CARE
Clinical Addiction
Research and Education

Benzodiazepines

CRIT program
May 2010

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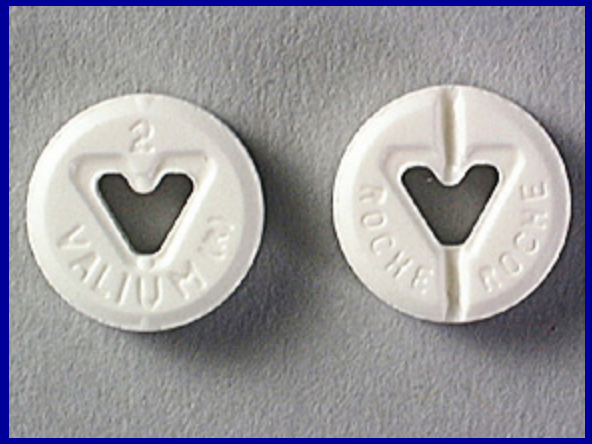
Learning objectives

At the end of this session, you should:

1. Understand why people use benzodiazepines
2. Know the characteristics of benzodiazepine intoxication and withdrawal syndromes
3. Understand the consequences of these drugs
4. Know the current options for treatment of benzodiazepine dependence

Roadmap

1. Case and controversies
2. History and Epidemiology
3. Benzo effects
4. Treatment



Case

- 29 yo man presents for follow-up at methadone clinic after inpatient admission for femur fracture from falling onto subway track from platform.
- Treated with clonazepam since age 16 for panic disorder. Takes 6mg in divided doses daily. Missed his afternoon dose, the day of the accident
- Started using heroin at age 23
- On methadone maintenance for 1 year, doing well, about to get his first take home

Thoughts

- Did BZDs cause his fall?
  - or did not taking BZDs cause his fall?
- Should he get take homes?
- Is it possible for him to come off of BZDs? How?
- Did teenage BZD treatment cause his heroin addiction?

History and Epidemiology

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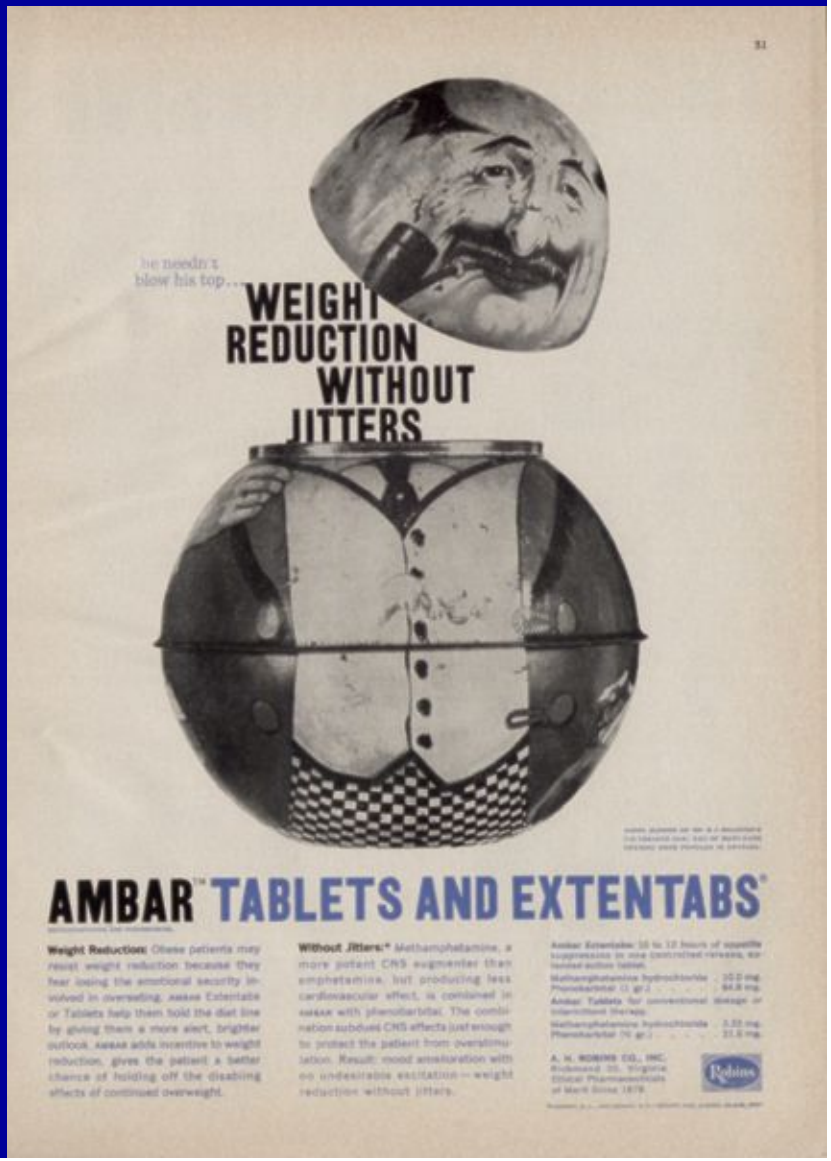
History

- First discovered in 1954 by a Austrian scientist, Leo Sternbach → Librium
- 1963 → Valium
- Used for anxiety, seizures, withdrawal, insomnia, drug-associated agitation



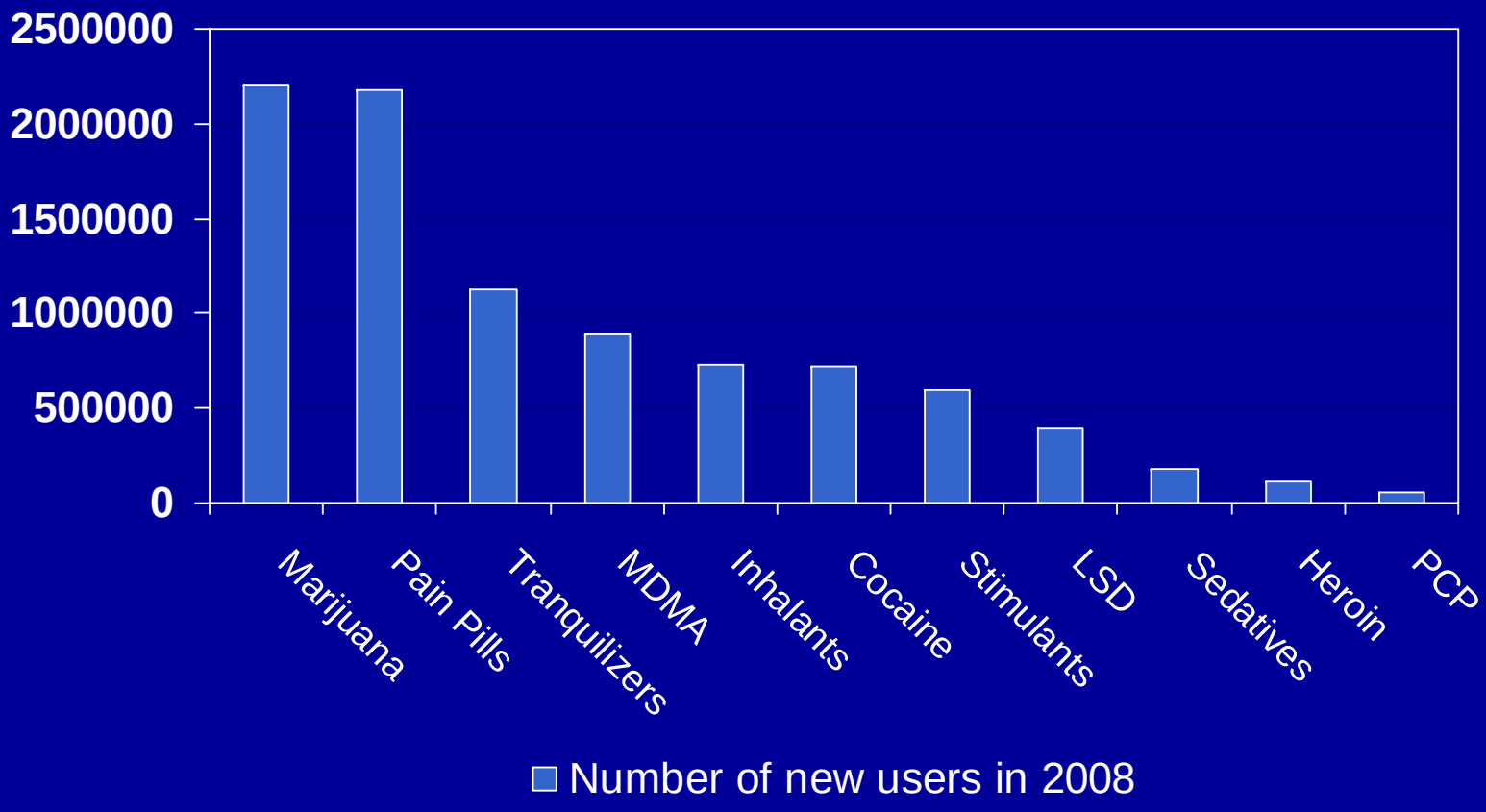
History

- Widely available starting in the 1960s
- 1973 – 87 million prescriptions
- 1980s – high potency benzodiazepines found to be more effective for panic and anxiety than other drugs
  - Advantages: rapid onset and less risk of dependence
- 2007 – 74 millions prescriptions

Widespread Use

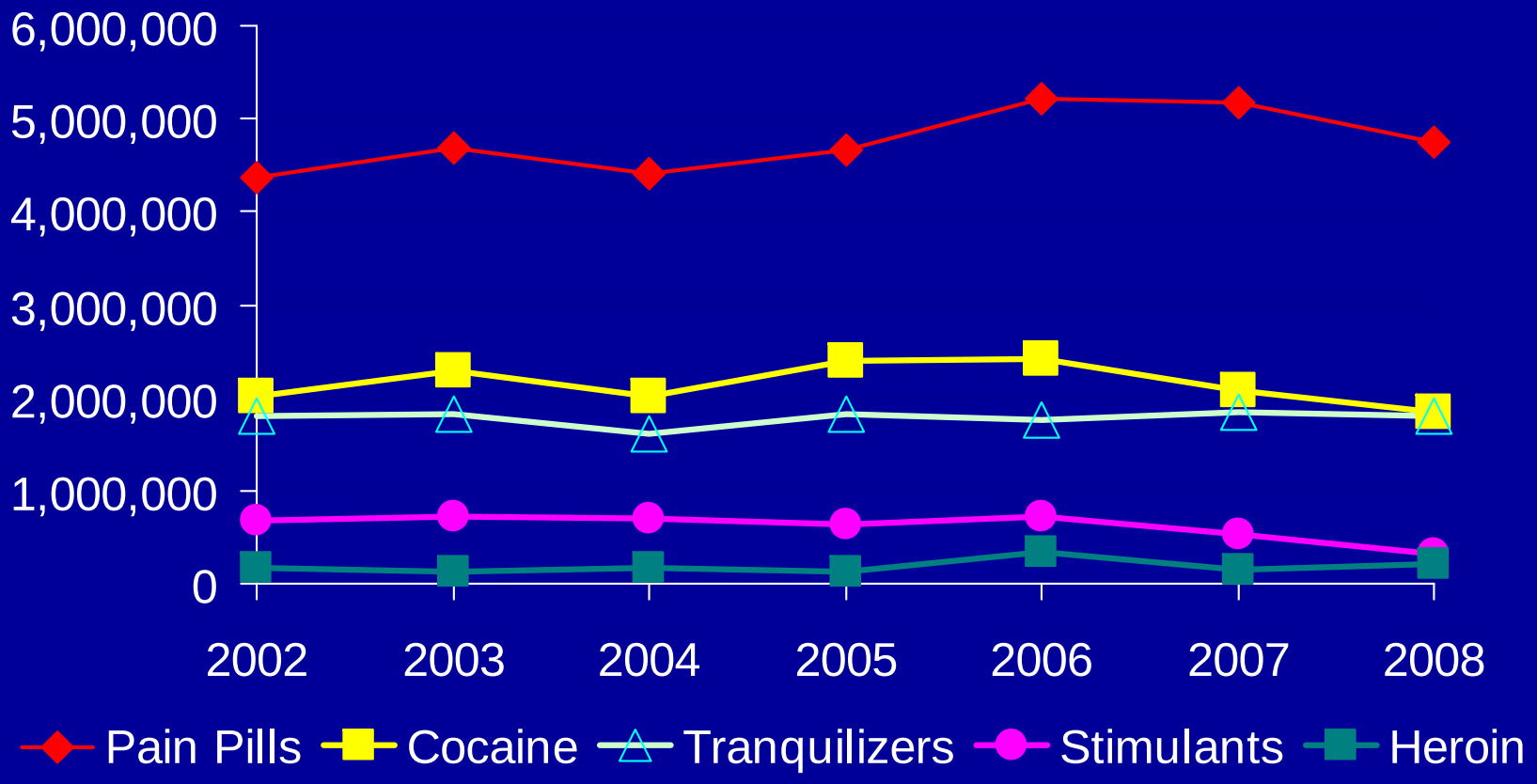
- Due to their significant margin of safety and effectiveness
  - BZDs are among the most prescribed psychotropic medications worldwide
  - On WHO essential drug list that should be available in all countries

New Users - 2008 NSDUH



Nonmedical use – “not prescribed for the respondent or that the respondent took only for the experience or feeling that the drug caused”

Past Month Use: 2002-2008

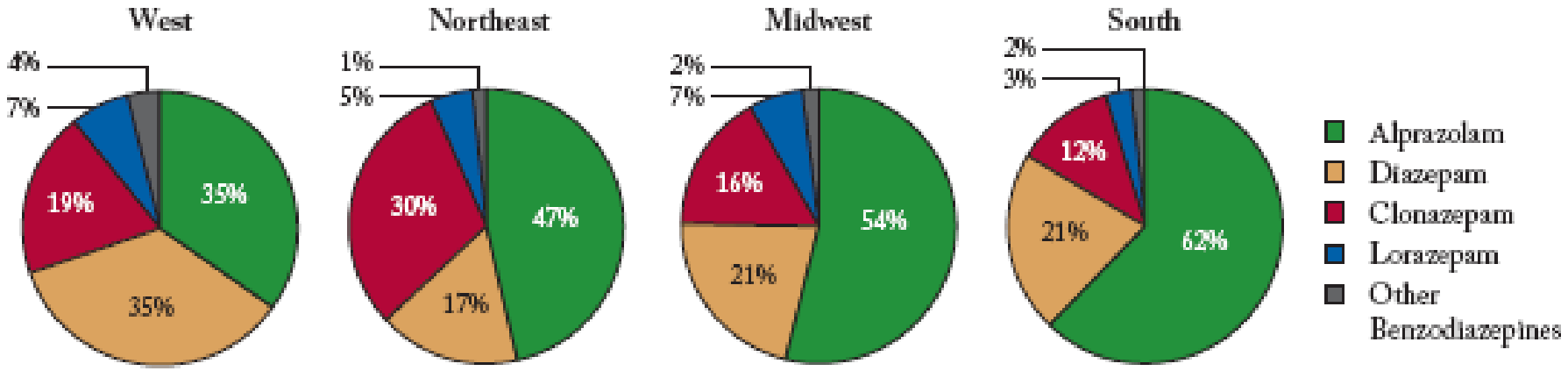


CRIT 2010 NSDUH 2008

DEA NFLIS 2006 Report

- Prescription drugs seized by law enforcement and analyzed forensics labs

Figure 1. Distribution of benzodiazepines within region, 2001–2005.



DEA NFLIS 2006 Report

- Prescription drugs seized by law enforcement and analyzed forensics labs: 2001-2005

Drug	Rx Dispensed	Items seized per 10k Rx Dispensed
Diazepam	65M	6.06
Alprazolam	169M	5.96
Morphine	23M	5.80
Oxycodone	161M	5.29
Clonazepam	82M	3.55
Hydrocodone	550M	1.63
Codeine	165M	1.06

Benzodiazepine Effects

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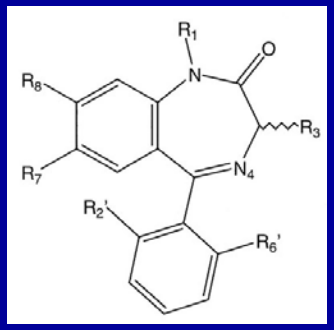
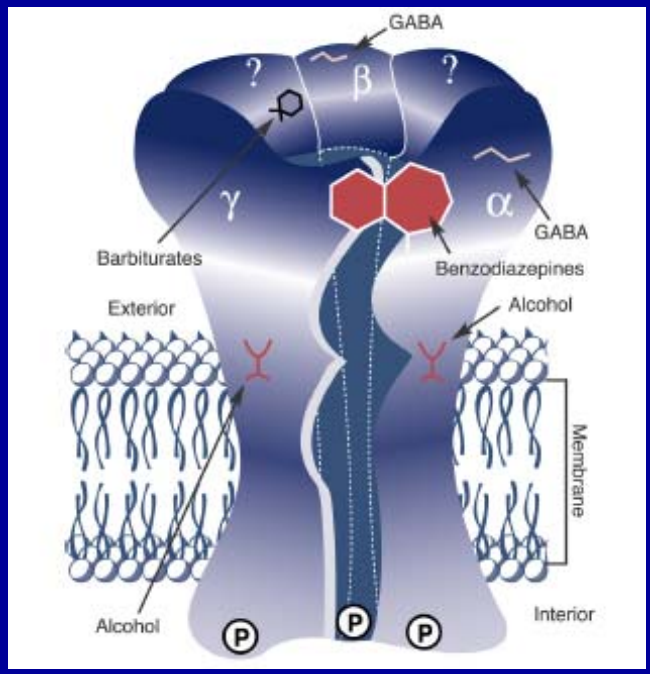
Why benzos?

- Indications for a prescription:
  - Anxiety, insomnia, nausea, seizure, agitation, procedural sedation
- Advantages:
  - Immediate anxiolysis vs. buspirone and SSRI
- Other reasons:
  - Started for acute indication, yet not discontinued
  - Boosting other sedating medications (opioids)
  - Euphoria seeking
  - Opioid or alcohol withdrawal or cocaine toxicity

Mechanism of Action

- Organic bases with BENZene ring + DIAZEPENE moiety
- Modulates the gamma-aminobutyric acid A (GABA-A) receptor boosting affinity of GABA for the receptor
  - GABA - chief inhibitory neurotransmitter
- BZDs slow the brain down
- GABA receptor density low in respiratory brainstem > limiting the incidence of respiratory depression





Classes of Benzos

- Side chains determine potency, duration of action, and elimination
- Short-acting – Oxazepam
  - few active metabolites, clearance unaffected by age or liver disease
- Intermediate-acting – Lorazepam
- Long-acting – Diazepam and chlordiazepoxide
  - active metabolites, tissue accumulation, impaired clearance with age and liver disease

Tolerance

- To sedative and euphoric effects in days
- To anti-epileptic effects limits use for chronic seizure control
- Incomplete tolerance to cognitive impairment
- To the anxiolytic effects “is practically nonexistent”

Up To Date. Sedatives and hypnotics: Pharmacology and epidemiology
Principles of Addiction Medicine, 4th edition. P.105-6.

Adverse Effects

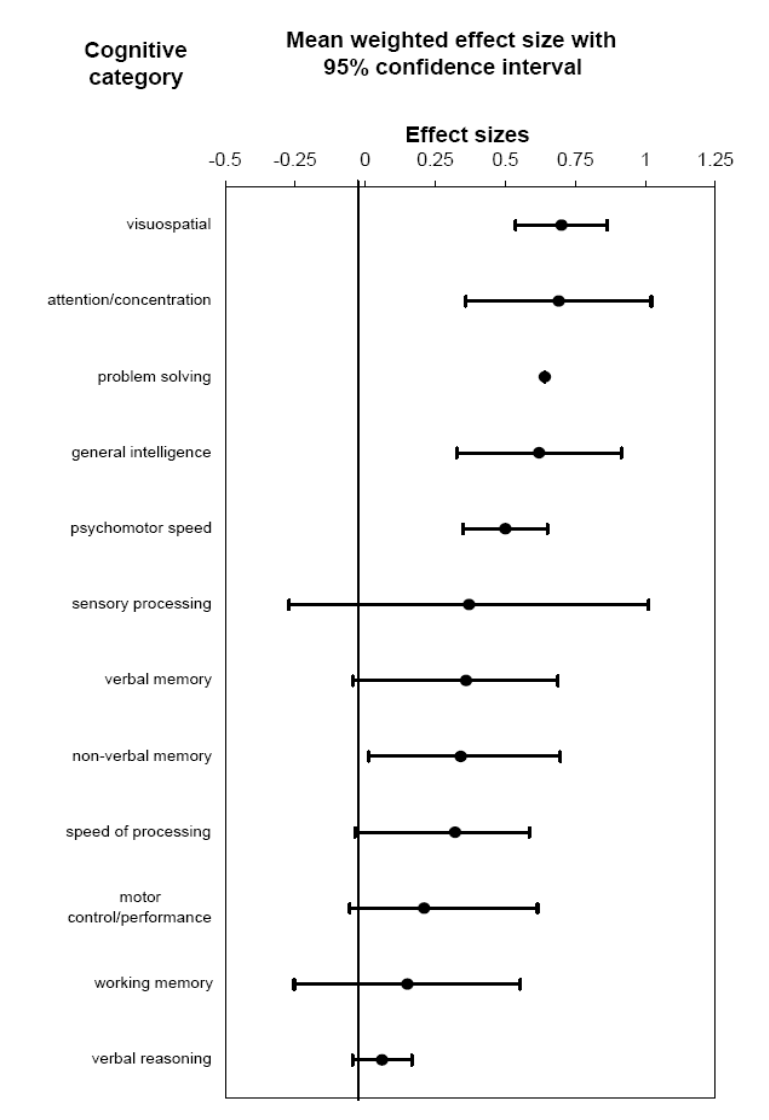
- Sedation
- Lethargy
- Respiratory Depression
- Impaired motor skills
- Impaired judgment
- Cognitive dysfunction
- Delirium
- Short-term memory impairment
- Anterograde amnesia
- Ataxia
- Hypotonia
- Depressed mood
- Exacerbation of COPD, sleep apnea

Patients often do not recognize their own impairment

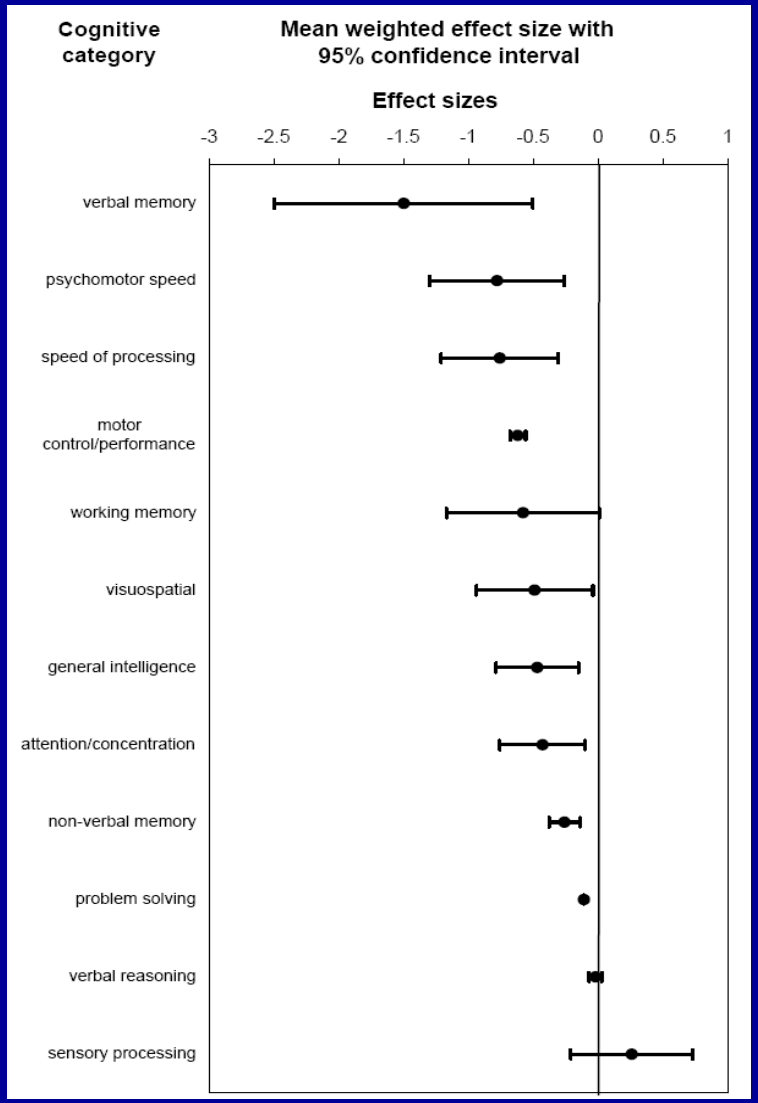
BZDs in elderly

- Among Medicare enrollees, hip fracture linked to BZDs, regardless of half-life
  - First 2wks is highest risk time
    - Wagner et al. Arch Intern Med 2004;164; 1567.
- Beers Criteria 2002 for potentially inappropriate medication use in elderly
  - Medium/high doses of short acting BZDs and all long-acting BZDs
    - Fick et al. Arch Intern Med 2003; 163; 2716.

Does the cognitive function of long-term benzo users improve following withdrawal?



Are they still impaired compared to controls or normative data?



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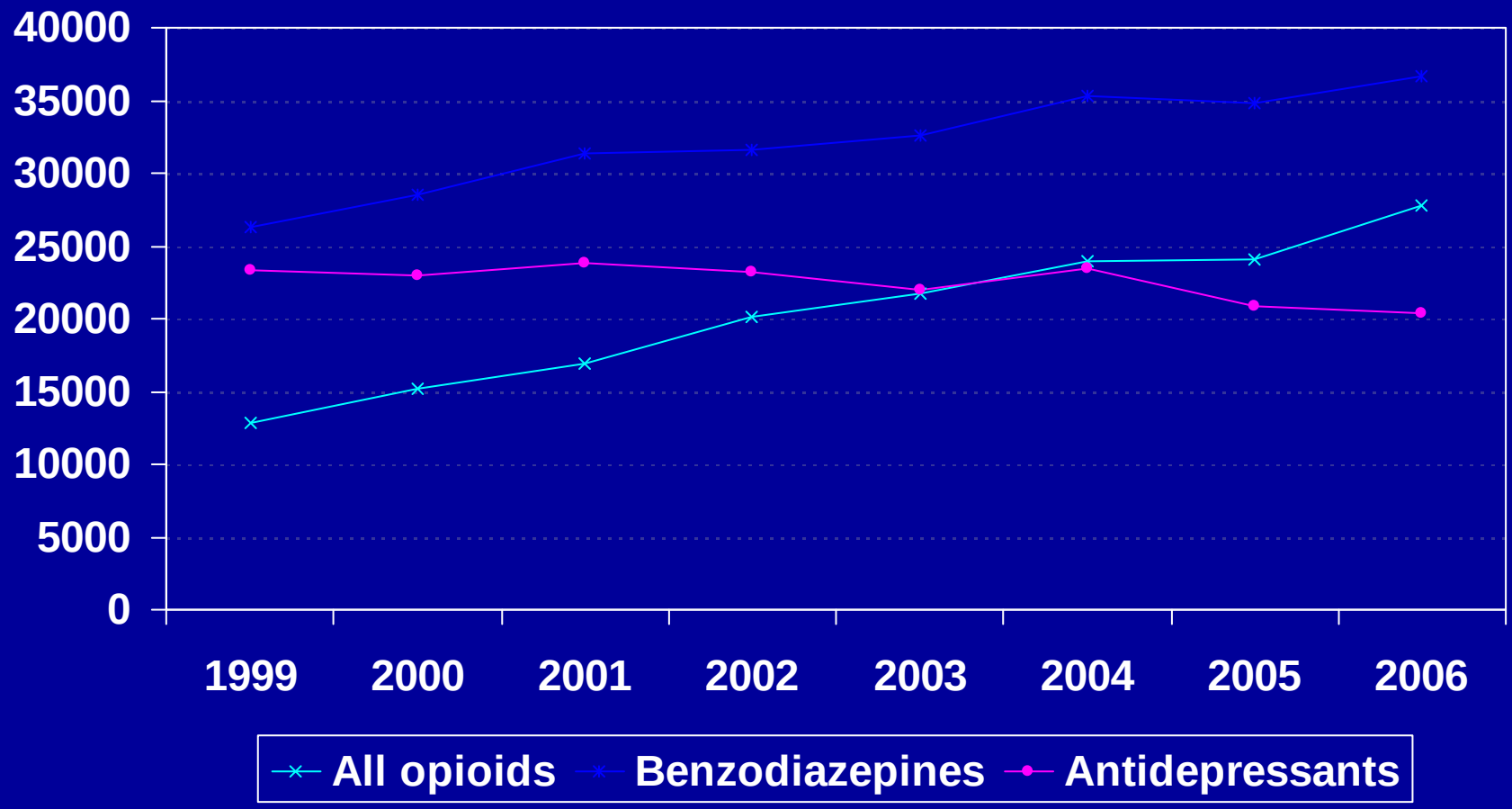
Barker. Arch Clinical Neuropsych 19 (2004) 437–454

Overdose

- Without concomitant sedating medications, benzos rarely cause life-threatening overdose
  - Sedated with normal vital signs
- Flumazenil – competitive antagonist of the GABA-A receptor that can reverse BZD actions
  - Risks of reversal (seizures and agitation) usually outweigh the benefits outside of precedural sedation

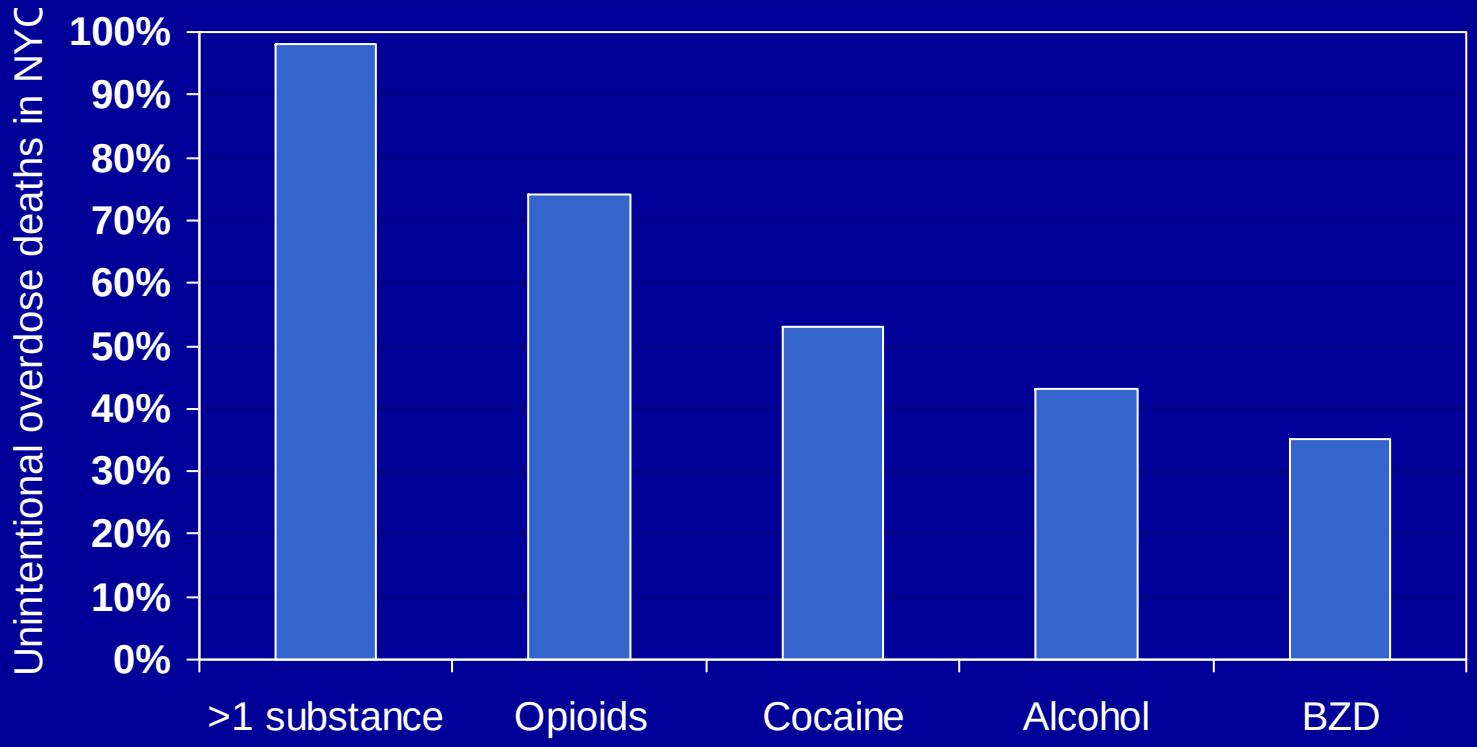
Principles of Addiction Medicine, 4th edition, chapter 47.
Up To Date. **Benzodiazepine poisoning and withdrawal**

Poisoning hospitalizations 1999-2006



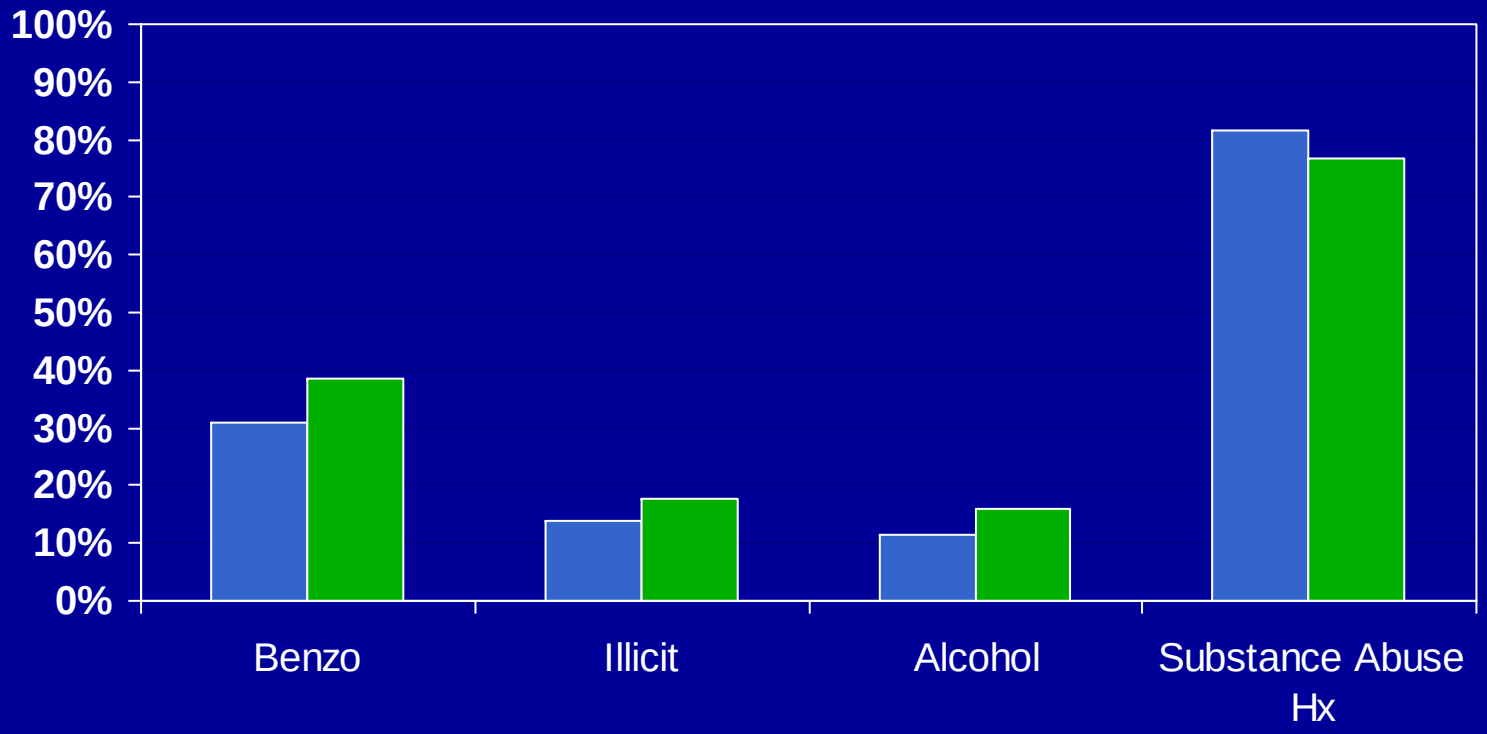
Coben et al. Am J Prev Med. 2010.

Overdose deaths in NYC 2006-2008



NYC Vital Signs. NYC DPMH. 2010

Opioid overdose deaths in WVa 2006



Paulozzi et al. Addiction 2009; 104:1541.

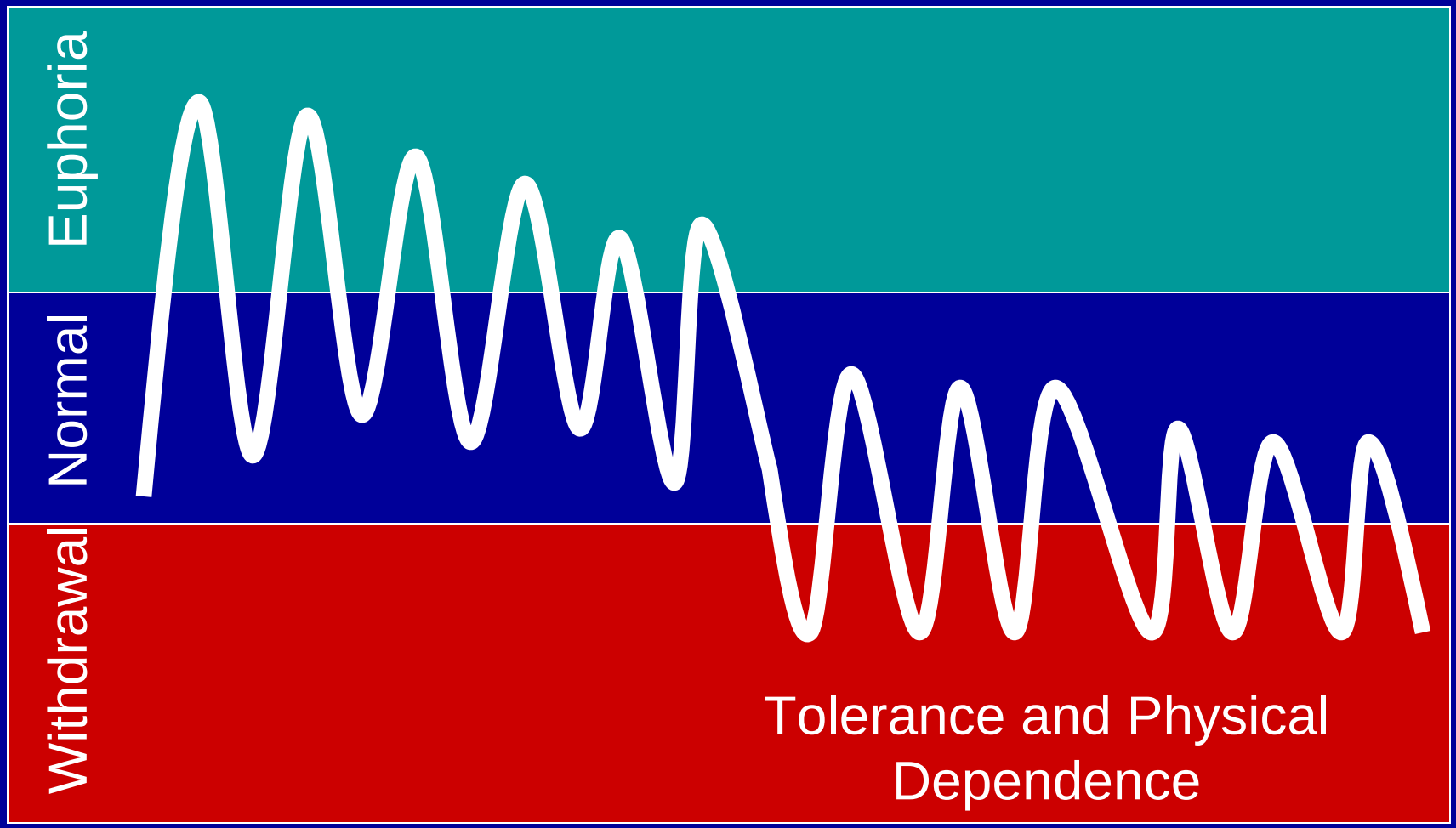
Benzos in Methadone Patients

Upon MMT entry in Israel

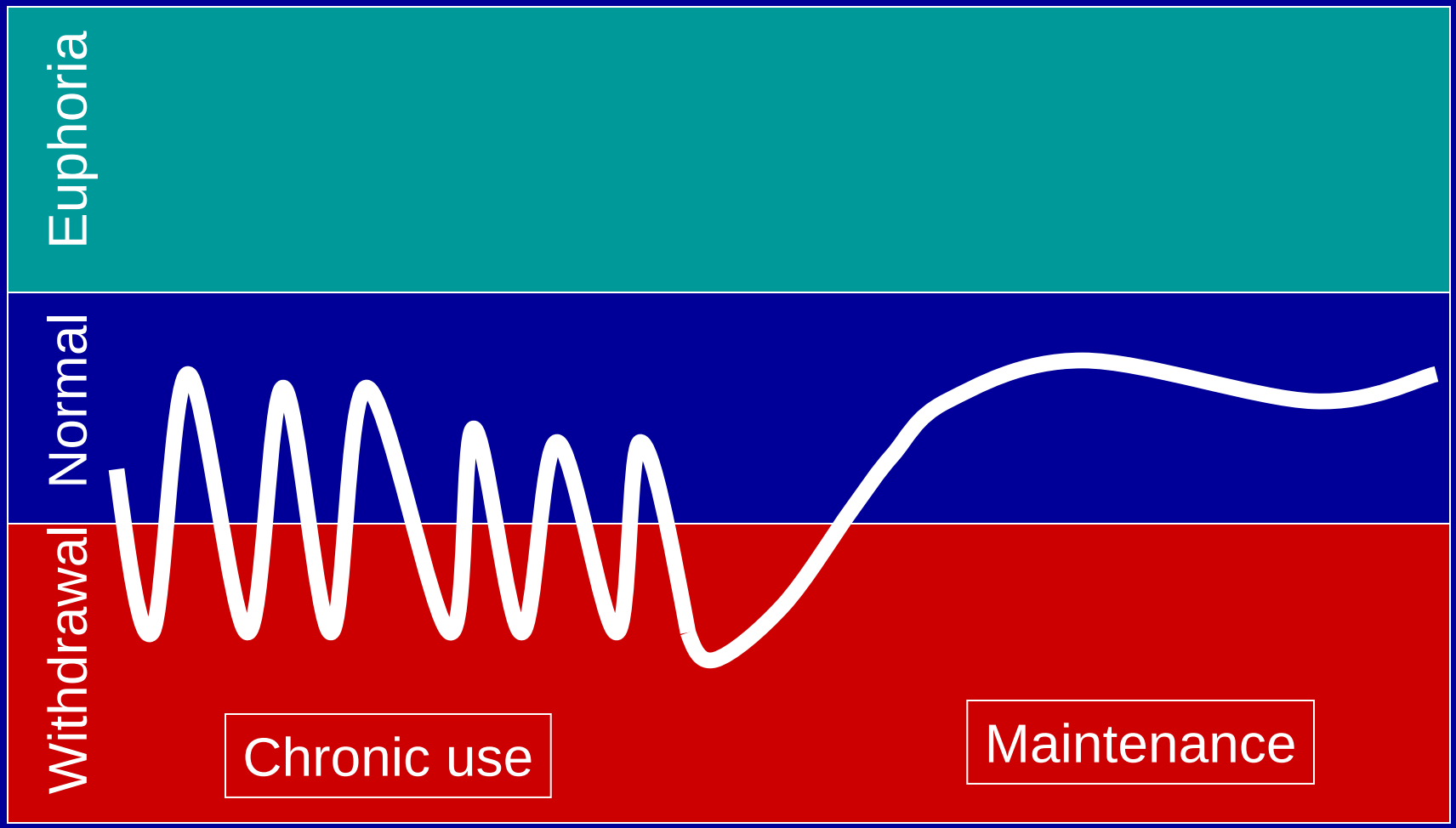
- 47% of patients abusing benzos ceased after 1 year
- 27% of patients not abusing benzos had started by 1 year
- Reasons for abuse included:
  - 87% to improve emotional state
  - 41% to boost other drugs
  - 40% for sleep
  - 24% to get high on benzos alone
  - 23% for withdrawal
  - 19% to reduce the effects of stimulants

Gelkopf et al. DAD 1999; 55: 63-68.

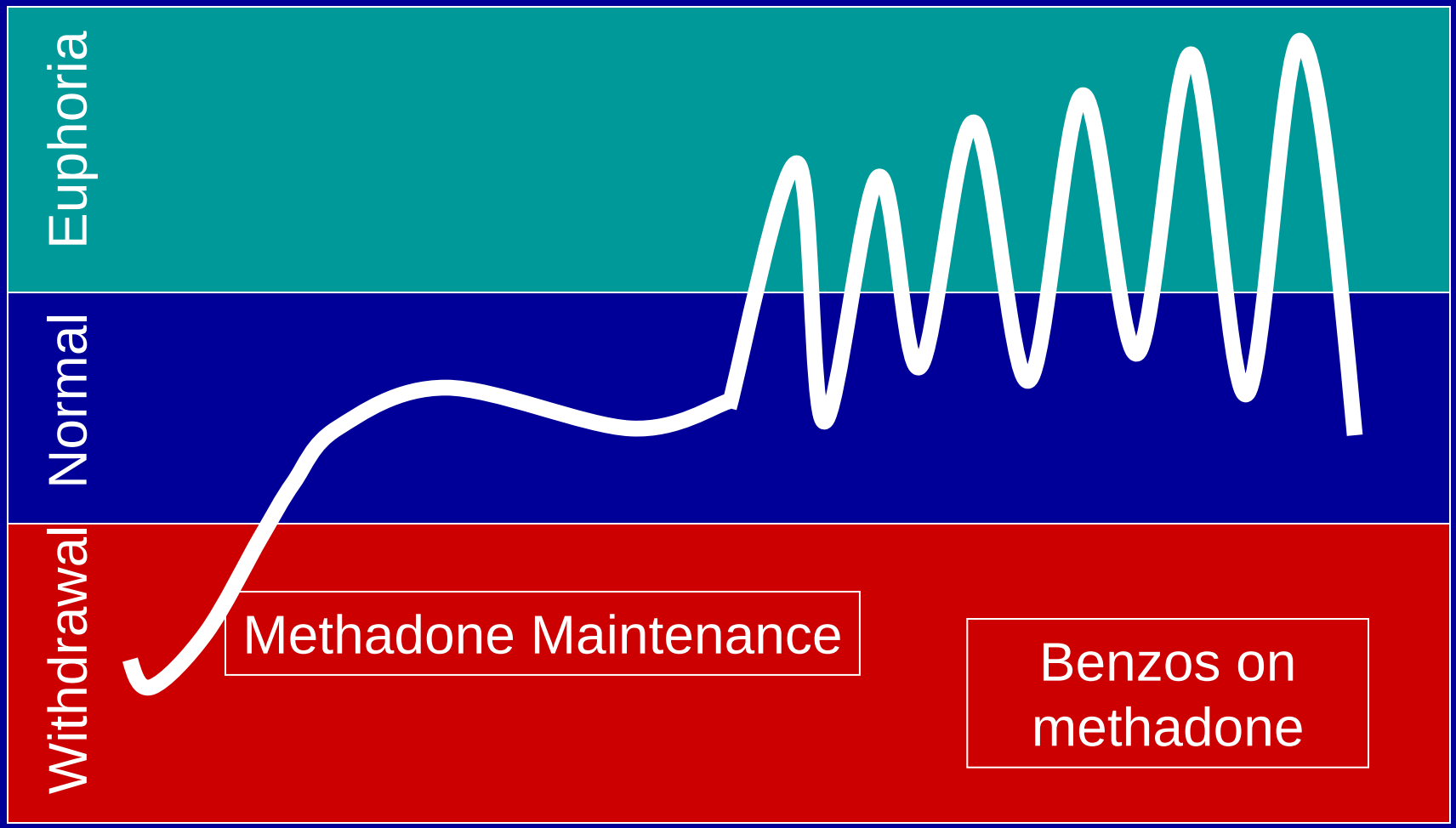
Acute to chronic opioid use



Methadone Maintenance



Boosting methadone with benzodiazepines



Overdose and oversedation

Among 250 opioid dependent subjects with previous methadone or buprenorphine prescriptions, reported the following symptoms when also taking benzos:

Symptom	Methadone	BPN
Extreme drowsiness	42%	24%
Unconsciousness	7%	3%
Overdose	7%	1%

Nielsen. Addiction 2007; 102: 616-622.

Withdrawal Syndrome

- Symptoms? >Similar to alcohol withdrawal
  - Tremors, anxiety, perceptual disturbances, dysphoria, psychosis, seizures
- Onset of symptoms?
  - Varies by how long BZD has been used and half-life
    - can occur w/in hours for short-acting or weeks for long-acting

Treatment

Prescribers are ambivalent

On the one hand

- Rarely the abuse drug of choice
- Given the amounts prescribed, benzo abuse is “remarkably low”
- Benzos work fast with few side effects
- Benefit maintained over time

Schenck CH; Mahowald MW Am J Med 1996 Mar;100(3):333-7.

On the other hand

- Non-medical use very common
- Concerning subgroups
  - Other sedating meds
  - Elderly
  - Other addictions
- Hard to discontinue
- Does not improve long-term course of PTSD
- Co-morbid depression may worsen

Stevens, Pollack. J Clin Psychiatry 2005; 66s2: 21-27

Which hand?

Consider when prescribing benzos

- Intent –
  - Are you treating a diagnosed medical problem?
- Effect –
  - Does the medication improve the patient's functional status or worsen it?
- Monitoring –
  - Are you assessing the patient at the peak or trough effect of the medication?

Withdrawing benzodiazepines

Don’t stop BZDs abruptly due to risk of withdrawal seizures

Strategy 1 - Taper over weeks to months

- Taper 10% starting dose every 1-2 wks
- Decrease taper amount and lengthen interval for final 25-35% of taper.

Consider cognitive behavioral therapy/SSRI during and after for breakthrough symptoms

Principles of Addiction Medicine. 4th edition. P. 581-4.

Withdrawing benzodiazepines

Don't stop BZDs abruptly due to risk of withdrawal seizures

Strategy 2 - Substitute and taper

1. Stabilize on phenobarbital using hx and symptoms
2. Dose TID
3. Taper 30mg per day or slower

Drug	Phenobarbital 30mg equiv.
Alprazolam	0.5-1mg
Clonazepam	1-2mg
Diazepam	10mg
Lorazepam	2mg

Consider cognitive behavioral therapy/SSRI during and after for breakthrough symptoms

Principles of Addiction Medicine. 4th edition. P. 581-4, 649.

Withdrawing benzodiazepines

Don't stop BZDs abruptly due to risk of withdrawal seizures

Strategy 3 – Taper with adjunct

- Short BZD taper (3 days?) and treat with anti-convulsant for 2-3 weeks
  - carbamazepine 200 TID or
  - valproic acid 250TID

Consider cognitive behavioral therapy/SSRI during and after for breakthrough symptoms

Principles of Addiction Medicine. 4th edition. P. 581-4.
Pages and Ries. Am J Addictions 1998:7;198.
Harris et al. Alcohol Alcohol 2000:35; 319-325.

BZD treatment – Cochrane Review

Cochrane review authors conclusions:

1. Gradual taper is preferable to abrupt discontinuation
2. Carbamazepine appears to be a helpful adjunct to gradual taper
3. Confirming the benefit of switching from short to long-acting at beginning of taper requires further study

Denis et al. Pharmacological interventions for benzodiazepine **mono-dependence** management in outpatient settings. *Cochrane Database of Systemic Reviews.* 2006.

Patient's perspective on chronic benzo use

- Purpose of benzos
  - Means of coping with stress/anxiety and insomnia
    - "Sometimes my life gets so up in the air that I say to my children, right now I wish I had a wafer-sized Valium."
  - Lifeline or life-transforming properties
    - "It makes me want to go on living."
    - "I think if it weren't for the chemicals I wouldn't be chugging along."
    - "I don't mentally think I would have survived without it and that's the truth."
  - Lack of awareness, underestimation, disregard for side effects
    - "He wouldn't have given it to me if he thought it was gonna hurt me."
    - "It's just a small, little, tiny white pill."
    - "It's the lowest dose that they make."
    - "My head always feels foggy."

Cook et al. JGIM 2007: 22; 1094-1100.

Patient's perspective on chronic benzo use

- Attitudes toward taper/ discontinuation
  - Resistance to taper
    - "I see no reason why I should put myself through hell… We don't have that long to live and we might as well enjoy ourselves while we're here."
    - "On numerous occasions I've tried to go off of it. And the reaction is I can't sleep and I'm totally wired. I'm up all night."
  - Rejection of psychological interventions
    - "I just don't want to. I'm not one of those people who can sit around and talk about my problems with strangers."
  - The physician-patient relationship
    - "I have complete faith in Dr. _____. I mean we go back a lot of years. Whatever he says, goes."

Cook et al. JGIM 2007: 22; 1094-1100.

Case

- 29 yo man presents for follow-up at methadone clinic after inpatient admission for femur fracture from falling onto subway track from platform.
- Treated with clonazepam since age 16 for panic disorder. Takes 6mg in divided doses daily. Missed his afternoon dose, the day of the accident
- Started using heroin at age 23
- On methadone maintenance for 1 year, doing well, about to get his first take home

Questions

- Did BZDs cause his fall?
  - Or did not taking BZDs cause his fall?
- Should he get take homes?
- Is it possible for him to come off of BZDs? How?
- Did teenage BZD treatment cause his heroin addiction?

What should be done about benzos?

- Prescribe with caution
- Educate patients
  - Safety first – Teens, mixing meds
  - Function over feelings
  - Risk of tolerance to benefits and withdrawal
  - Communication among prescribers
- Discontinue if risks outweigh the benefits

Thanks!

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Benzos in Methadone Patients

Among 361 cocaine/heroin users enrolled in a contingency management trial, benzodiazepine use was associated with

- Increased cocaine use during treatment
- Blunted response to CM

Ghitza er al. DAD 2008; 97:150-157.

Prescription Drug Misuse

- Higher doses than prescribed
- More frequently than prescribed
- Without a prescription
- Reasons other than intended by the prescriber

Self-medication

- One physician survey reported that:
  - 26% of psychiatrists
  - 11% of other physcians

  Used unsupervised benzodiazepines in the past year

Principles of Addiction Medicine, 4th edition p.535.

Benzodiazepine kinetics

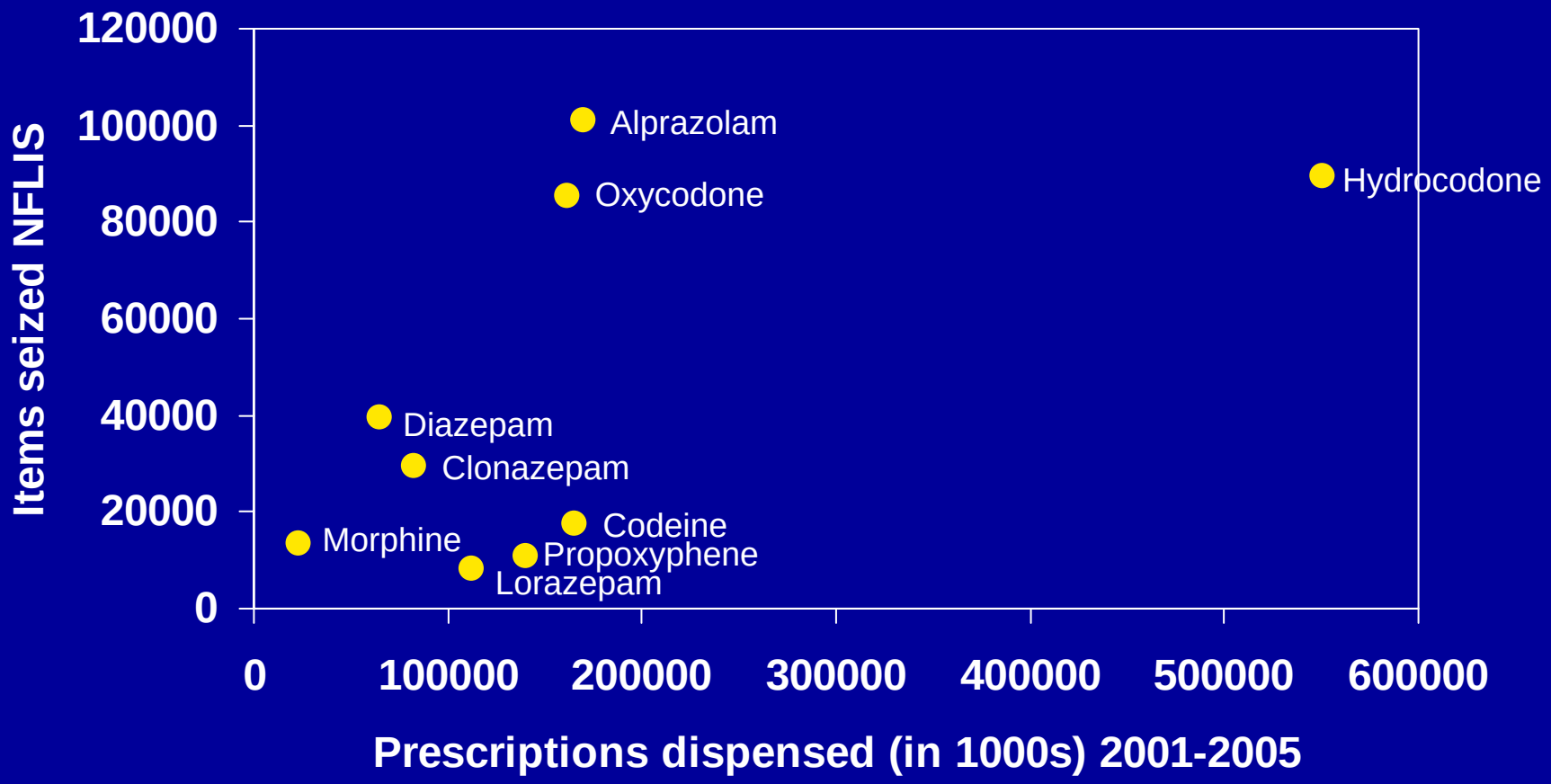
Generic name	Brand name	Usual dose (oral)	Oral peak (hr)	Half-life (hr) parent	Metabolite activity*	CYP3A4 interactions
Alprazolam	Xanax	0.25-0.5 mg	1-2	6-27	Inactive	Yes
Clonazepam	Klonopin	0.25-0.5mg	1-2	18-50	Inactive	Limited
Chlordiazepoxide	Librium	5-25 mg	0.5-4	5-30	Active	Yes
Clorazepate	Tranxene	7.5-15 mg	1-2	Prodrug	Active	No
Diazepam	Valium	2-10 mg	0.5-1	20-50	Active	Limited
Lorazepam	Ativan	0.5-3 mg	2-4	10-20	Inactive	No
Flurazepam	Dalmane	15-30 mg	0.5-1	2-4	Active	Limited
Flunitrazepam	Rohypnol	0.5-2 mg	1-2	16-35	Active	Limited
Midazolam	Versed	0.025-0.1 mg	1-2	1.5-3	Active	Yes
Oxazepam	Serax	10-30 mg	2-4	5-20	Inactive	No
Temazepam	Restoril	7.5-30 mg	1-2	3-19	Inactive	No
Triazolam	Halcion	0.125-0.25 mg	0.7-2	2-3	Inactive	Yes
Zolpidem•	Ambien	5-10 mg	1-2	1.5-4.5	Inactive	Limited

Duration of action of compounds having active metabolite(s) is significantly greater than predicted by half-life of parent.

* Half-life of active metabolite(s) may exceed 50-100 hours.

• Nonbenzodiazepine hypnotic.

DEA NFLIS 2006 Report



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Pharmacology & Kinetics

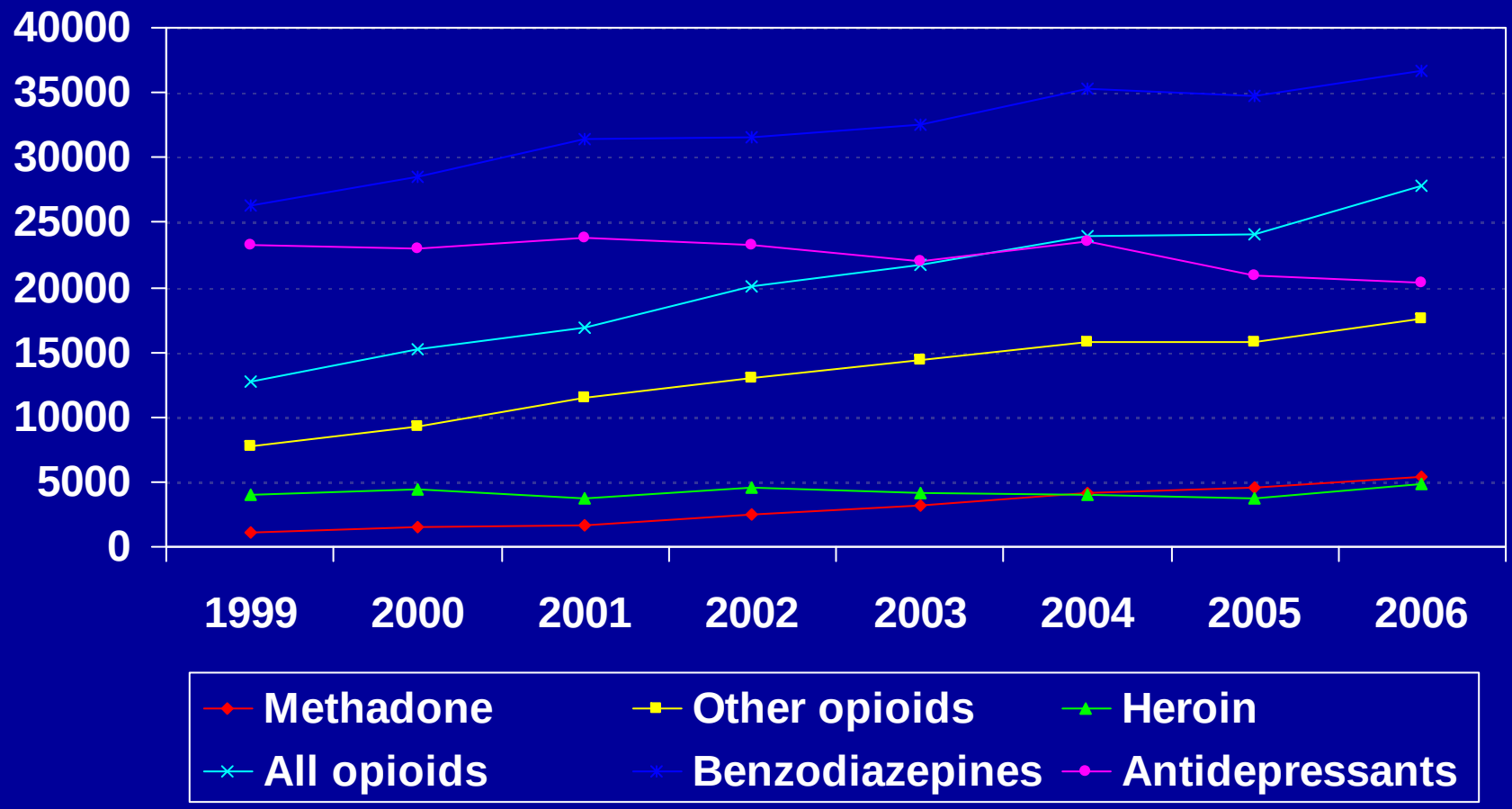
- Acts on GABA receptors by potentiating it's inhibitory effects on the CNS
- Kinetics divided into three groups:
  - Short acting
    - Triazolam (Halcion), Oxazepam (Serax), Alprazolam (Xanax)
    - Midazolam (Versed) → but has more active metabolites
  - Intermediate acting
    - Lorazepam (Ativan), Temazepam (Restoril)
  - Long acting
    - Diazepam (Valium), Chlordiazepoxide (Librium), Clonazepam (Klonopin)
- Rapidly absorbed in GI tract, metabolized in liver

Withdrawal syndrome

Marked decrease or cessation of benzodiazepines after several weeks of regular use and 2 or more …

- Autonomic hyperreactivity
- Increased hand tremor
- Insomnia
- Nausea or vomiting
- Hallucinations
- Psychomotor agitation
- Anxiety
- Tonic-clonic seizures

Poisoning hospitalizations 1999-2006



Coben et al. Am J Prev Med. 2010.

Benzos for panic disorder
Anxiolysis maintained – dose decreased

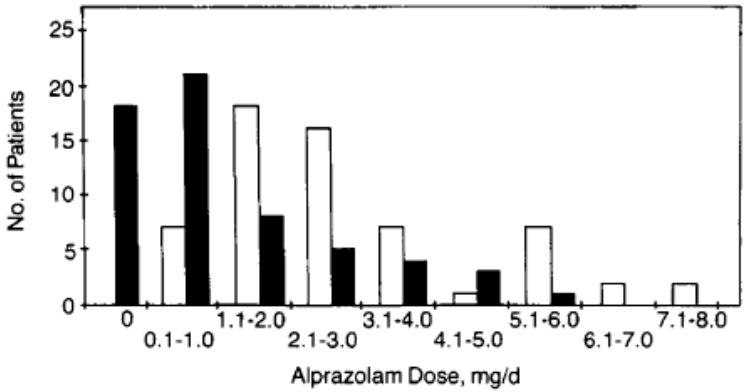


Fig 1.—Frequency distribution of daily alprazolam dose at discharge (open bars) and follow-up (FU) (closed bars) illustrates reduction in dose (36 [60%] of patients) or discontinuation of alprazolam (18 [30%] of patients) at FU. Mean ± SEM dose was 3.1 ± 0.2 mg/d at time of discharge for total group and 1.2 ± 0.2 mg/d at FU (1.8 ± 0.2 mg/d for patients continuing to receive alprazolam at FU, discharge vs FU, both groups, $P<.001$, paired t test, two-tailed).

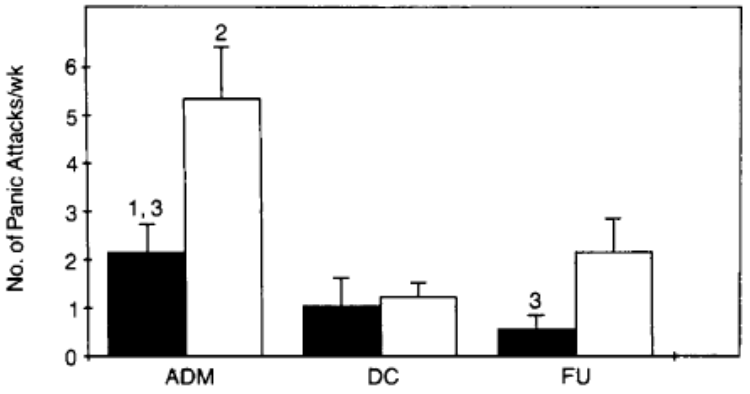
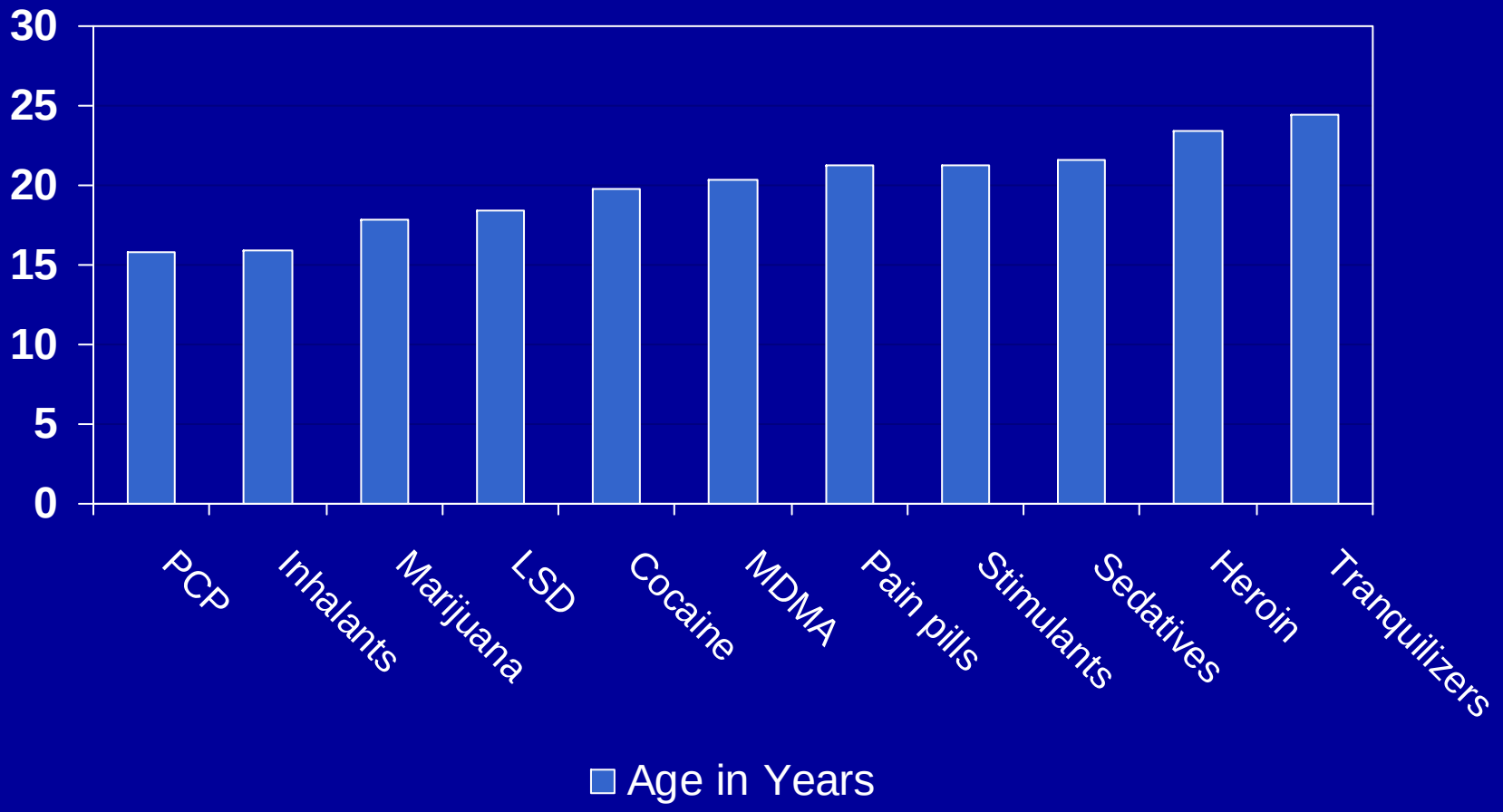


Fig 2.—Frequency of panic attacks at admission (ADM), discharge (DC), and follow-up (FU) for subgroups receiving (open bars) and not receiving (closed bars) alprazolam at FU. 1 indicates patients not receiving alprazolam at FU: ADM vs DC, $P<.05$, and ADM vs FU, $P=.01$, paired t test, two-tailed; 2, patients receiving alprazolam at FU: ADM vs DC, $P<.001$, and ADM vs FU, $P=.005$, paired t test, two-tailed; and 3, patients not receiving alprazolam at FU vs patients receving alprazolam at FU: status at ADM, $P<.05$, and status at FU, $P<.05$, Student's t test, two-tailed.

Nagy et al. Arch Gen Psychiatry 1989: 46; 993.

N=60 – Natural history observation cohort

Mean Age at First Use 2008 NSDUH



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Z drugs

- Zolpidem (ambien), esopiclone (lunesta) and zaleplon (sonata)
- Same GABA target
- Case reports of withdrawal and abuse
- Post-marketing surveillance indicates low abuse potential considering the amount prescribed

Urine testing

- Urine specimens contain little parent BZD
- Many immunoassays detect oxazepam: less likely clonazepam, lorazepam or triazolam unless present in high doses
- Chlorazepate, chlordiazepoxide, diazepam, and temazepam are metabolized to oxazepam

Cognitive Function

- Many studies find no cognitive impairment with long-term BZD
- Others find impaired psychomotor, learning, concentration and visuospatial function
- Improvement when discontinued, though function still worse at 6 months
- Most patients do not recognize impairment

Metabolism

- Primarily hepatic, typically by CYP2C19 and/or CYP3A4
- Oxazepam, temazepam, and lorazepam are not metabolized by the liver, and excreted by the kidney

Up To Date. **Benzodiazepine poisoning and withdrawal**