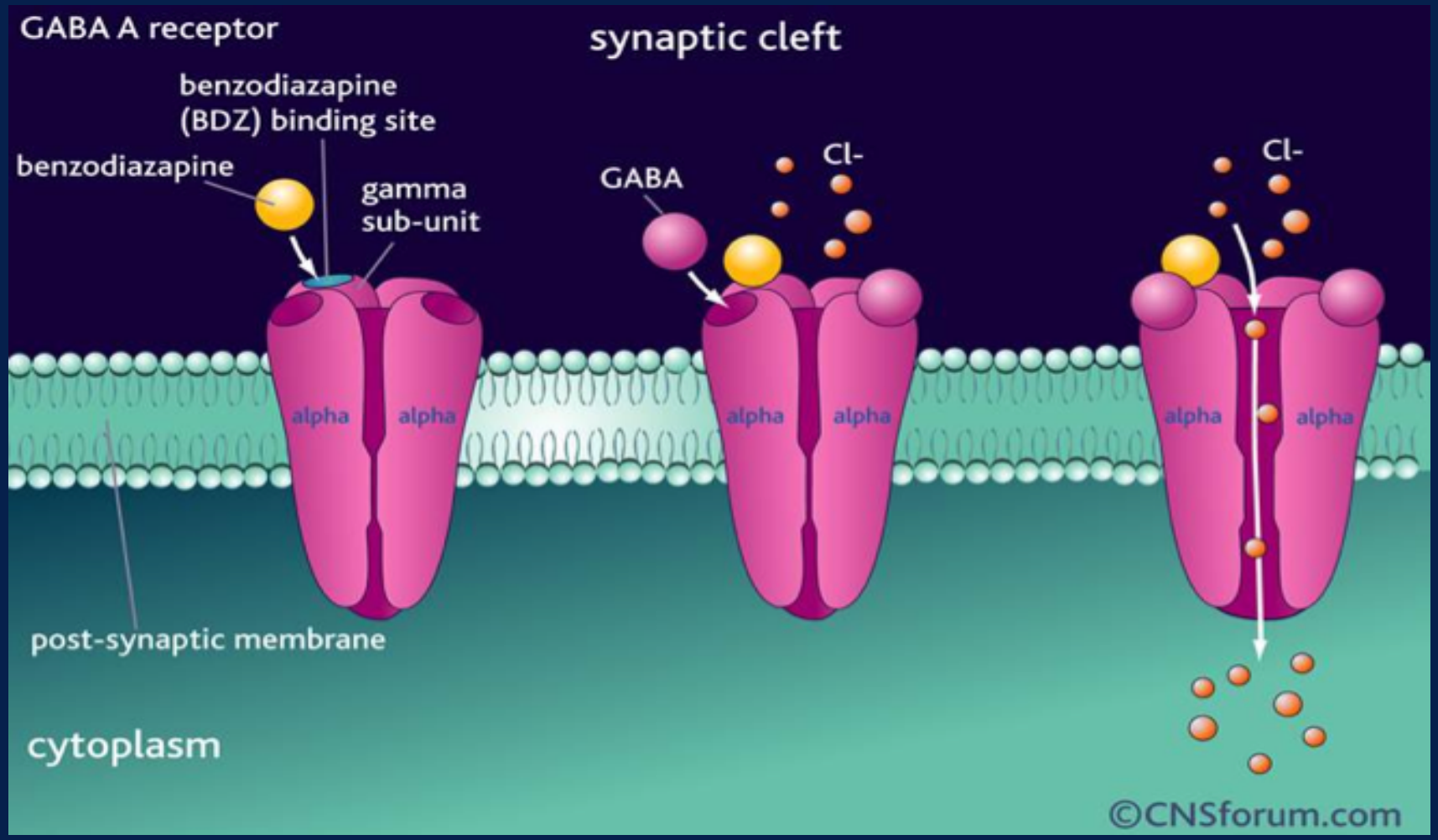
- Benzodiazepines
  - Bind a cleft of α and γ subunits
  - Increase the affinity of the receptor for GABA (frequency) : Chloride channel opening
  - BZD needs GABA

- Barbiturates (propofol):
  - Bind α subunit
  - Increase duration of channel opening
  - BBT does need GABA

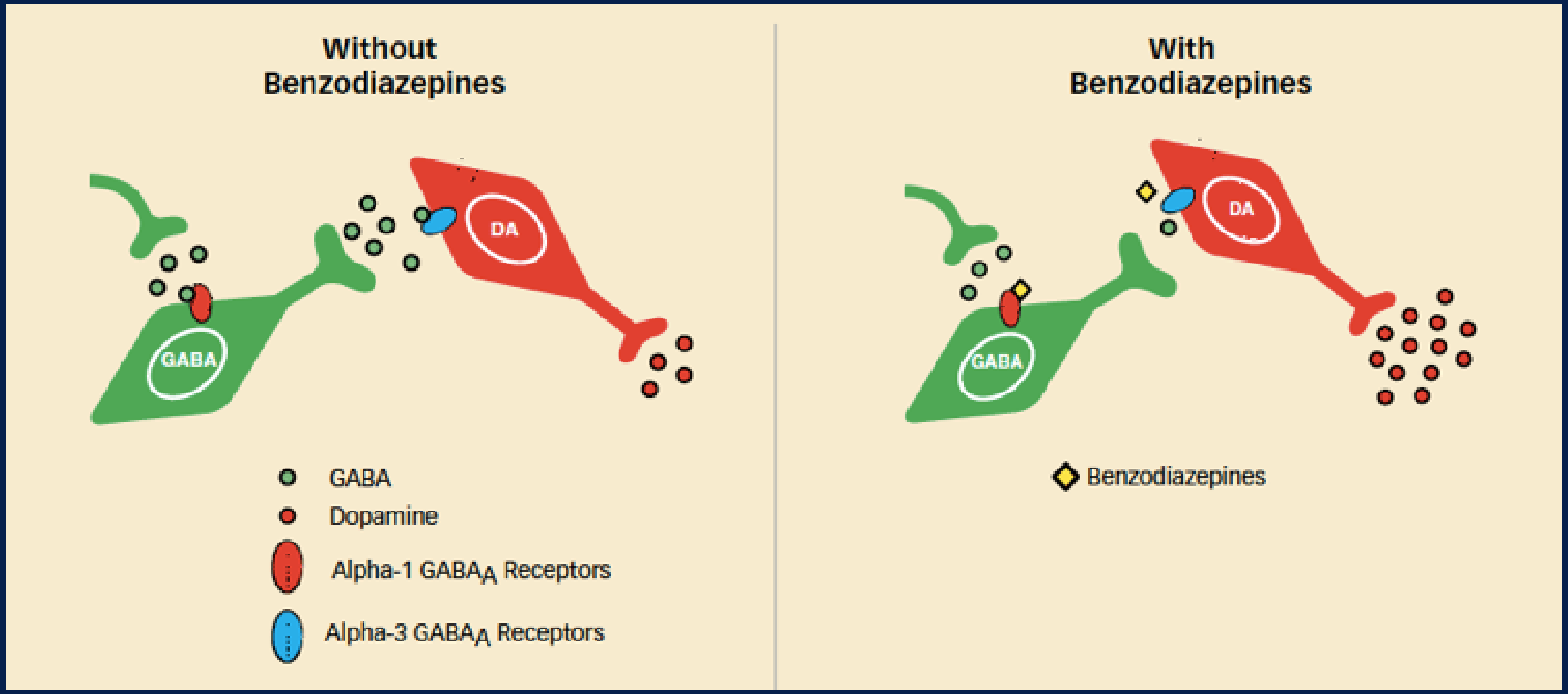
Steps in Synaptic Transmission



Neurobiology ($GABA_A$ Receptor)



Mechanism of Benzodiazepine Addiction (hypothesis)



Epidemiology

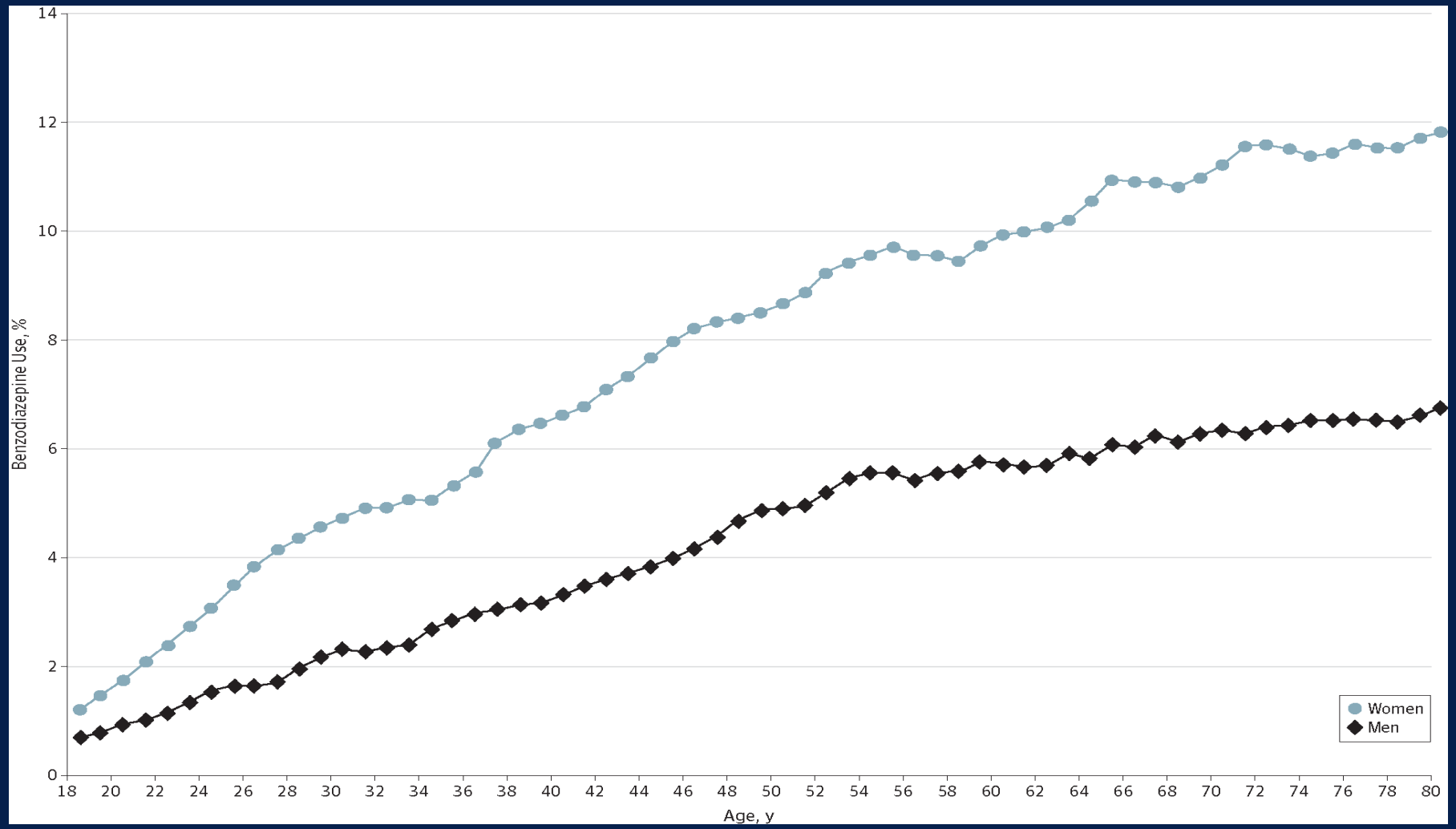
- 80% of pts with benzo use disorder use other drugs
- 30-50% of pts with ETOH use disorders in detox and 44% of IV drug user also use BZD
- Average benzodiazepine use is about 2 c:: 1

- Use of benzodiazepines increases with age
- In the US, roughly 9 of 10 older adults who use benzodiazepines on a long-term basis are prescribed by PCP

Epidemiology

Percentage of Population in the United States in 2008 With Any Benzodiazepine Use by Sex and Age

BZD Use %



12% women

7% men

18

Age

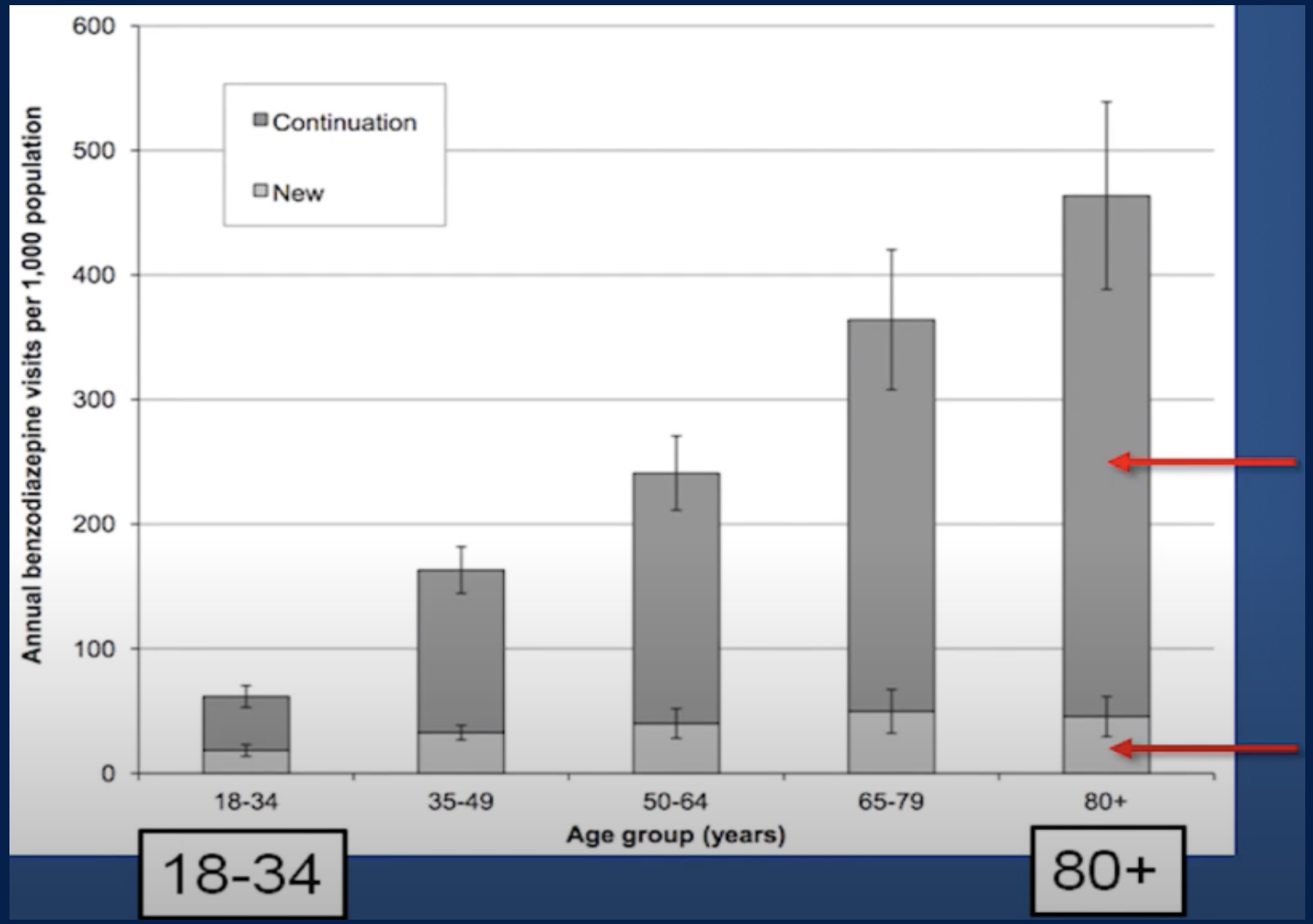
80

Olfson M, et al. JAMA Psychiatry 2015;72(2):136-142.

Epidemiology

Use Of Benzodiazepine Accumulates With Age

Annual BZD visits per 1,000 population



Continuation

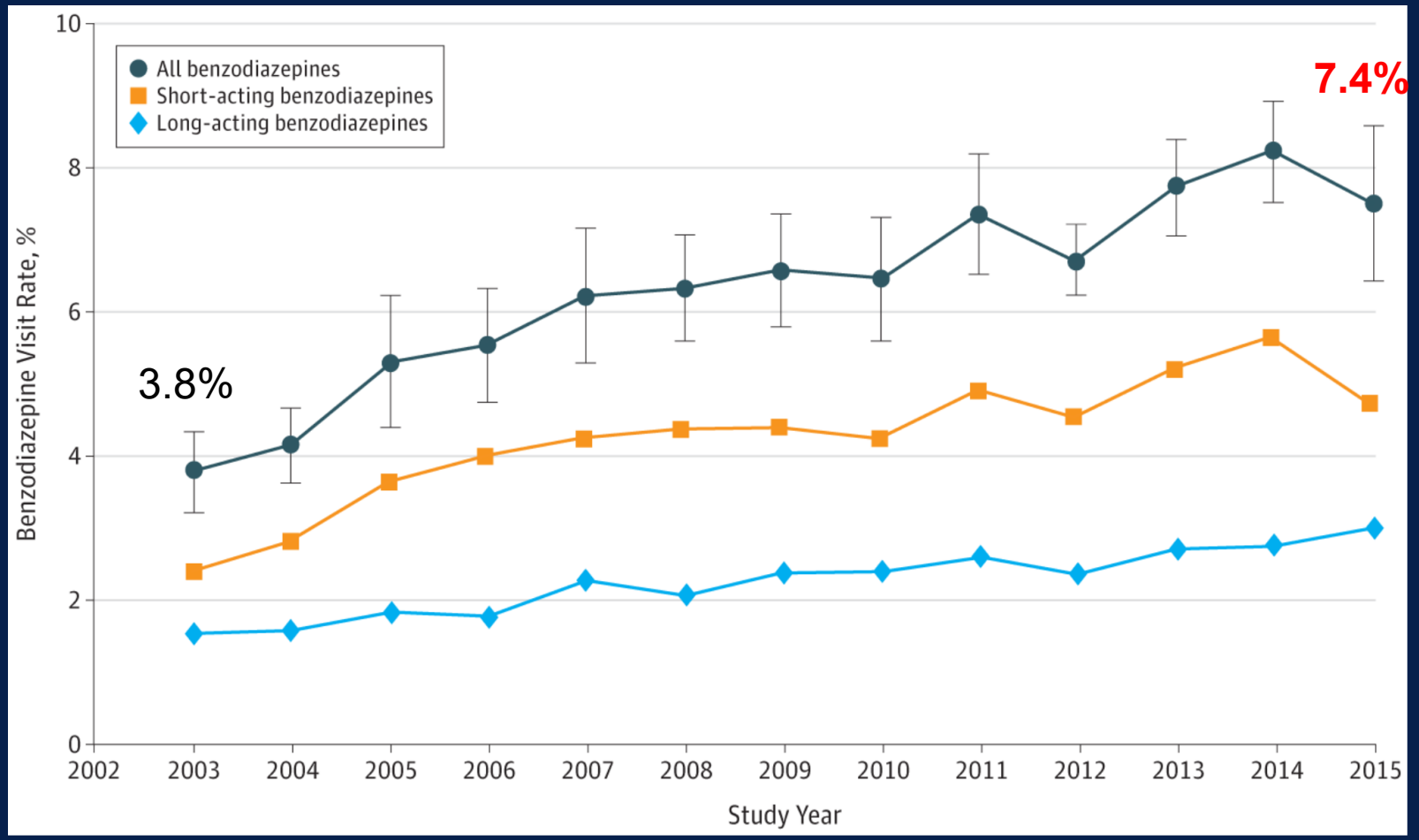
New

Age

Maus et al. JAGS 2016

Epidemiology

Benzodiazepine Visit Rate in United States



Benzo visit Rate %

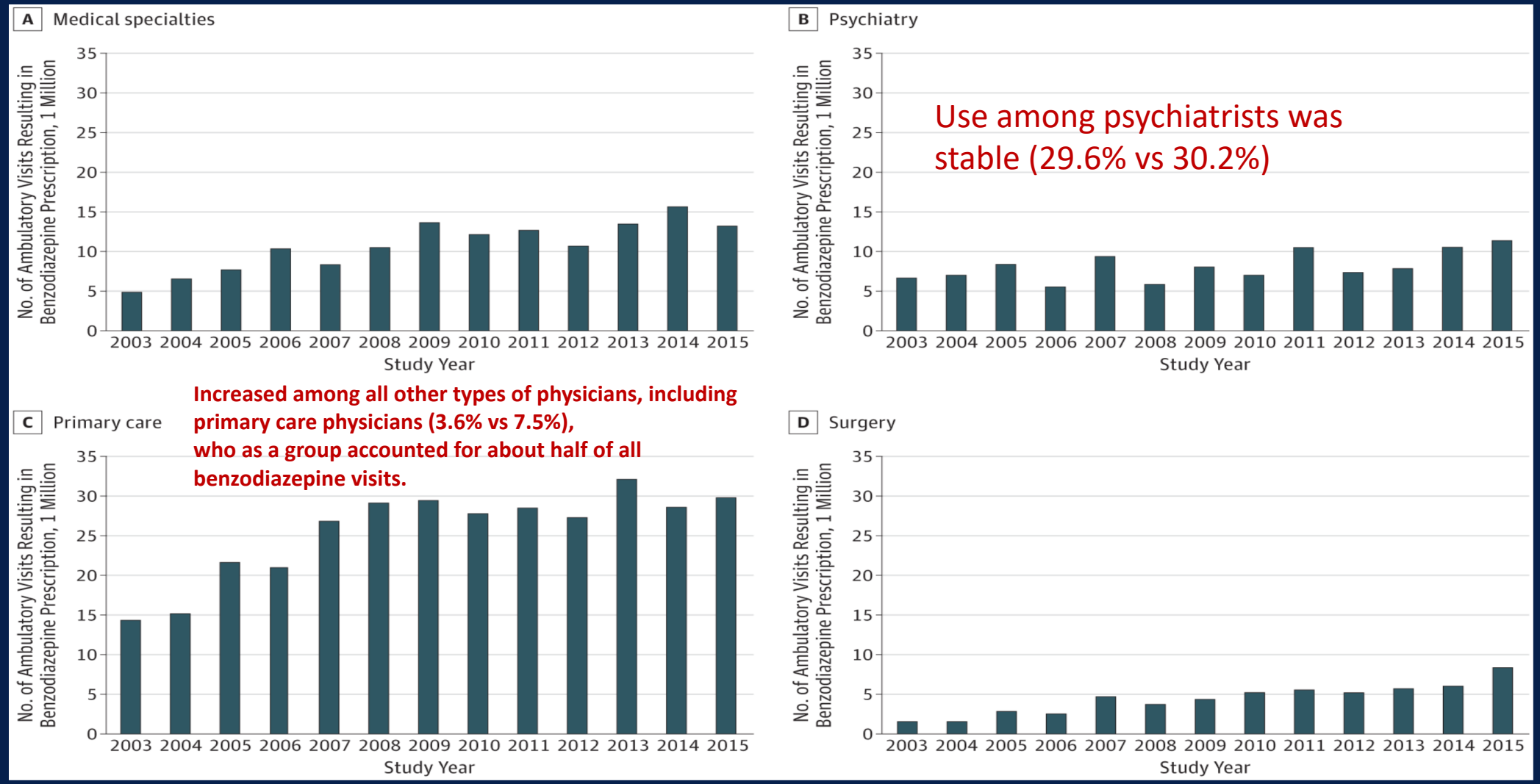
Year

95% increase in BZD-related visits in 12 years

Agarwal SD, Landon BE. JAMA Netw Open. 2019 Jan 4;2(1)

Epidemiology

Benzodiazepine Visit By Specialty in United States



No of Ambulatory Visits Resulting in BZD Prescription, 1 million

Year

Agarwal SD, Landon BE. JAMA Netw Open. 2019 Jan 4;2(1)

Concurrent Use of Other Substances

- Rarely the initial or primary substance of abuse
- Rarely used alone to produced intoxication
- Usually abuse with other substances
- Healthy patients prefer placebo to benzodiazepines

- ETOH use disorder patients and their offspring are more likely to experience mood elevation with benzodiazepines

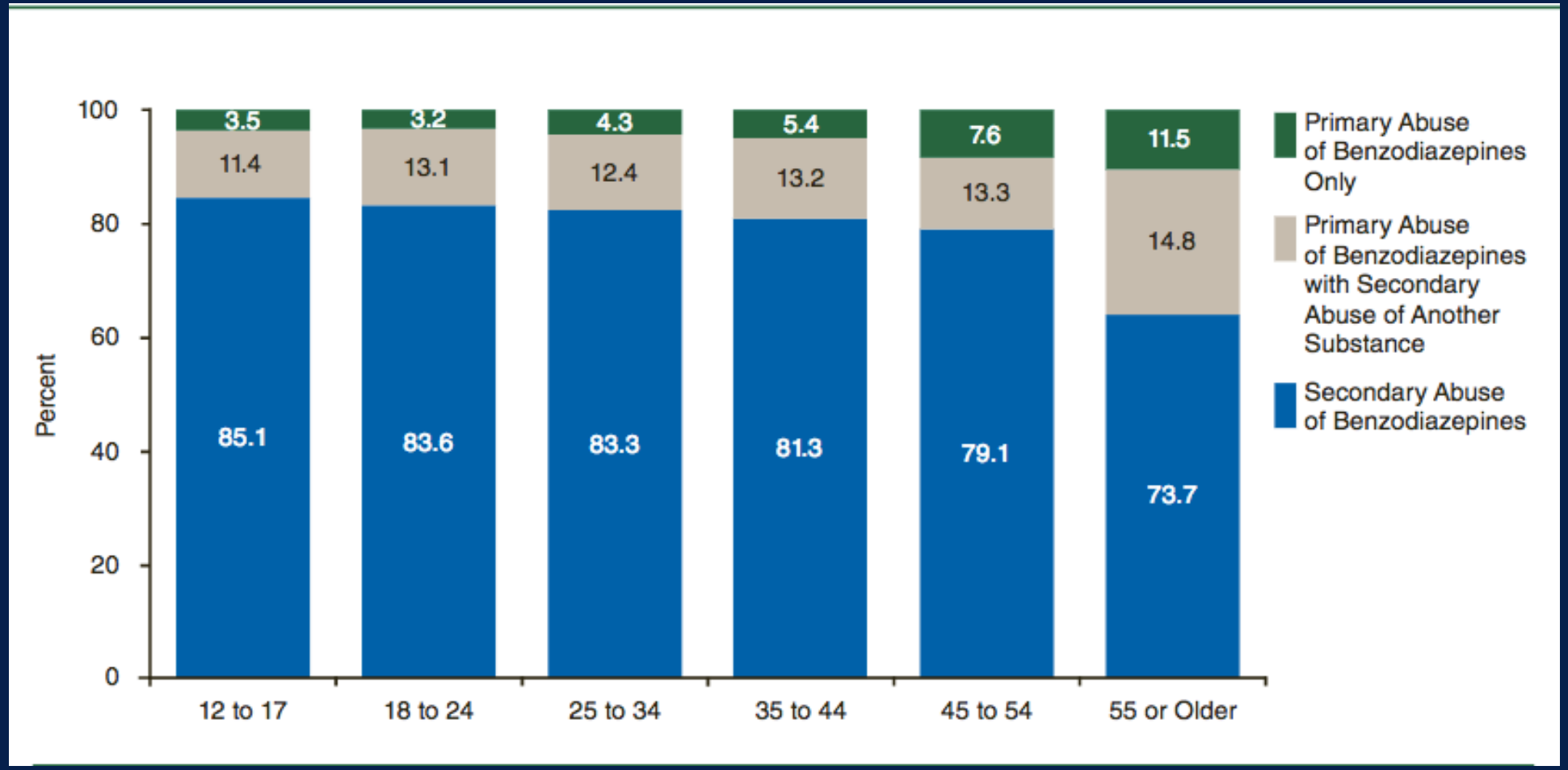
Concurrent Use of Other Substances

- A high percentage of alcohol dependent patients use benzodiazepines regularly (29-76%)
- 70-96% of patients admitted to inpatient addiction treatment on high dose benzodiazepine use have concurrent dependence on other substances
- It is uncommon to see patients with substance use disorder just on benzodiazepines. Concurrent use with other drugs is common just with benzodiazepine use
- BNZD are prescribed in 1 out of 5 patients on opioids

- Lethality when sedatives-hypnotics are combined with:
  - ETOH + BNZ
  - methadone + BNZ
  - buprenorphine + BNZ
  - Other CNS depressants + BNZ

Epidemiology

Primary and Secondary Benzodiazepine Admissions, by Age in 2008



Benzodiazepines + Opioids

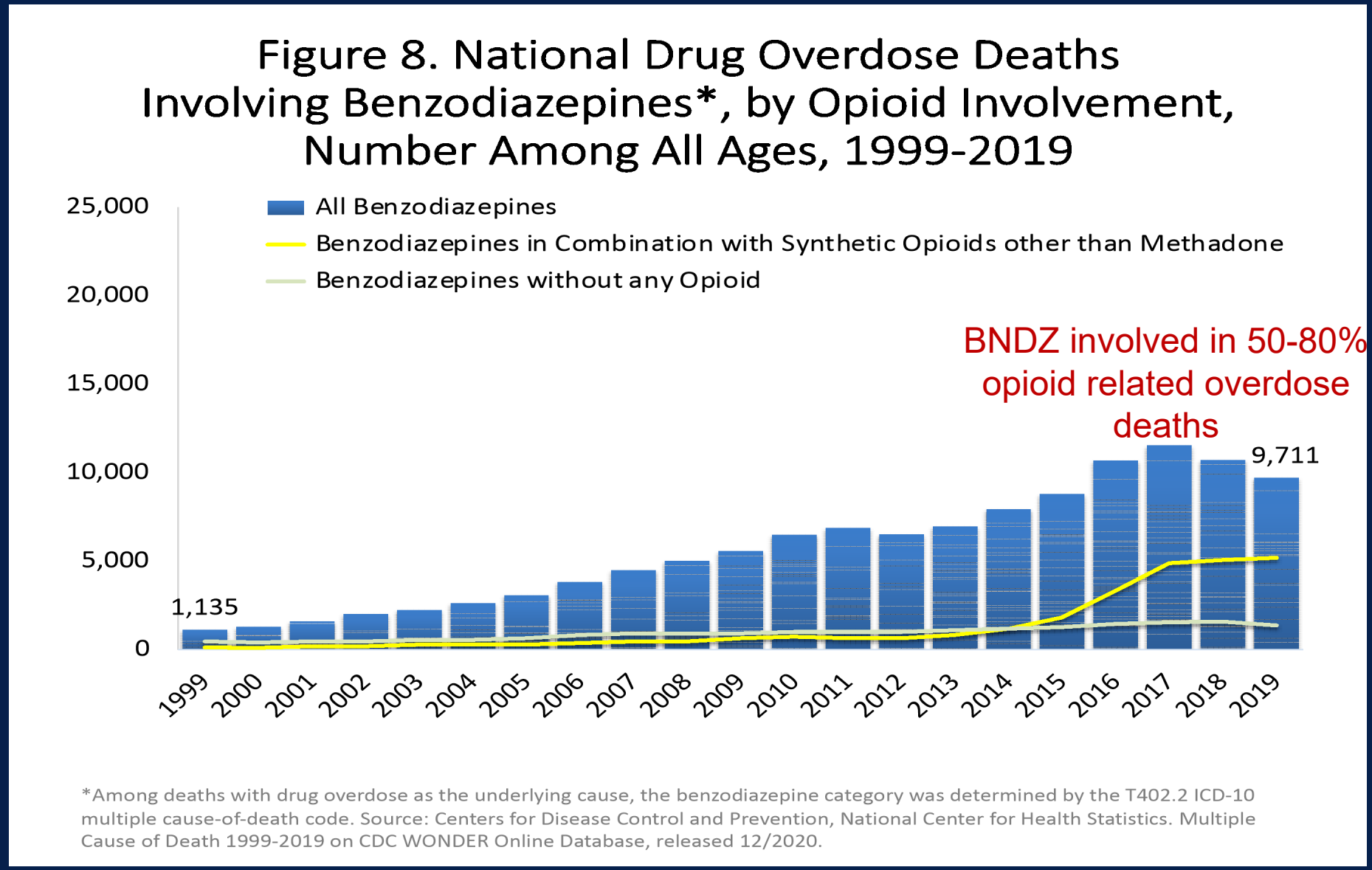
- Benzodiazepines (BZs) are the most frequently cited co-intoxicants involved in opioid-related morbidity and mortality.

- In 2010, the CDC reported 16,651 pharmaceutical opioid-related overdose deaths based on death certificate data- almost one of every three opioid-related deaths in 2010 also involved BZs

- On August 31, 2016 FDA issued a drug-safety communication about risks when opioid pain or cough meds are combined with BZs.

(Hwang et al., 2016; Jones, Mack & Paulozzi, 2013; DEA 2013)

National Drug Overdose Deaths involving BZDs, by Opioid Involvement, Number among All Ages, 1999-2019



AMERICAN SOCIETY OF ADDICTION MEDICINE
FOUNDED 1954
ASAM

Top Five Drugs Most Frequently Involved In Drug Overdose Deaths In United States

2010

Rank	Reference Drug	Number of Deaths	Percent
	N=38,329		
1	Oxycodone	5,256	13.7
2	Methadone	4,408	11.5
3	Cocaine	4,312	11.2
4 →	Alprazolam	3,677	9.6
5	Heroin	3,020	7.9

2017

Rank	Reference Drug	Number of Deaths	Percent
	N=70,237		
1	Fentanyl	27,299	38.9
2	Heroin	15,982	22.8
3	Cocaine	14,948	21.3
4	Methamphetamine	9,356	13.3
5 →	Alprazolam	6,647	9.5

Hedegaard H et al. Drugs most frequently involved in drug overdose deaths: United States, 2011–2016. National Vital Statistics Reports; vol 67 no 9. 2018

ED Visits: Risk of Serious Outcomes

	12-34 yo	35-44 yo	45-64 yo	65+
BZD alone	28%	30%	37%	39%
BZD + opioids	37%	43%	47%	59%
BZD + alcohol	35%	43%	51%	55%
BZD + opioids + alcohol	39%	47%	57%	70%

SAMHSA, DAWN Report, 12/18/2014

Epidemiology

- Most frequent abused pharmaceutical second only to opioids
- Alprazolam is the most frequently abused followed by Clonazepam, Lorazepam, and Diazepam
- BZDs are prescribed at about 65.9 million office-based doctor visits. That's a rate of 27 annual visits per 100 adults

National Health Statistics Report that examined data from the 2014-2016 National Ambulatory Medical Care Survey (NAMCS) 2019.

Substances Involved In Drug Related Er Visits For Misuse Or Abuse 2004, 2009, 2011

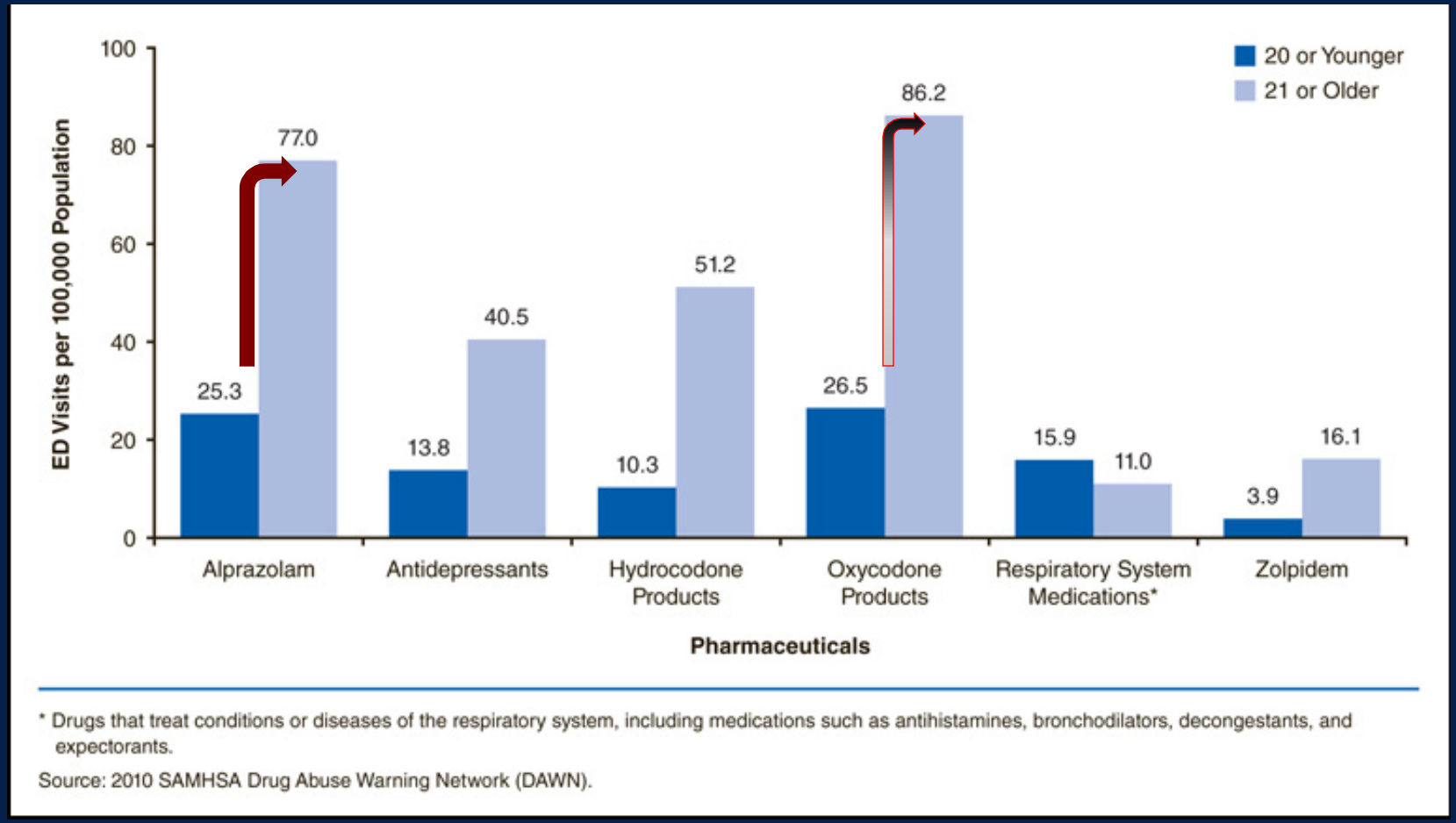
Table 2. Selected Substances Involved in Drug-Related Emergency Department (ED) Visits for Misuse or Abuse of Drugs: 2004, 2009, and 2011

Substances	Number of ED Visits in 2011*	Rate of ED Visits per 100,000 Population in 2011	Percent Change, 2004 to 2011**	Percent Change, 2009 to 2011**
Total ED Visits	**2,462,948**	**790.4**	**52%**	**19%**
Illicit Drugs	1,252,500	402.0	NC	27%
Cocaine	505,224	162.1	NC	NC
Marijuana	455,668	146.2	52%	19%
Heroin	258,482	83.0	NC	NC
Illicit Stimulants	159,840	51.3	NC	68%
Other Illicit Drugs	131,178	42.1	86%	60%
Pharmaceuticals	1,428,145	458.3	114%	13%
Anti-anxiety and Insomnia Medications	501,207	160.9	124%	14%
Alprazolam	154,016	49.4	155%	NC
Clonazepam	76,557	24.6	122%	NC
Lorazepam	50,399	16.2	127%	NC
Zolpidem	37,225	11.9	152%	NC
Narcotic Pain Relievers	420,040	134.8	153%	NC
Oxycodone Products	175,229	56.2	220%	NC
Hydrocodone Products	97,183	31.2	96%	NC
Methadone	75,693	24.3	74%	NC
Morphine Products	38,416	12.3	144%	NC

Emergency Department Visits Involving Misuse or Abuse of Selected Pharmaceuticals per 100,000

Population, by Age and Drug: 2010

Faster onset of action and shorter duration greater potential for misuse



* Drugs that treat conditions or diseases of the respiratory system, including medications such as antihistamines, bronchodilators, decongestants, and expectorants.

Source: 2010 SAMHSA Drug Abuse Warning Network (DAWN).

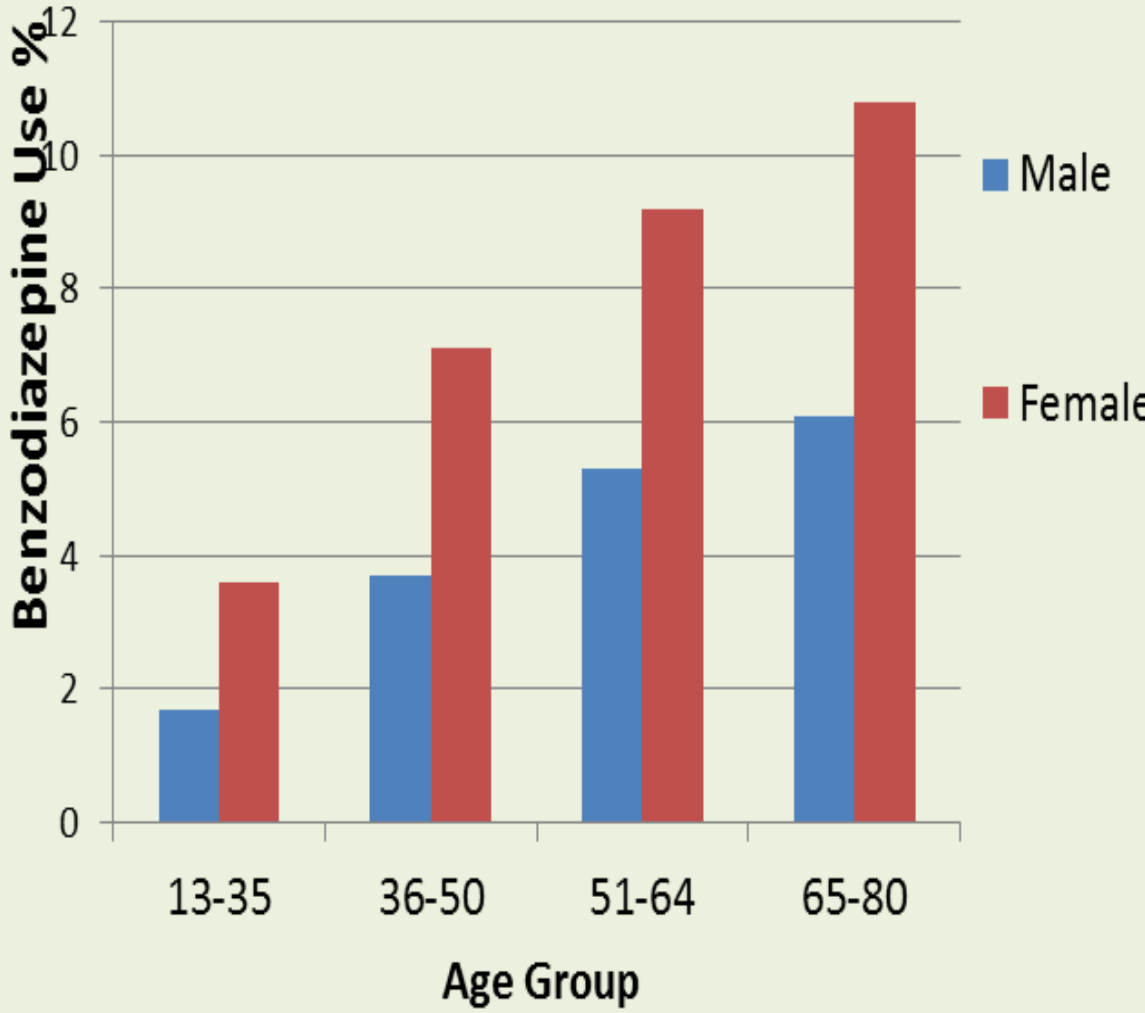
Prevalence of Benzodiazepine Use

Benzodiazepines:

- Use is nearly twice as prevalent in women
- Increased utilization with increasing age
- Proportion of long-term use increases with age
- Prescribed at greater rates than antidepressants for the treatment of depression and anxiety

Olfson M, et al. JAMA Psychiatry, 2015. **72**(2): p. 136-42.; Bernardy NC, et al. J Gen Intern Med, 2013. 28(S2): p S542-8; Demyttenaere, K., et al.,. J Affect Disord, 2008. **110**(1-2): p. 84-93.; Benitez, C.I., et al., Am J Geriatr Psychiatry, 2008. **16**(1): p. 5-13.; Maudsley Prescribing Guidelines in Psychiatry 12th Edition. 2015

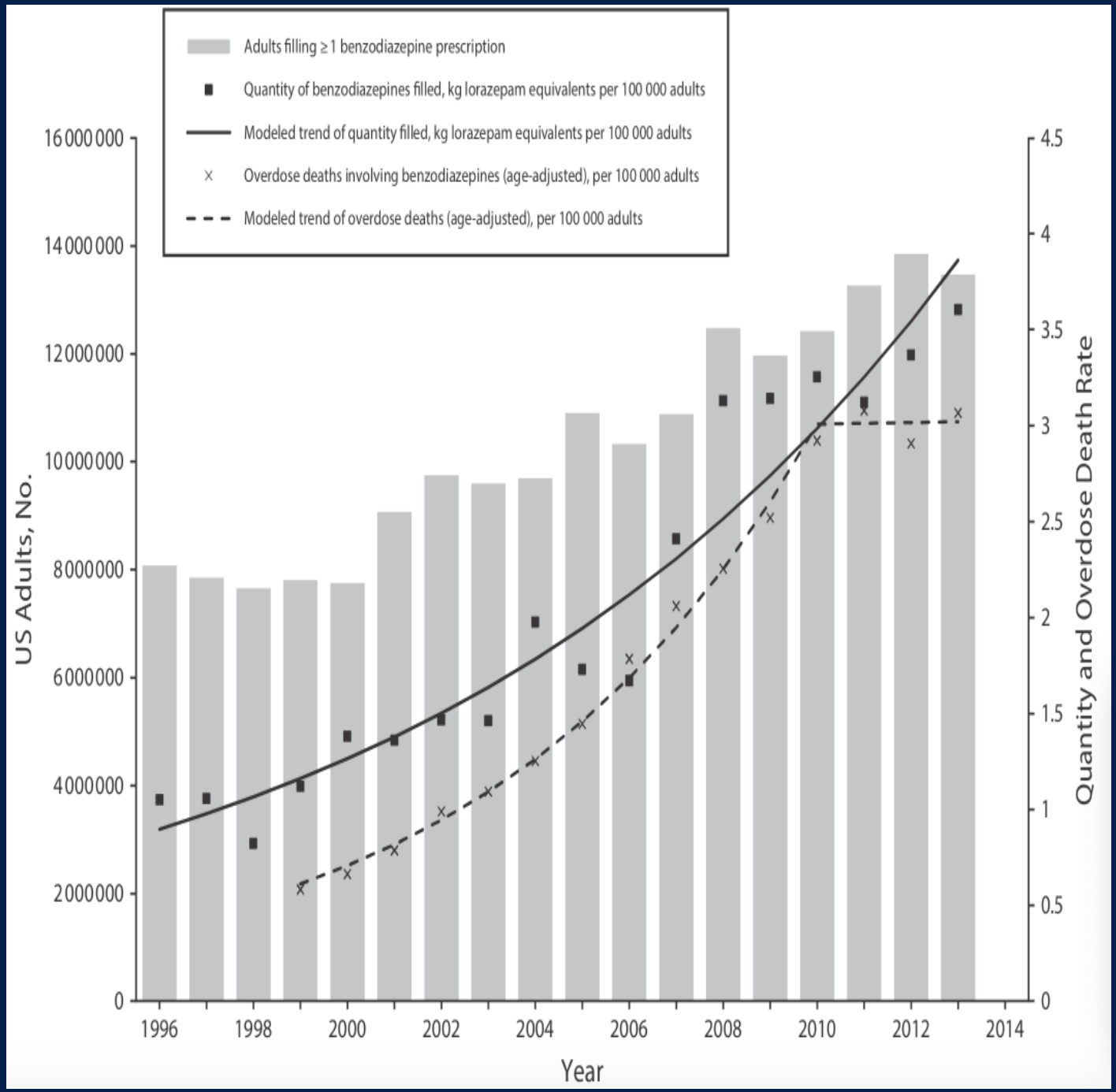
Figure 1. Prevalence of benzodiazepine use in the United States



Olfson M. JAMA Psychiatry, 2015. **72**(2): p. 136-42.

Increasing Benzodiazepine Prescriptions and Overdose Mortality in the United States, 1996–2013

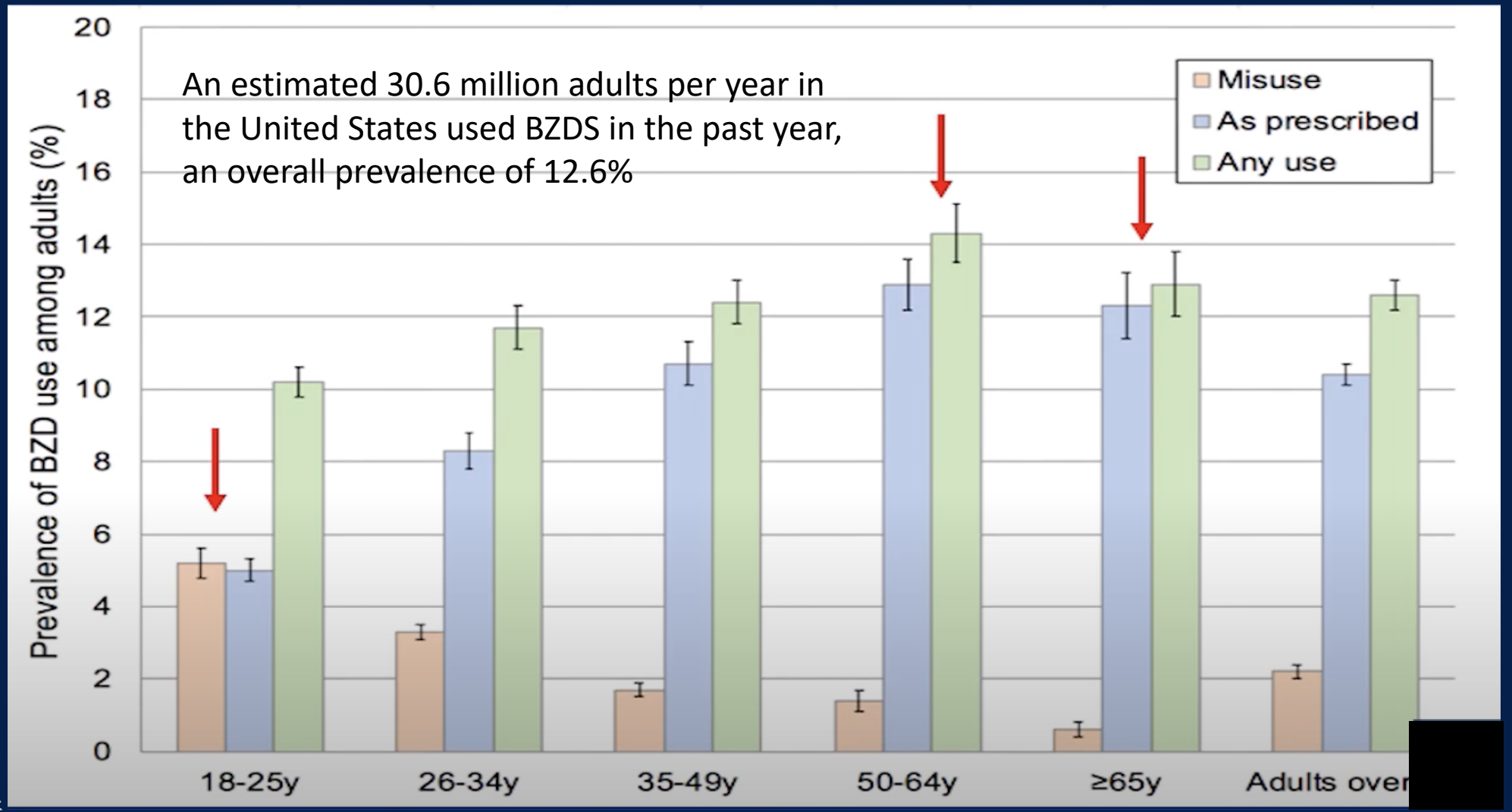
Between 1996 and 2013, the number of adults who filled a benzodiazepine prescription increased by 67 percent, from 8.1 million to 13.5 million.



Bachhuber MA et al Increasing Benzodiazepine Prescriptions and Overdose Mortality in the United States, 1996-2013. Am J Public Health. 2016;106(4):686–688.

Olfson M. JAMA Psychiatry, 2015. 72(2): p. 136-42.

BZD Use Accumulates With Age



Prevalence of prescription benzodiazepine use and misuse among 2015 and 2016 NSDUH respondents **(N=86,186),** by age group

[a]NSDUH, National Survey on Drug Use and Health

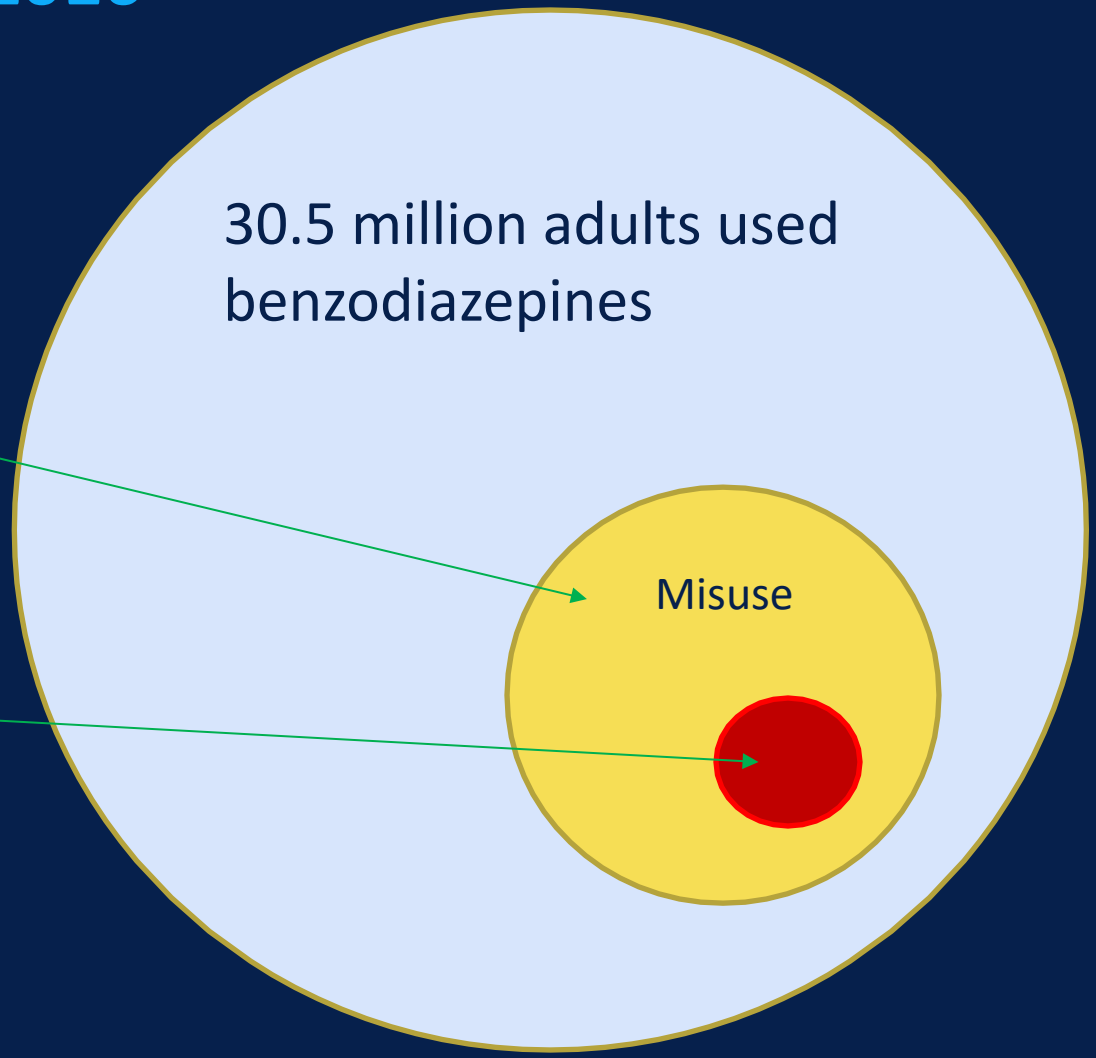
Maust DT, Lin LA, Blow FC. Benzodiazepine Use and Misuse Among Adults in the United States. *Psychiatr Serv*. 2019;70(2):97-106. doi:10.1176/appi.ps.201800321

Benzodiazepine Use, Misuse, and Use Disorder Among Adults in the United States: Annual Average, 2015-2016

5.2 million adults misused benzodiazepines

0.5 million adults had benzodiazepine use disorders:

- 0.3 million had benzodiazepine dependence
- 0.2 million had benzodiazepine abuse



Blanco C, Han B, Jones CM, et al. Prevalence and correlates of benzodiazepine use, misuse, and use disorders among adults in the United States. J Clin. Psychiatry. 2018; 79(6)

Case: RR

Mr. RR did not receive his alprazolam refill from his PCP because, after taper, patient returned to his original dose and ran out of the prescription sooner. Mr. RR is upset and decided to see a psychiatrist who had planned to prescribe medication if ROI to contact PCP is signed.

Case: RR

Mr. RR reports that his heart has been racing and his insomnia has worsened; his friend states that, for the past four days, he has been having difficulty following conversations and focusing on daily tasks. He has been off alprazolam for seven days. Mr. RR denies any recent psychosocial stressors and does not endorse feelings of guilt, helplessness, or hopelessness. Furthermore, he denies any fever, nausea, vomiting, diarrhea, myalgia, abdominal cramps, or seizures. He denies any recent alcohol or illicit drug use.

Factors Associated With Prescribing Benzos

- Anxiety
- Insomnia
- Pain
- Chronic Medical Condition
- Female
- White
- Retirement Low income
- Elderly
- Smoking
- Poor Health
- >1 Prescriber
- Computer prescribing

Agarwal SD, Landon BE. JAMA Netw Open. 2019 Jan 4;2(1)

Benzodiazepines and Addiction

Benzodiazepines are often not the primary substance abused and, when combined with other substances (e.g., alcohol ,opioids), can have fatal consequences

- 5-10% - Patients newly started on benzodiazepines develop a substance use disorder
- 50% - Patients with substance use disorder history will develop a benzodiazepine use disorder
- 58-100% - Patients prescribed chronic benzodiazepines become physically dependent

Guina, J., et al., J Psychiatr Pract, 2015. **21**(4): p. 281-303.; *Substance Abuse: A Comprehensive Textbook (4th ed.). Baltimore. MD: Lippincott. Williams & Wilkins. 2004. pp. 302-312.;* Substance Abuse and Mental Health Services Administration. The TEDS Report: Substance Abuse Treatment Admissions for Abuse of Benzodiazepines. . Rockville, MD., June 2, 2011.

Benefits and Risks

- Population
  - Therapeutic dose dependent
  - Prescribed high-dose dependent (sedative use disorder)
  - Recreational benzodiazepine use
- Risk factors for benzo use disorder:
  - Longer duration of BNZ use
  - Higher Benzodiazepine doses
  - Lower level of education
  - Greater insomnia severity
  - Current antidepressant use

Benefits and Risks

ACTION		CLINICAL USE
Anxiolytic	Relief of anxiety	Anxiety and panic disorders, phobias
		Agitated Psychosis
Hypnotic	Promotion of sleep	Insomnia
Myorelaxant	Muscle relaxation	Muscle spasms, spastic disorders
Anticonvulsant	Stop fits, convulsions	Fits to drug poisoning, some form of epilepsy, alcohol withdrawal
Amnesia	Impairment of short-term memory	Premedication for operations, sedation for minor surgical operations

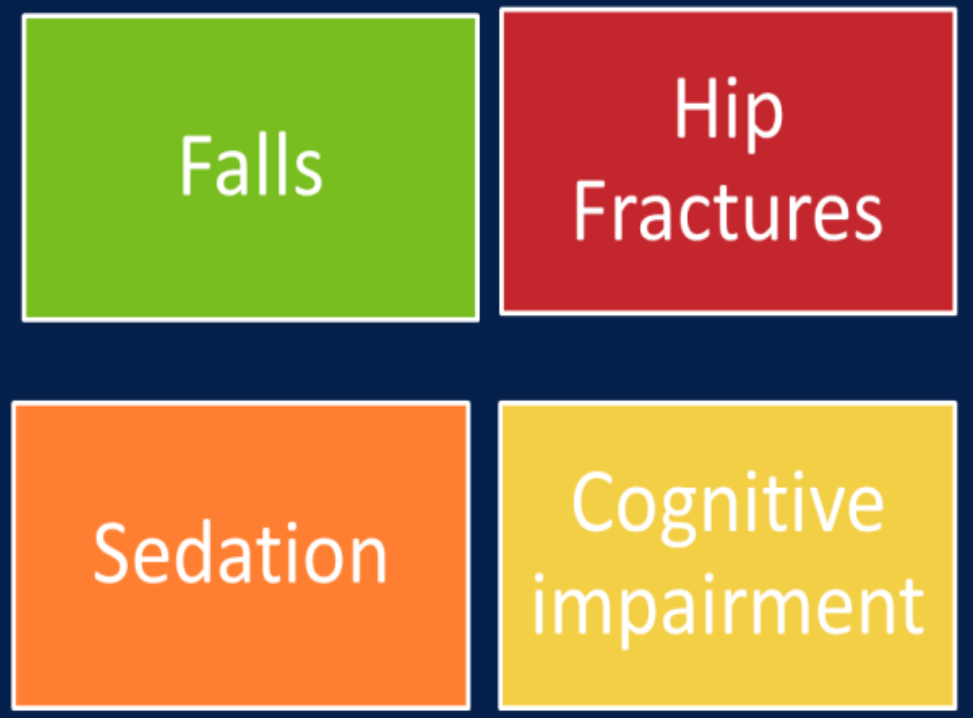
Benefits and Risks Prior to Prescribing Benzodiazepines

TOLERANCE and DOSE ESCALATION = WITHDRAWAL

- Examine the risk-benefit ratio
- Avoid nonbenzodiazepine hypnotic
- Short-term use (4 weeks)

Benefits and Risks (Concerns)

- Long term use have shown deficits in learning, memory, attention, and visual spatial ability
- Anterograde Amnesia
- Adverse effects:
  - May contribute to psychomotor impairment and increase the risk of falls and automobile accidents
  - Psychomotor impairment is characterized by:
  - - Slow reaction time
  - - Diminish speed and accuracy for motor tasks
- Increase risk (50%) of hip fractures and recurrent falls in the elderly population
- OD with Benzodiazepine alone are almost never lethal (high therapeutic index) but OD with BBT alone can be



Cumming et al. Benzodiazepines and Risk of Hip Fractures in Older People. *CNS Drugs* **17,**2003

Benefits and Risks (Concerns)

- The 2015 American Geriatrics Society Beers Criteria recommend avoiding benzodiazepines in this population. Despite these consensus recommendations and known risk factors:
  - Benzodiazepine use is three times more prevalent in older adults compared to younger adults
  - Roughly one-quarter of long-term benzodiazepine use is in patients ≥65 years of age

Considerations When Prescribing Bzs

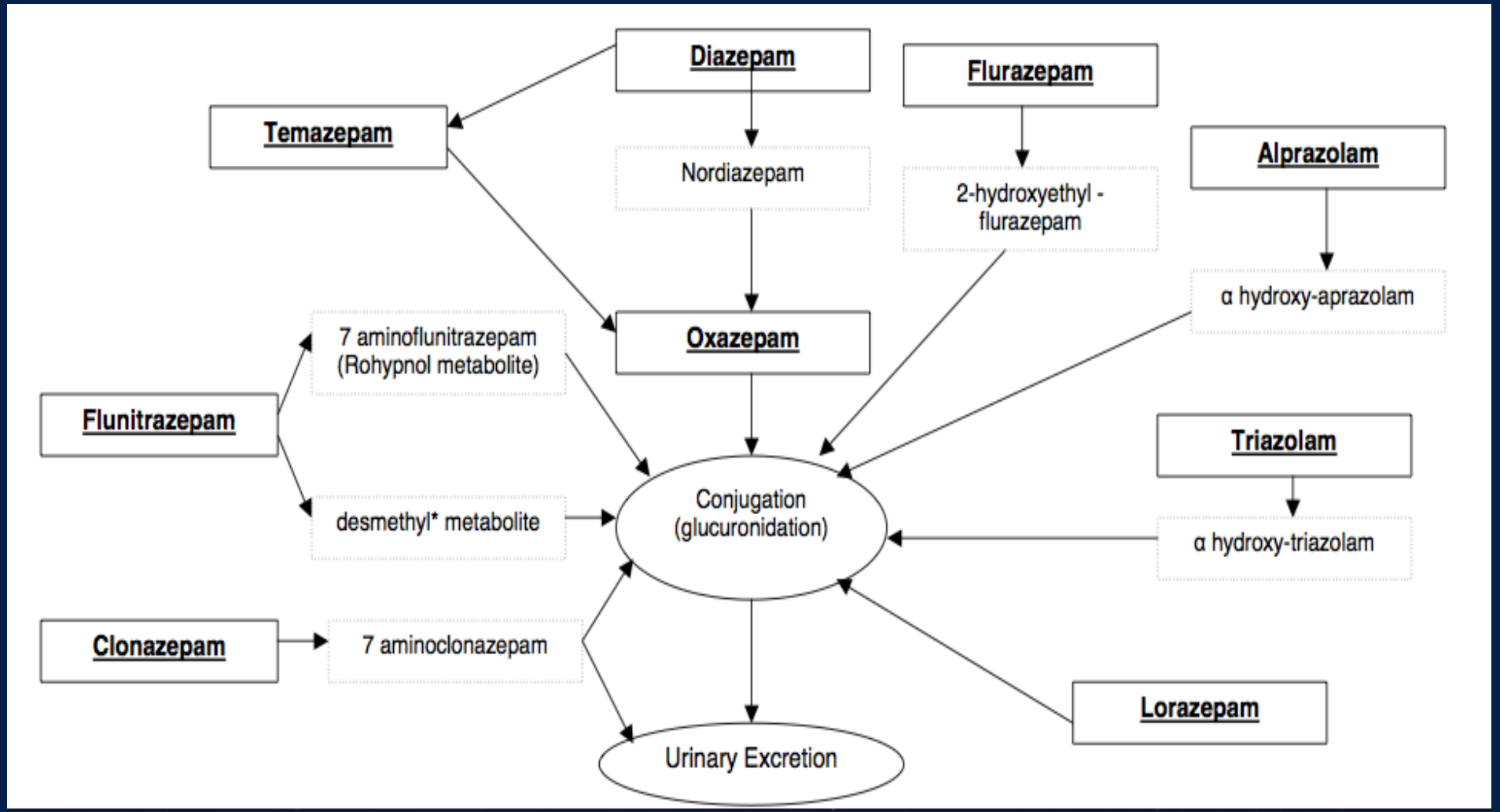
- Examine the risk-benefit ratio
- Avoid nonbenzodiazepine hypnotic (Alternative)
- Inform patient of planned duration of therapy
- Prescribe for brief periods
- No refills without follow up
- Use random urine toxicology
- Attempt to taper dose
- Always check the Prescription Drug Monitoring Program (PDMP) before and during the treatment
- Formalize written treatment agreement

Phases of Sedative-Hypnotic Treatment and Related Syndromes

Equivalent Doses And Elimination Half-lives Of Benzodiazepines

Benzodiazepines	*Approximately Equivalent Dosage (Mg)*	*Elimination Half-life (Hrs)- (Active Metabolite)*
Alprazolam *	0.5	6-12
Chlordiazepoxide	25	5-30 (36-200)
Clonazepam*	0.5	18-50
Diazepam	10	20-100 (36-200)
Flunitrazepam	1	18-26 (36-200)
Flurazepam	15-30	(40-250)
Lorazepam*	1	10-20
Oxazepam	20	4-15
Temazepam	20	8-22
Triazolam*	0.5	2

Benzodiazepine Metabolism



Types of Benzodiazepines

- 2-Keto benzodiazepines (Clonazepam, Diazepam, Chlordiazepoxide)
  - All have long half-lives (23-100 hours)
  - All have active metabolites (commonly desmethyldiazepam)
  - Some administered as Prodrug

- 3-Hydroxy Benzodiazepines (Oxazepam, Temazepam, Lorazepam)
  - Intermediate half-lives (most 10-15 hours)
  - No active metabolites (better in elderly/hepatic impaired)
  - Metabolized outside the liver (only need glucoronidation)

- Triazolo Benzodiazepines (Alprazolam, Triazolam)
  - Short to Intermediate half lives (anywhere from <12 hours)
  - Some have active metabolites

Pharmacokinetics

BZDs are differentiated by their pharmacokinetic profiles, based on *lipophilicity and metabolism*:

- **Half-life** (short, intermediate, long)
- **Onset-of-action** (rapid, intermediate, slow)
- **Metabolic pathways** (with or without active metabolites, with or without P450 involvement)

Pharmacokinetics

LONG-ACTING

- Chlordiazepoxide
- Diazepam
- Clonazepam

MEDIUM-ACTING

- Lorazepam
- Oxazepam
- Temazepam

SHORT-ACTING

- Alprazolam
- Triazolam
- Midazolam

Case: RR

PE: He was found to be tachycardic (pulse, 110 beats/min) and hypertensive (blood pressure, 170/90 mm Hg). His medical workup, including CBC count, electrolyte panel, liver function tests, blood glucose level, and urine toxicology screen were within normal limits.

Case: RR

MSE: Casually dressed male who appeared to be restless and irritable with twitches in his face and complains about tinnitus. He was oriented to time, place, and person. His speech was normal in rate and content. His mood was subjectively anxious and objectively dysphoric, and his affect was congruent with mood. His thought form was linear, and goal directed. There was no evidence of paranoid ideations/delusions. He denied any auditory or visual hallucinations. He scored 30/30 on the Mini-Mental State Examination. He had good insight and judgment. He endorsed passive suicidal ideations, no plan. He denied any homicidal ideations

Management of Benzodiazepine Withdrawal

Variable presentation:

- There are no pathognomonic signs and symptoms of benzodiazepine withdrawal
- Assess for subjective and objective symptoms
- May have few concurrently observable hyper-adrenergic signs or vital sign fluctuations (unlike acute alcohol withdrawal)

Symptoms Of Anxiety State	*Symptoms Less Common In Anxiety States-relatively Specific To Benzodiazepine Withdrawal*
Anxiety, panic attacks, agoraphobia	Perceptual distortions, sense of movement
Insomnia, nightmares	Depersonalization, derealization
Depression, dysphoria	Hallucinations (visual, auditory)
Excitability, restlessness	Distortion of body image
Poor memory and concentration	Tingling, numbness, altered sensation
Dizziness, light headedness	Formication (skin “crawling”)
Weakness “jelly legs”	Sensory hypersensitivity (light, sound, taste, smell)
Tremor	Muscle twitches, jerks, fasciculation
Muscle pain, stiffness	Tinnitus
Sweating, night sweats	Psychotic Symptoms
Palpitations	Confusion, delirium
Blurred or double vision	Convulsions

Management of Benzodiazepine Taper

Challenging process for both patients and doctors <u>if you do not have a treatment plan</u>

Strategies:

- Gradual dosage tapering (avoid prn dosing)
- Psychological Support
- Reasons for prescribing
- Lifestyle
- Personality

Management of Benzodiazepine Taper

- Consider dosage and type of benzodiazepine
- Environment stresses
- Amount of available support
- Prepare for months or a year for the taper
- Individualize treatment adjusted to patient's needs (personalized treatment)

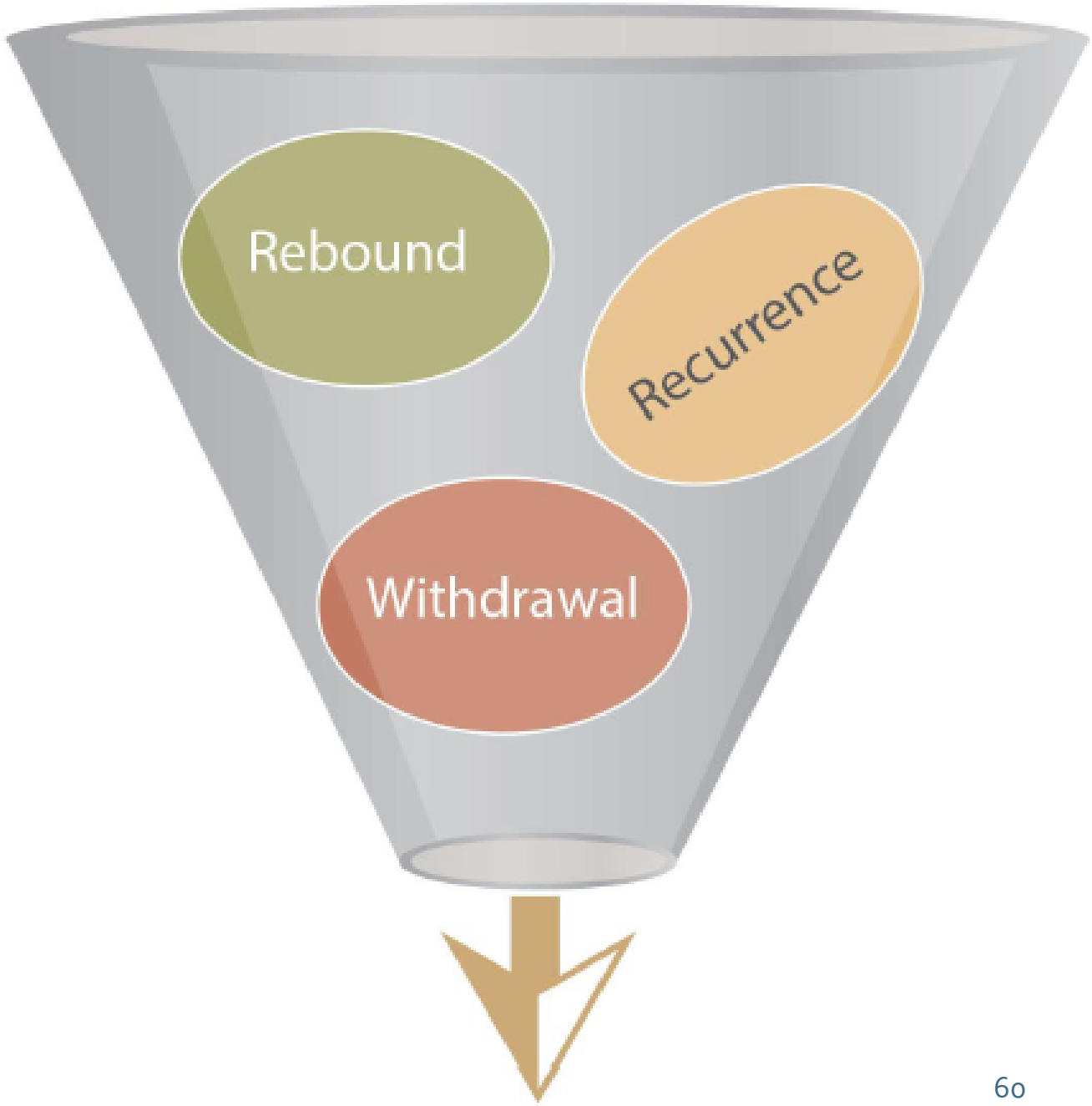
Management of Benzodiazepine Withdrawal /Taper

Time course and severity are influenced by:

- Duration of use: short vs. long term use
- Dose: low/therapeutic dose vs. high dose
- Pharmacokinetics: short vs. long acting
- Host factors: comorbid pathology or substance use disorder

What is the difference between withdrawal, rebound and recurrence?

- Recurrence: the person experiences the same symptoms and severity of symptoms that existed prior to treatment
- Rebound: occurs when a drug is withdrawn and the individual experiences anxiety symptoms that are more severe than those experience prior treatment
- Withdrawal: the time-limited development of unique symptoms as the result of discontinuing or decreasing the use of a psychoactive drug



Management of Benzodiazepine Withdrawal

Time and Severity can vary

- Short Acting BZs and those with active metabolites when stopped, can lead to WD sx within hours
- Long Acting BZs with active metabolites can take 48 hours – 7 days for WD sx to emerge
- Severe WD from BZs can be accompanied by delirium

Management of Benzodiazepine Withdrawal

Duration of use and therapeutic dose:

>10 days use with therapeutic dose:
some experience transient insomnia

<2 weeks with therapeutic dose:
Most experience rebound

>2 months with therapeutic dose:
Most experience mild withdrawal

Of patients who take a benzodiazepine for more than a month, 47% (n=1048) become dependent.

De Las Cuevas et al 2003

Management of Benzodiazepine Withdrawal

Duration of use and therapeutic dose:

- >4 to 6 months with therapeutic dose;
- Most experience mild to moderate withdrawal

- >12 months with therapeutic dose:
- 20-80% experience moderate to severe withdrawal

Management of Benzodiazepine Withdrawal: When to Taper

- Over-sedation
- Cognitive impairment
- Concurrent Rxs or use of high-risk CNS depressants medications
  - Other BZs, non-BZ hypnotics, and OPIOIDS

- Alcohol use disorder and other SUDs
- Overuse, misuse, or BZ use disorder
- Patient request
- Other

MANAGEMENT/Systematic Discontinuation

- Tapering
- Substitution and tapering

MANAGEMENT/Systematic Discontinuation

- Rate for dosage varies for different types of benzodiazepine pts:
  - Withdrawal shows in 1- 7 days depending on half lives
  - One-eight to one-tenth of the daily dose (10-25% weekly)
  - Taper between 4 weeks to 6 months or even more

Management of Benzodiazepine Withdrawal

Pharmacological /Strategies Treatment of Withdrawal

- Taper over months:
- Convert to longer acting agent like Clonazepam, Chlordiazepoxide, Diazepam)
- Taper gradually while starting alternative therapies if needed (months)
- Rebound psych meds for anxiety/sleep (Trazadone, Mirtazapine, Buspirone)
- Use of Anticonvulsant carbamazepine or valproate

Ashton H. The diagnosis and management of benzodiazepine dependence. *Curr Opin Psychiatry*. 2005; 18:249-255.

When do you see withdrawal symptoms?

- Short acting BZD: oxazepam, triazolam, temazepam, alprazolam
- Short acting sedative-hypnotics: pentobarbital, secobarbital, meprobamate, metaqualone
  - Withdrawal onset in 12-24 hrs with
  - Peak of withdrawal intensity-day 1 to 5
  - Duration of acute withdrawal- 7 to 21 day

When do you see withdrawal symptoms?

- Long-acting BZD and sedative-hypnotics: diazepam, chlordiazepoxide, phenobarbital
  - Withdrawal Onset within 5 - 14 days of cessation
  - Peak of Withdrawal Intensity - Days 1 to 9
  - Duration of Acute Withdrawal - 10-28 days
    - Protracted withdrawal symptoms for months

Phenobarbital Substitution and Taper

- Substitution of benzodiazepine with equipotent dose of phenobarbital
- For inpatient, medically monitored setting only
- Effective Strategy for:
  - High dose dependent
  - Poly-Substance Dependence
  - Concurrent Alcohol/other Sedative Hypnotic
  - Unknown or erratic polypharmacy drug use

Phenobarbital Substitution and Taper

- Establish Stabilization Dose by Computing Phenobarbital equivalents
  - Alprazolam 1 mg=PB 30 mg
  - Clonazepam 2mg=PB 30 mg
  - Diazepam 10 mg=PB 30 mg
  - Lorazepam 2 mg=PB 30 mg
  - Carisoprodol 700 mg=PB 30 mg
- PB should be give TID or QID
- Maximum PB starting dose 500mg/day

Phenobarbital Substitution and Taper

- Monitor patient for signs of toxicity before administering each dose
- Signs of PB toxicity are easy to observe:
  - Sustained horizontal nystagmus
  - Ataxia
  - Slurred Speech
  - If intoxication observed:
    - If 1 sign of toxicity observed, skip one dose
    - If 2 signs of toxicity observed, skip 2 doses
    - Recalculate new daily dose

Phenobarbital Substitution and Taper

- Once stabilization dose is established: maintain patient on initial dose for two days
- If patient has neither signs of withdrawal or toxicity, then patient is moved to the withdrawal phase
- Decrease phenobarbital 30 mg/day unless signs of toxicity or withdrawal are seen
- If patient develops objective signs of withdrawal. Daily dose is adjusted upward by 50% and patient is stabilized before continuing withdrawal

Pregnancy

- Pregnant and lactating women are relatively contraindicated due to:
  - Ability of benzodiazepines to cross fetal placental barrier and to pass into breast milk
  - Teratogenic effects
  - Floppy baby syndrome
  - Neonatal withdrawal

Flumazenil

- Reverse the sedation produced by a benzodiazepine (Acute O.D with benzodiazepine)
- Nonspecific competitive antagonist of benzodiazepine receptor
- May up regulate BZ receptors
- IV use 1 mg monitor pt every 30-60 minutes
- Adverse effects: seizures, cardiac arrhythmias and acute precipitated withdrawal

Z-Drugs (Selective Nonbenzodiazepine Hypnotics)

- Zaleplon
- Zolpidem
- Eszoplicone
- Zoplicone*

- Lower the risk for residual daytime drowsiness due to shorter duration of action
- Short term use
- Bind to sub-types of $GABA_A$ receptors – *α1 subunit* that specifically modulate sleep and therefore are thought to have less unwanted side effects

- SE: risk of increased sleep- related behaviors

- Apply the general principles prescribing benzodiazepines to the Z-drugs

Barbiturates

- The oldest sedative hypnotics
- Classified in three different pharmacokinetics category
- In the past used for treatment of anxiety disorders
- BBT: *low therapeutic index*
- Replaced by benzodiazepines
- BBT induce the synthesis of hepatic cytochrome P450, thus alter their own metabolism and the metabolism of other meds

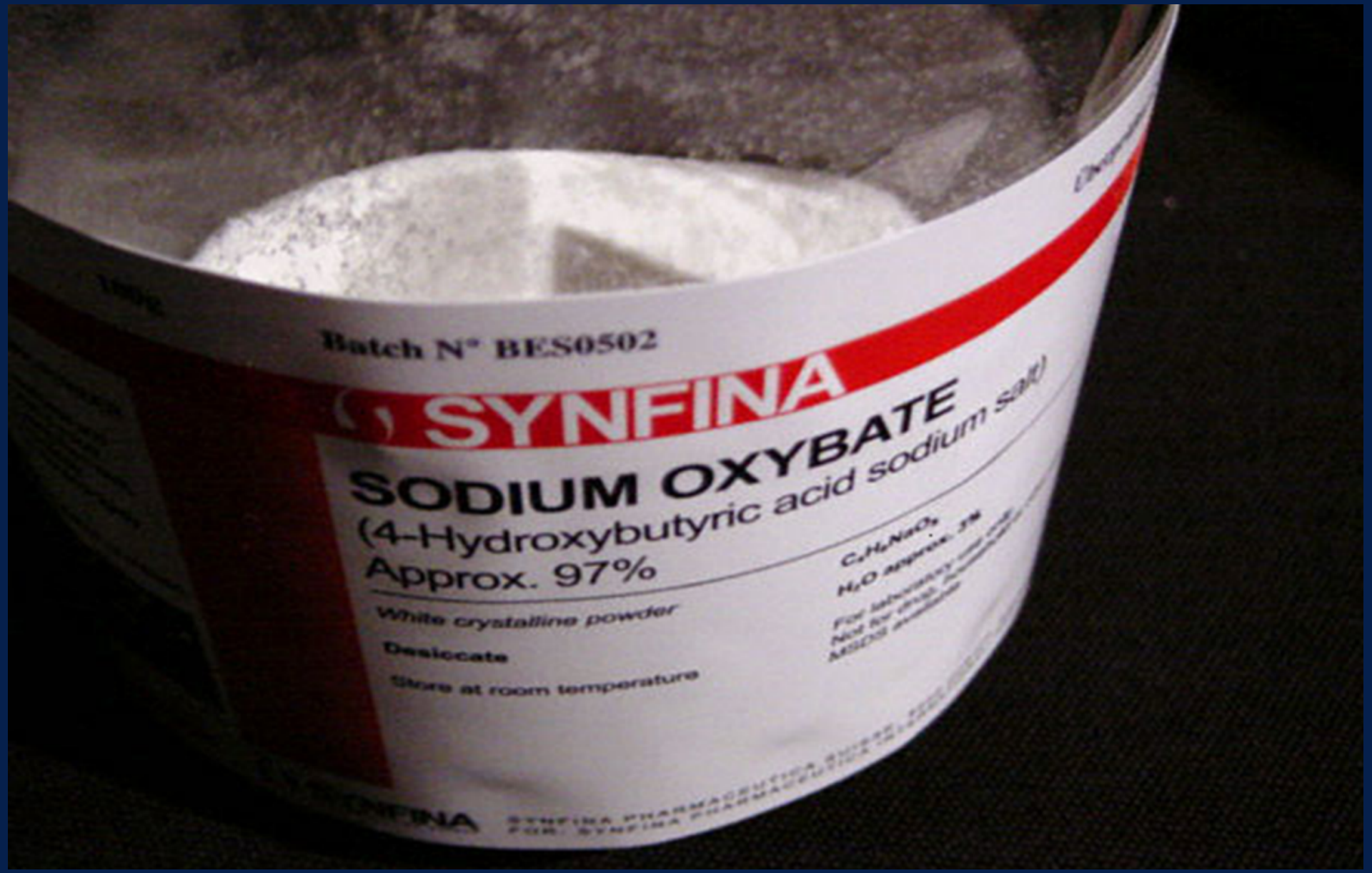
Barbiturates

Duration of Action	*LS*	*Onset*	*Duration*	*Use*
Ultrashort	H	10-20 s	20-30 min	IV anesthesia
Thiopental				
Methohexital				
Short/Intermediate	M	20-40 min	5-8 h	Surgical anesthesia and sleep induction
Amobarbital				
Secobarbital				
Pentobarbital				
Long	L	Over 1 h	10-12 h	Prolong sedation and seizure control
Phenorbarbital				
Meprobarbital				

GHB

Gamma-Hydroxy-Butyrate

“When I wake up,
I feel completely refreshed.
In comparison to the other drugs that
are supposed to be ‘clean,’
G really is clean.”


Batch N° BES0502
SYNFINA
SODIUM OXYBATE
(4-Hydroxybutyric acid sodium salt)
Approx. 97%
White crystalline powder
Desiccate
Store at room temperature

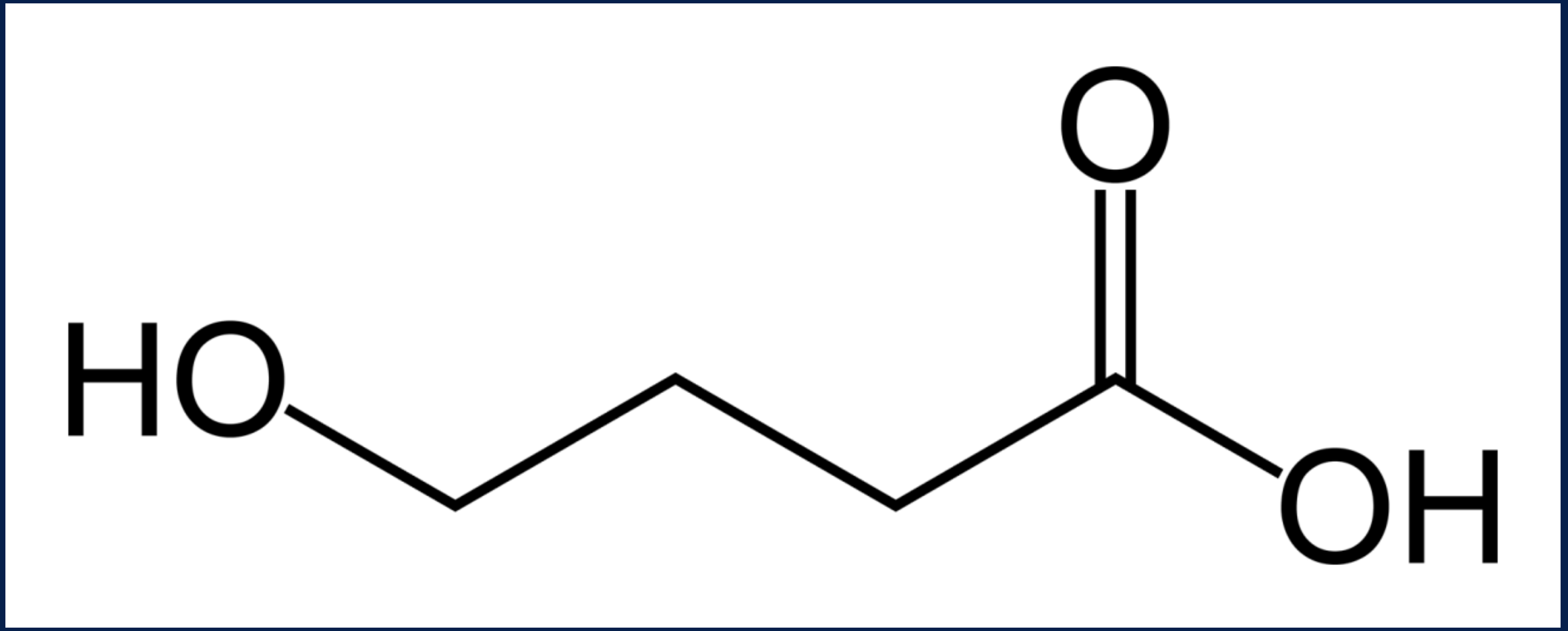
Effects

- Sensual drug, like MDMA, but also resulting in “the greatest sex ever.”
- Relaxation, tranquility, placidity, mild euphoria, disinhibition.
- Temporary amnesia (hence “the date rape drug”).

Neurobiology

- GHB is a neurotransmitter.
- It is both a precursor and a metabolite of GABA.
- Activity on both the $GABA_B$ and the GHB binding sites, results in:
  - Temporary suppression of dopamine,
  - Subsequent marked release of dopamine, and
  - Increased release of endogenous opioids.
- It is a highly regulated Schedule III medication for narcolepsy (Xyrem).

The Molecular Structure



Intoxication

- Steep dose-response curve:
  - Ataxia, loss of coordination.
  - Respiratory depression, bradycardia.
  - Coma, persistent vegetative states, death
  - Overdose is a real danger (LD50 is only 5 times the recreational dose).
  - Synergistic effect with alcohol/other sedatives.
- Treat as a medical emergency:
  - ABCs, consider Intensive Care Unit admission.
  - Atropine for bradycardia.

Withdrawal

- Withdrawal is rare but severe.

- Mild withdrawal may persist for several weeks after cessation of use:
  - Anxiety, tremor, insomnia.
  - “Feelings of doom.”

- Severe withdrawal resembles barbiturate withdrawal:
  - Treat with benzodiazepines.

Long Term Features

- Physiological dependence.
- Most patients who overdose on GHB recover completely.

- No FDA approved medications.
- MET and CBT are the major treatment modalities.

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