

Benzodiazepines

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Objectives

1. Appreciate the epidemiology and risks of benzodiazepine misuse
2. Be able to identify patients who are misusing benzodiazepines
3. Be able to formulate practical and individualized treatment strategies for benzodiazepine misuse.

Indications

- Anxiolytic: chronic anxiety, phobias, panic attacks
- Sedative and hypnotic: sleep disturbance and anesthesia
- Anticonvulsant: status epilepticus, epilepsy
- Muscle relaxant: muscle spasm/spasticity
- Alcohol Withdrawal

Neurobiology- GABA-A receptor complex

- Each receptor has five subunits
- Most include two α , two β , and one γ , δ , ϵ , π , or θ
- Activation= influx of Cl ions, and a hyperpolarization
- Therefore, it inhibits the excitability of neuron
- Benzos: Bind to cleft of α and γ ; increase *frequency* of channel opening
- Barbiturates: Bind to α , and increase *duration* of opening

Subunit selectivity for specific agents

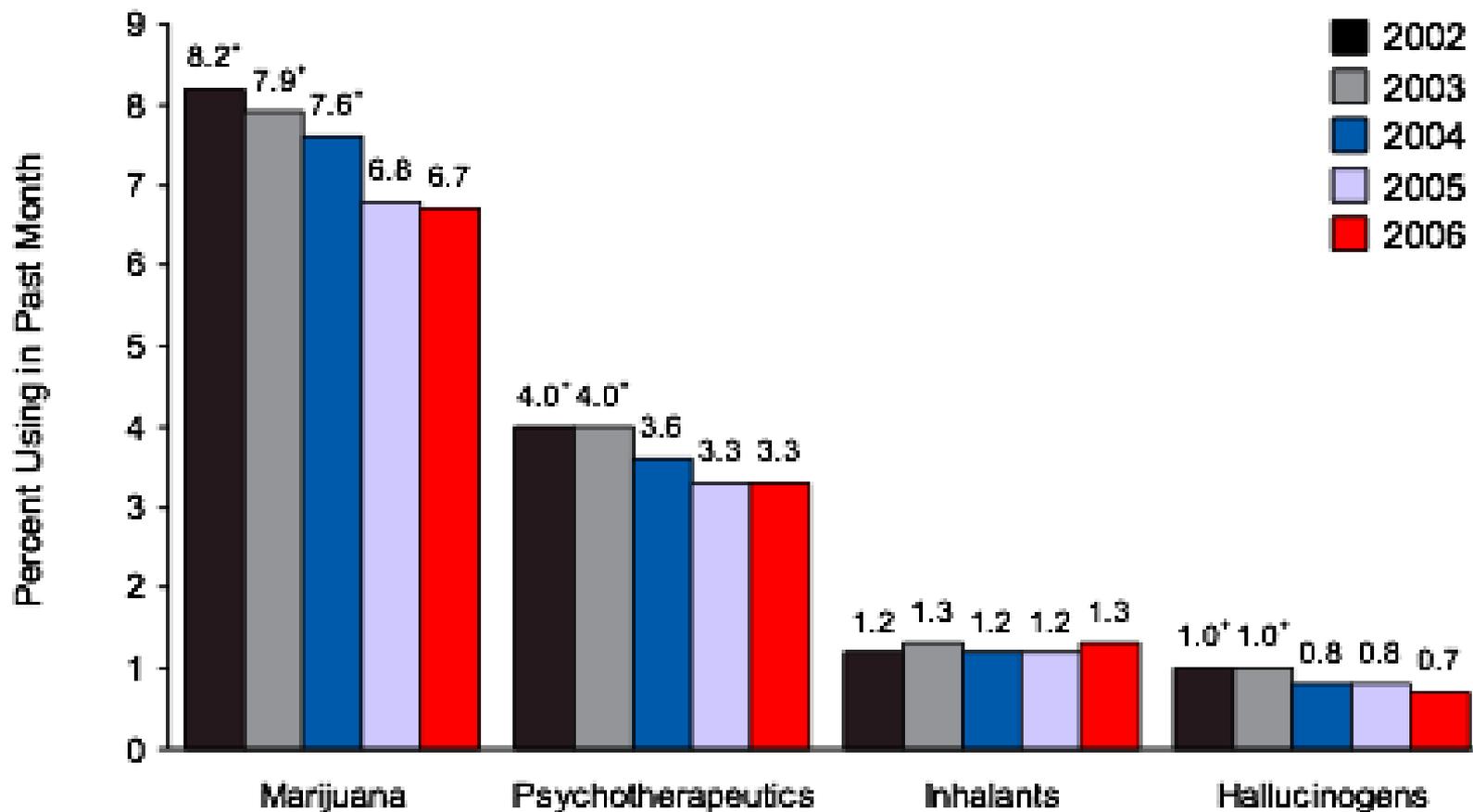
- $\alpha 1-3, 5$ + any β and $\gamma 2$: benzodiazepines
- $\alpha 1$: selective non-benzo hypnotics [Z-drugs]
- $\alpha 1-6$ + γ or δ : alcohol
- $\beta 3, \beta 2$: anesthetics
- $\beta 3, \alpha 6$: barbiturates

Subunit effects

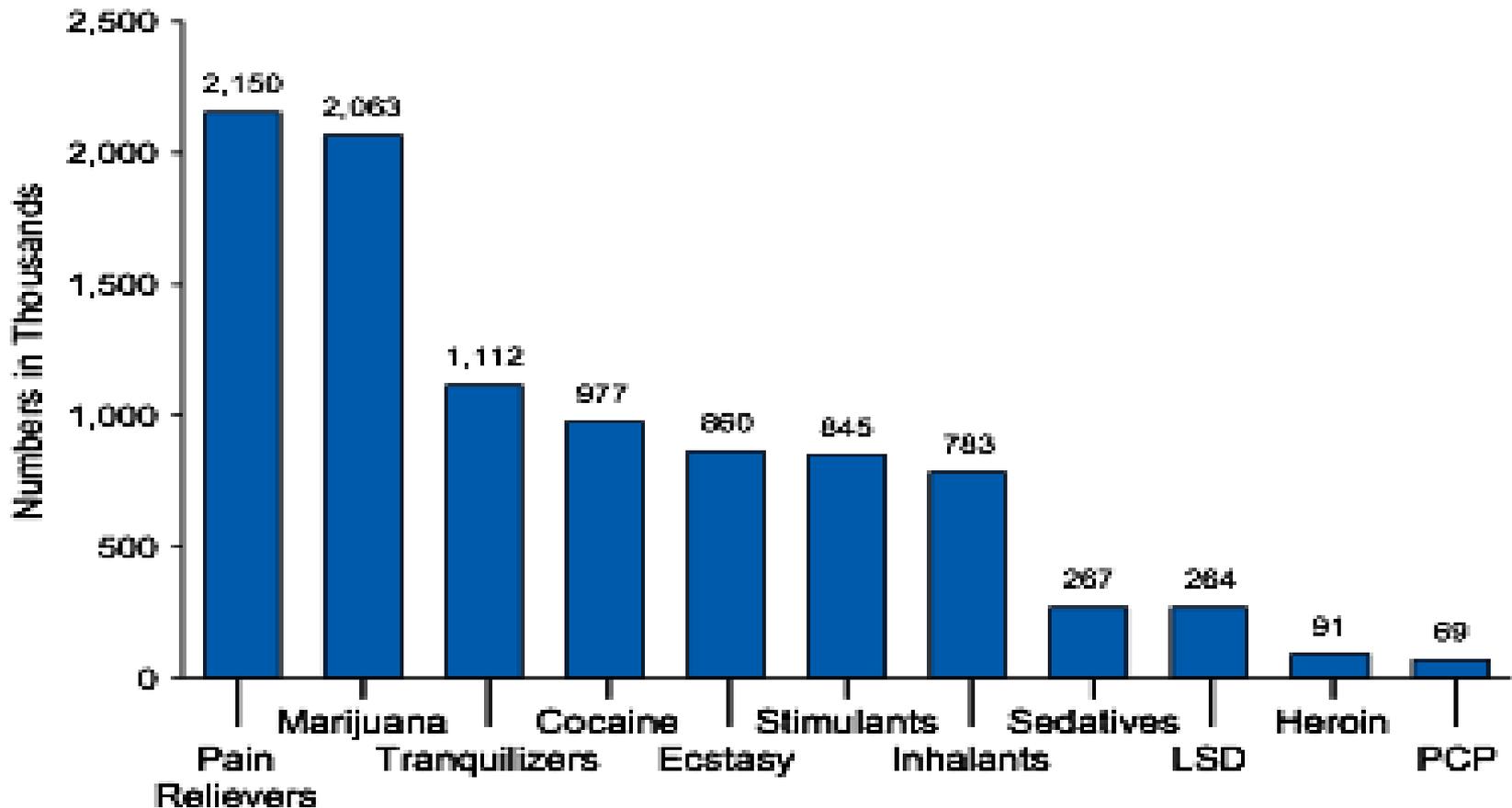
- $\alpha 1$: Sedation, sleep, reinforcement
- $\alpha 2$: anxiolysis
- $\alpha 5$: learning and memory
- $\alpha 3, \alpha 5$: sensorimotor processing
- $\gamma 2$: physiologic dependence

Epidemiology

Past month use, ages 12-17, 2002-2006 [NSDUH, 2006]



Past Year Initiates, 12 and older, 2006 [NSDUH, 2006]



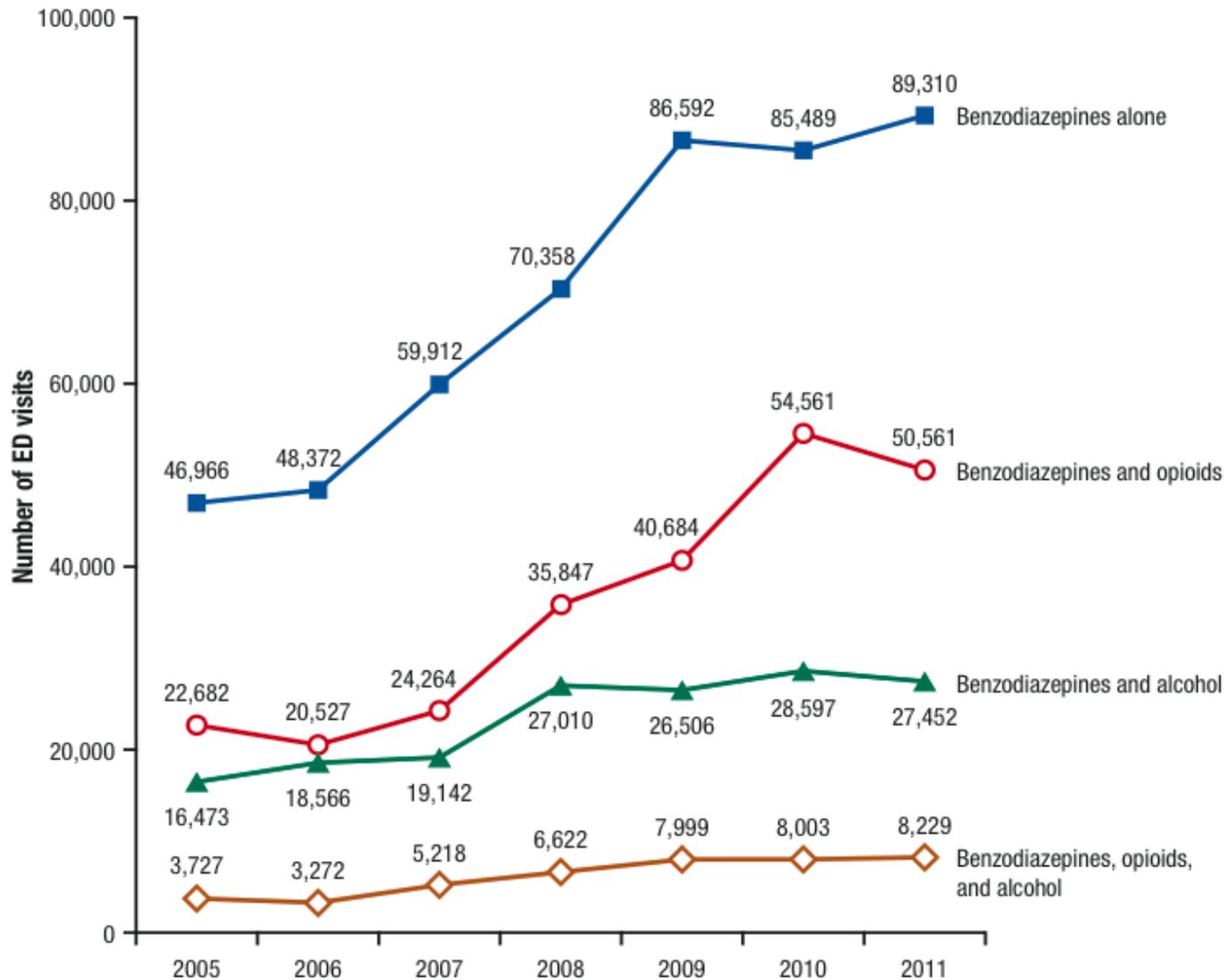
Past year prevalence of illicit drug use among 12th graders, 2006

Drug	Prevalence (%)	Drug	Prevalence (%)
marijuana	31.5	Ecstasy	4.1
vicodin	9.7	Meth	2.5
amphetamines	8.1	Crack	2.1
Cough medicine	6.9	“Ice”	1.9
sedatives	6.6	steroid	1.8
tranquilizers	6.6	LSD	1.7
Cocaine	5.7	ketamine	1.4
Cocaine powder	5.2	Rohypnol	1.1
inhalants	4.5	GHB	1.1
Ritalin	4.4	heroin	0.8
OxyContin	4.3	Phencyclidine	0.7

Epidemiology

- Drugs used in suicide attempts in 2009: pain relievers 38.1% [hydrocodone, oxycodone], benzos 28.7% [clonazepam, alprazolam, zolpidem]
- Alcohol a very commonly involved substance

FIGURE 1. Estimated number of emergency department (ED) visits involving benzodiazepines alone or in combination with opioids or alcohol,* by year and drug combination (patients aged 12 and older): 2005 to 2011



* No other drugs were involved.

Source: 2005 to 2011 SAMHSA Drug Abuse Warning Network (DAWN).

TABLE 2. Predicted risk (in percent) of a more serious outcome* from emergency department (ED) visits involving benzodiazepines alone or in combination with opioids or alcohol, 2005 through 2011, by drug combination and age (patients aged 12 and older)**

Drug combination	Aged 12 to 34	Aged 35 to 44	Aged 45 to 64	Aged 65 or older
Benzodiazepines alone	28%	30%	37%	39%
Benzodiazepines and opioids	37%	43%	47%	59%
Benzodiazepines and alcohol	35%	43%	51%	55%
Benzodiazepines, opioids, and alcohol	39%	47%	57%	70%

* All estimated risks are statistically significantly greater than 20% at the .05 level.

** No other drugs were involved.

Source: 2005 to 2011 SAMHSA Drug Abuse Warning Network (DAWN).

Major Hazards

Side Effects

- Benzodiazepines have been associated with the emergence or worsening of depression
- Over sedation, motor impairment, slowed cognition and amnesia
- Slurred speech, ataxia, impaired gag reflex
- Anterograde amnesia, learning difficulties and impairments in attention and concentration
- However, tolerance to these side effects can occur this can lead to complicated withdrawal

Mortality?

- BMJ, 2014 March 19.
- Effect of Anxiolytic and Hypnotic drug prescriptions on mortality hazards:
Retrospective cohort study [Weich et al.]
- N=34727 with prescribed sedative/hypnotics vs. 69416 matched controls over a 7 year period in UK
- Age adjusted hazard ratio for mortality = 3.46
- Dose response associations found for benzos and z-drugs

Mortality?

- Kripke DF, Langer RD, and Kline LE [BMJ 2012]
- USA cohort
- N=10529 patients with hypnotic prescriptions, and 23676 matched patients with no such scripts
- Followed 2.5 years
- **Results:**
- For groups prescribed
 - Up to 18 doses/year: HR 3.60
 - >132 doses/year: HR 5.32
 - Not explained by pre-existing medical conditions

Mortality?

- Mallon, Broman, and Hetta [2009] – Sleep Medicine
- Regular hypnotic use associated with significantly increased all cause mortality
- Men: HR 4.54
- Women: HR 2.03

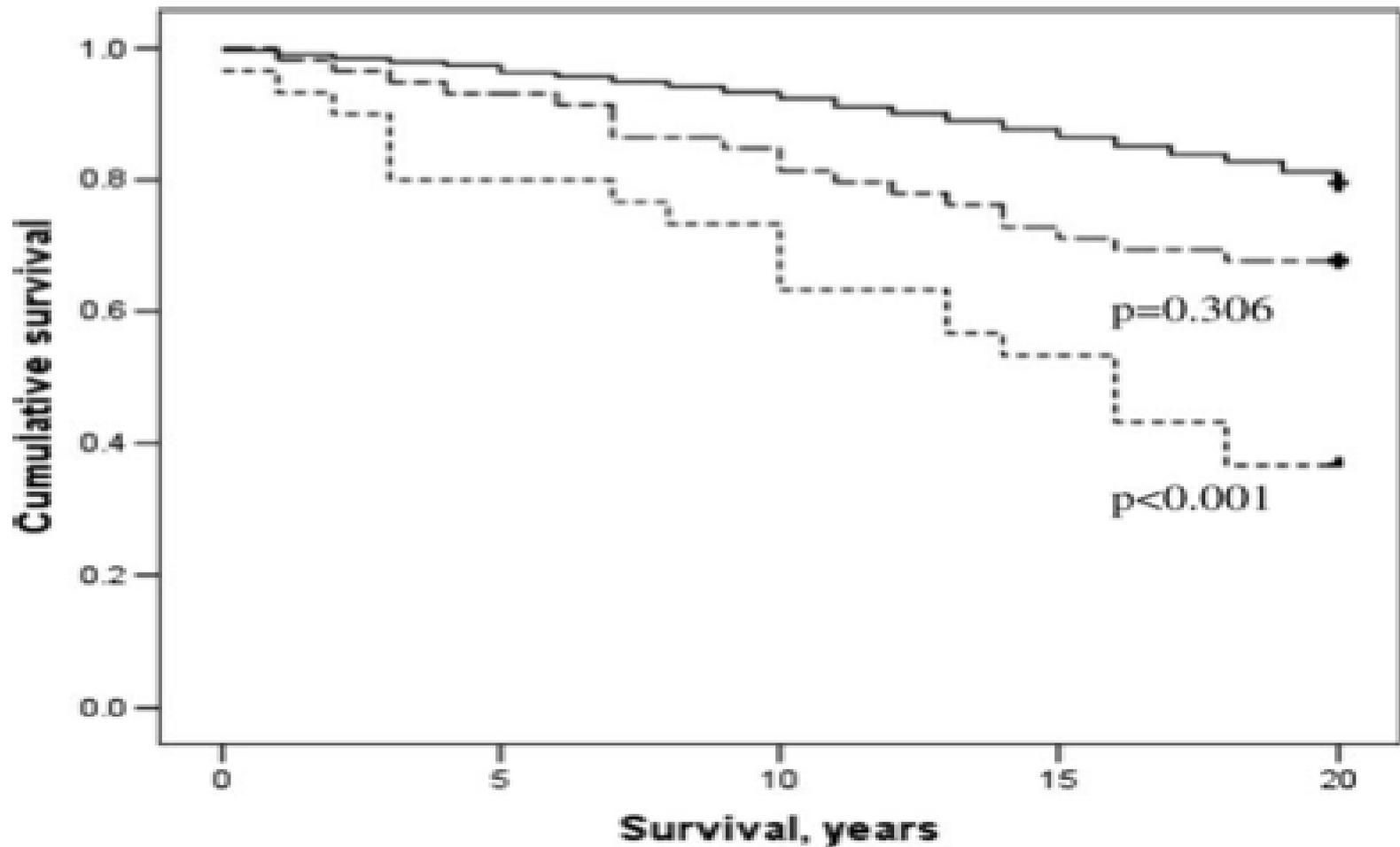


Fig. 1. Survival in men using hypnotics sometimes or regularly compared to men not using hypnotics. (—) No hypnotic usage; (---) Hypnotic usage sometimes; (-.-) Regular hypnotic usage.

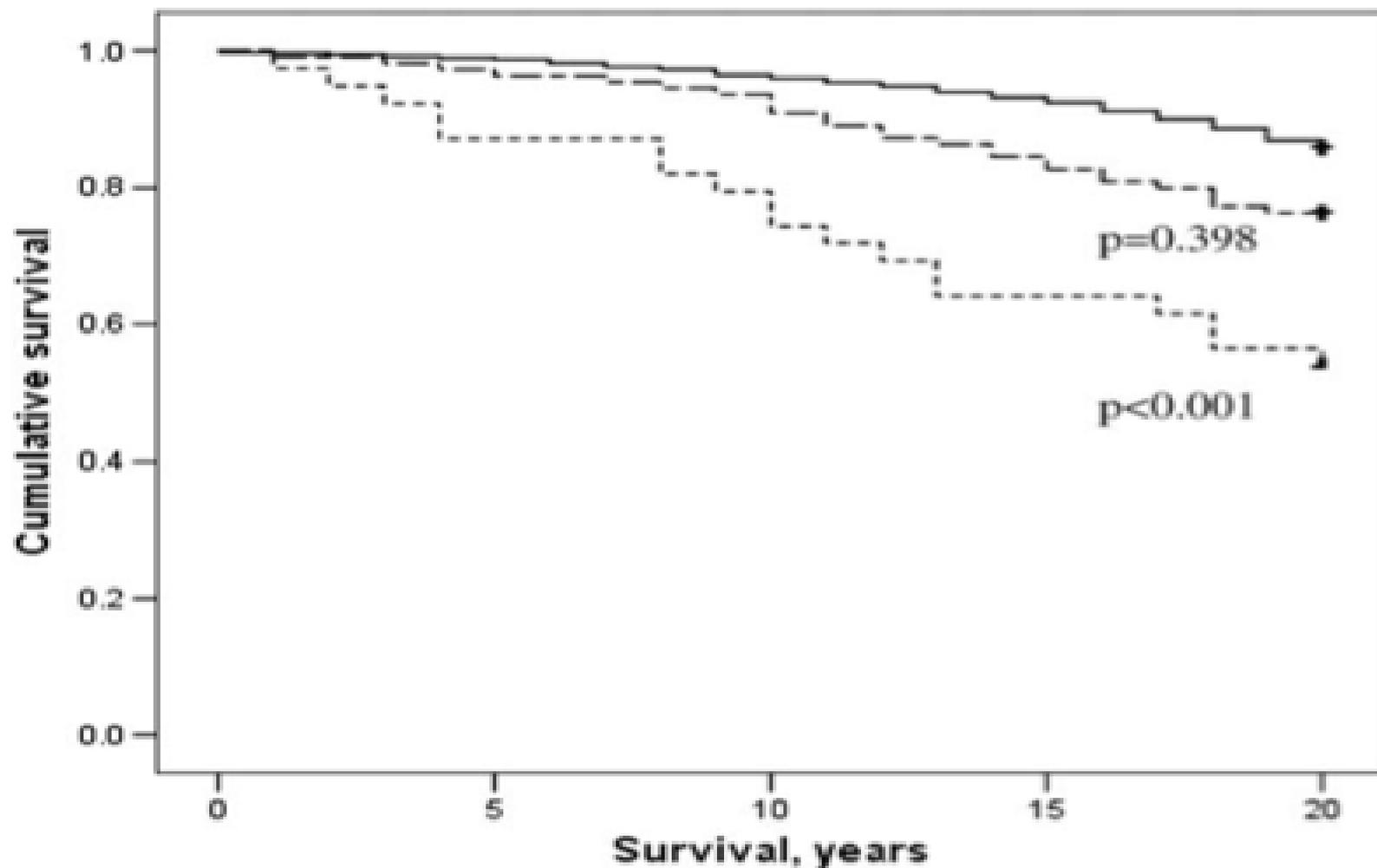
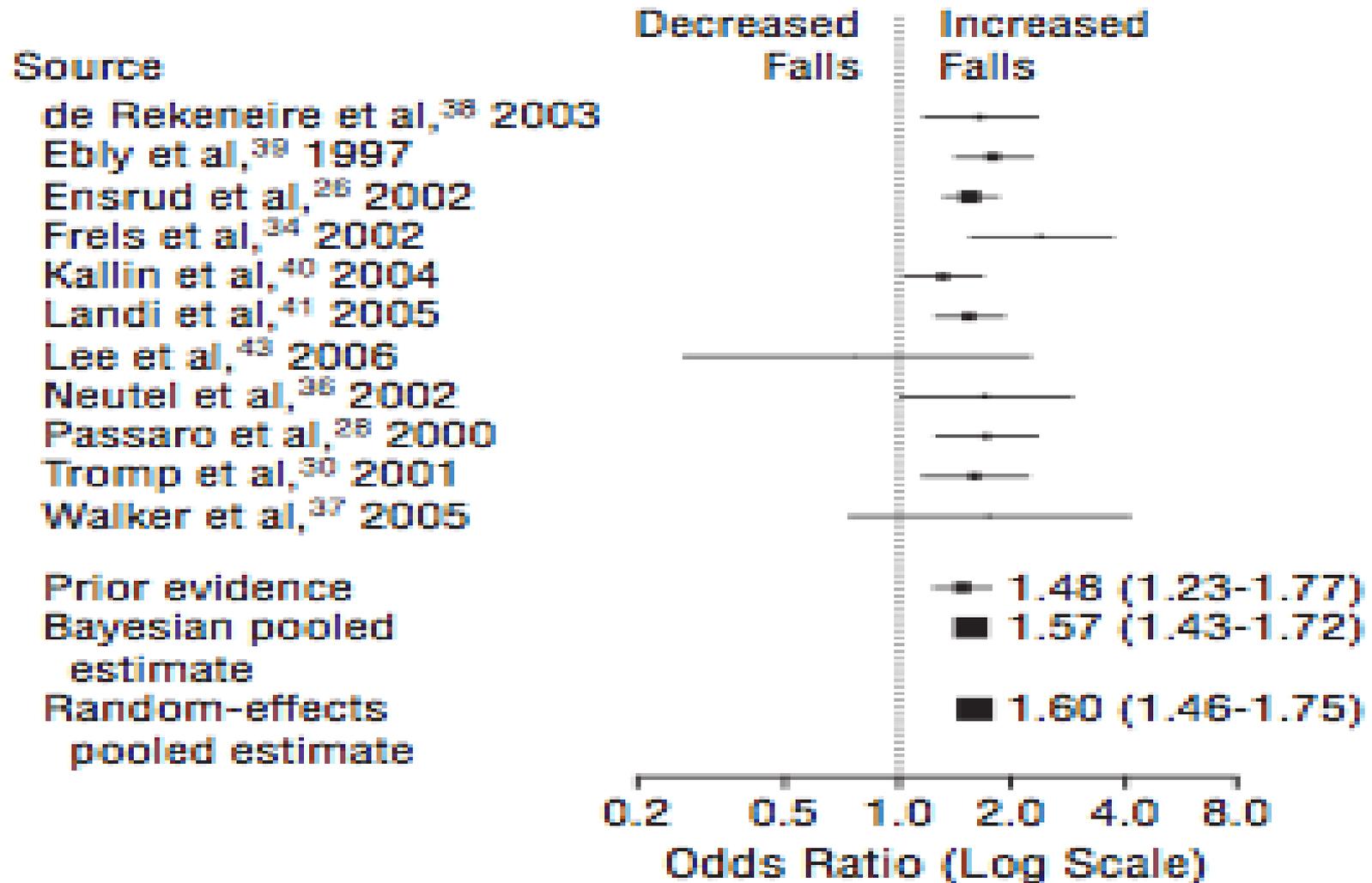


Fig. 2. Survival in women using hypnotics sometimes or regularly compared to women not using hypnotics. (—) No hypnotic usage; (---) Hypnotic usage sometimes; (· · ·) Regular hypnotic usage.

Risk of Falls in Elderly

- Increased with short half –life benzos
- Increased with high dose
- SSRIs also seem to increase fall rates [OR 1.8]
- In at least one study, SSRI fall rate close to that of benzodiazepines
- Woolcott et al. [2009]- meta analysis in Archives of Internal Medicine

Benzodiazepines



Sedatives/hypnotics

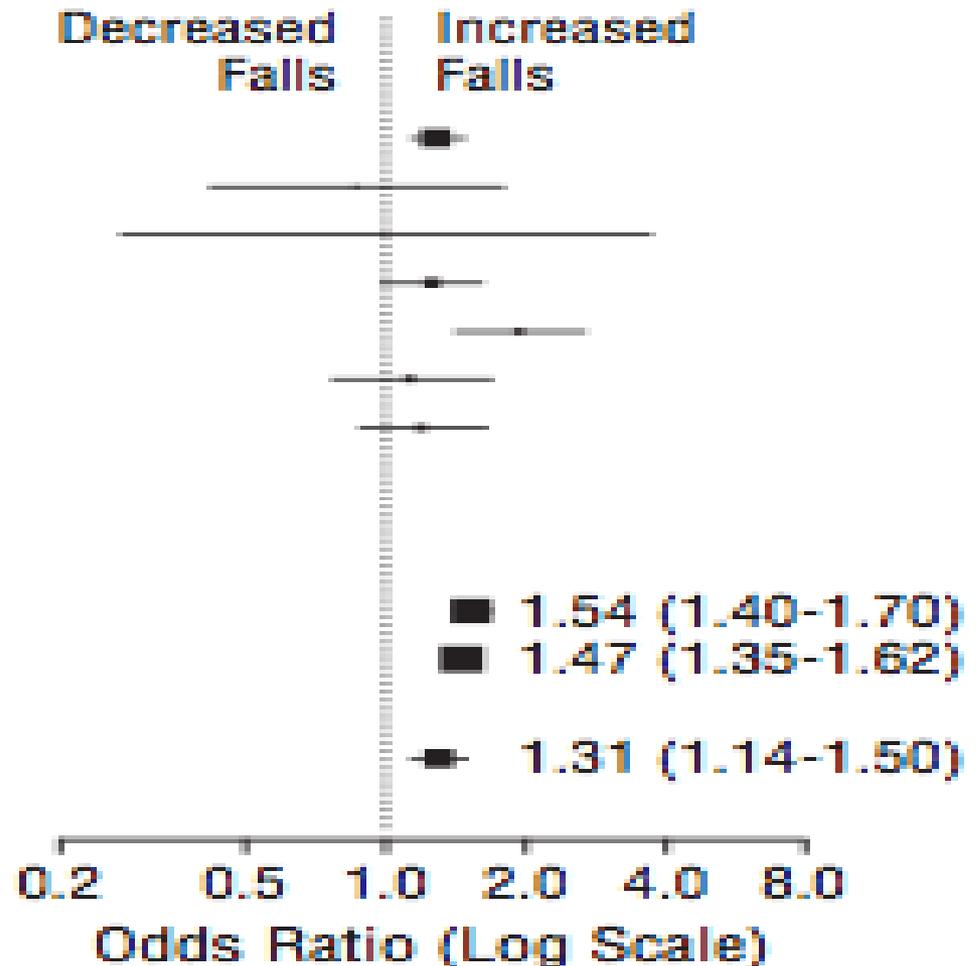
Source

Avidan et al,²⁴ 2005
Chu et al,²⁵ 2005
Gluck et al,³⁵ 1996
Landi et al,⁴¹ 2005
Lawlor et al,⁴² 2003
Rozenfeld et al,⁴⁴ 2003
Tromp et al,²⁹ 1998

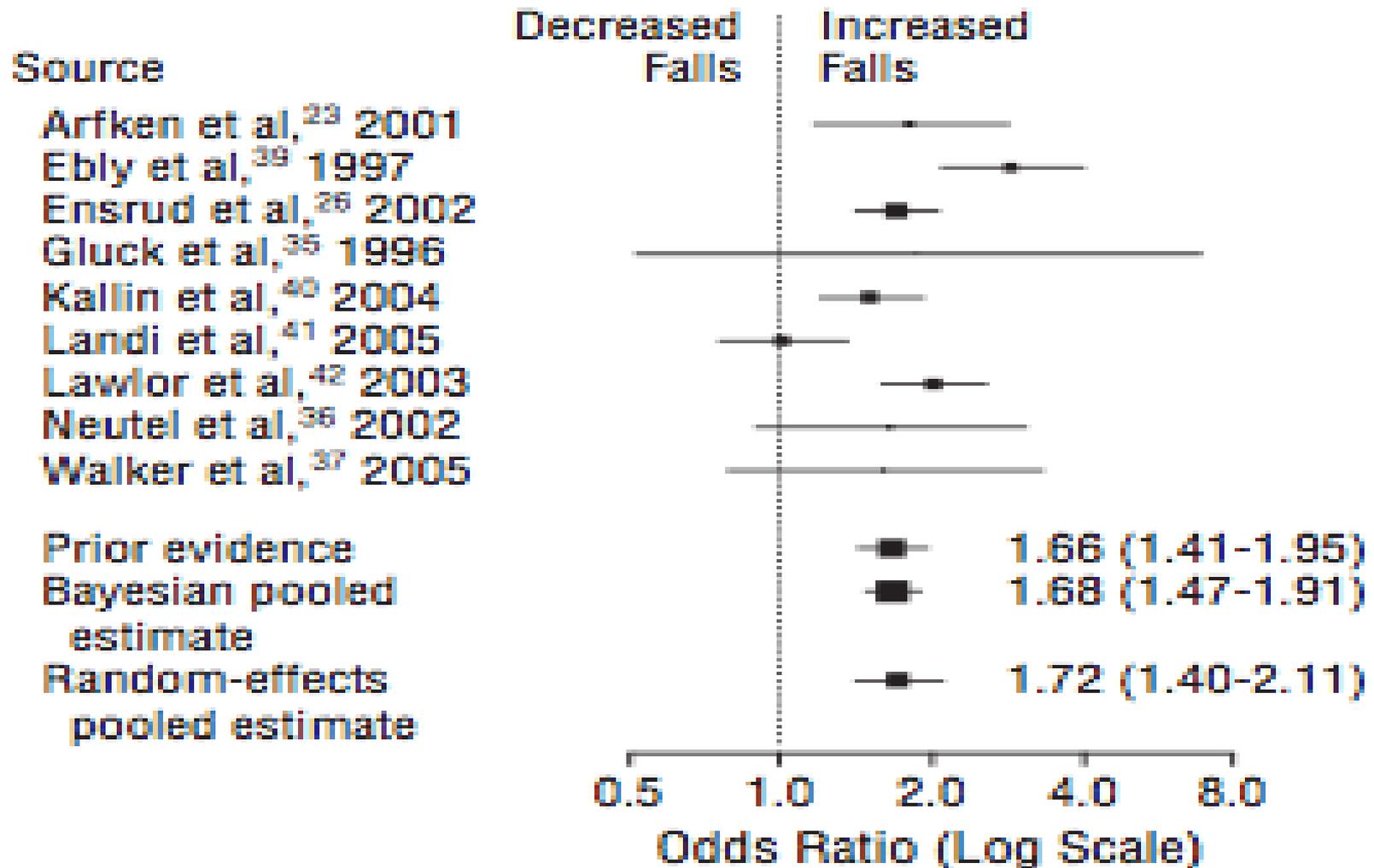
Prior evidence

Bayesian pooled
estimate

Random-effects
pooled estimate

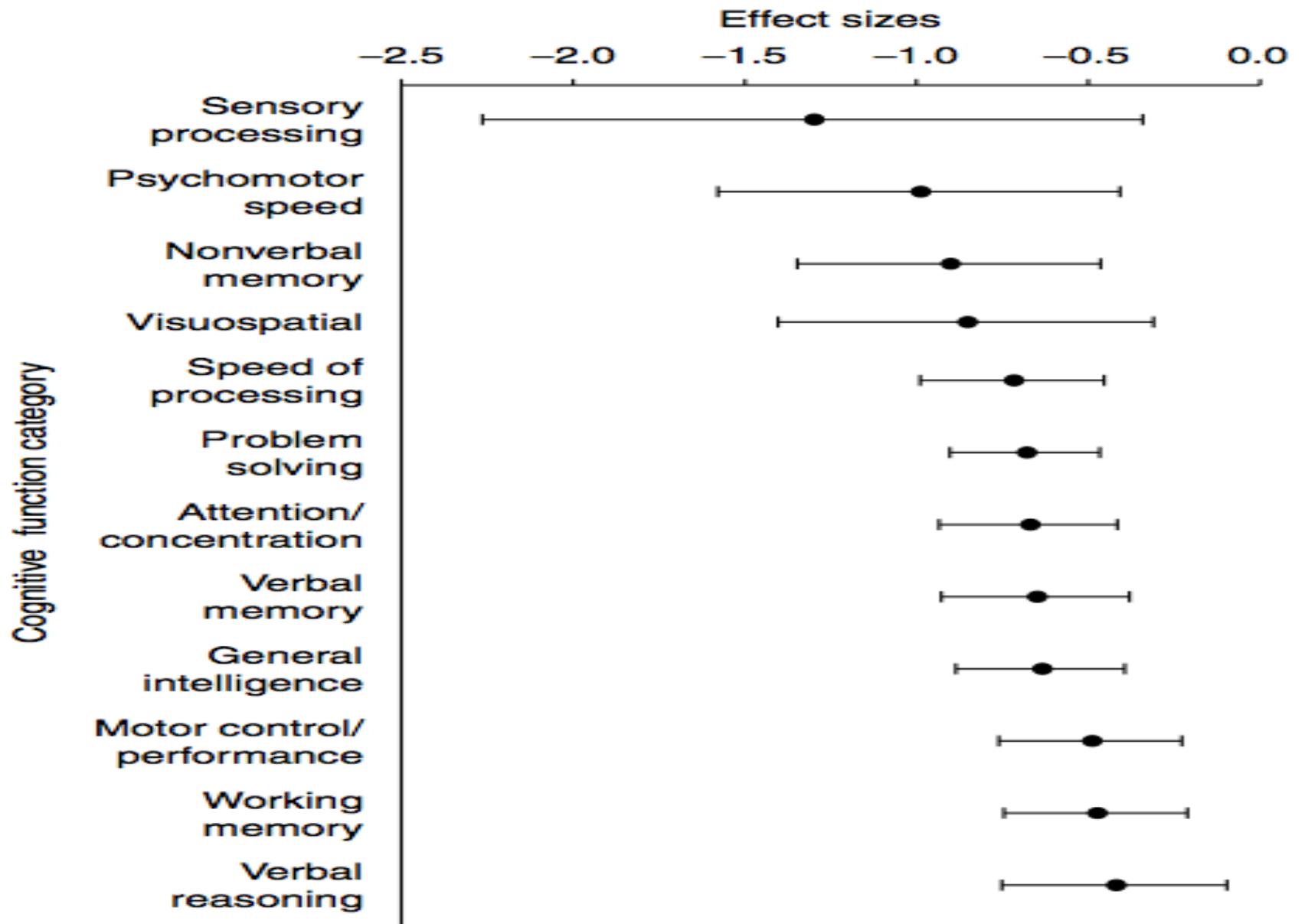


Antidepressants



Risk of Dementia and cognitive decline

- Barker et al. [2004]- Cognitive decline with regular benzodiazepine use
- Wu et al. [2009]- American Journal of Geriatric Psychiatry
- Subjects with dementia had
 - higher cumulative dose of sedative/hypnotics
 - longer duration of BZDs exposure
 - and more likelihood to be long-term BZDs users.



Cognitive Effects

- Anterograde amnesia [new learning]
- Not retrograde amnesia [old learning]
- Not procedural learning
- Unrelated to sedation
- Worse with higher doses

Abuse and Addiction

Benzodiazepine use, abuse, and dependence

- “Although benzodiazepines are invaluable in the treatment of anxiety disorders, they have some potential for abuse and may cause dependence or addiction. It is important to distinguish between addiction to and normal physical dependence on benzodiazepines. Intentional abusers of benzodiazepines usually have other substance abuse problems. Benzodiazepines are usually a secondary drug of abuse-used mainly to augment the high received from another drug or to offset the adverse effects of other drugs. Few cases of addiction arise from legitimate use of...

- O'Brien, CP. Benzodiazepine use, abuse, and dependence. J clin Psychiatry 2005;66 Suppl 2:28-33

Benzodiazepines

- Clinical uses include in treatment of insomnia, as an anxiolytics or muscle relaxant, anesthesia, antiepileptic.
- Alprazolam, clonazepam, diazepam, and lorazepam - among the 200 most commonly prescribed drugs in US.
- 0.1-0.2% of US population is dependent on benzodiazepine (3-6 hundred thousand)
- Associated with misuse, tolerance and dependence.

2008 SAMSHA National Drug Survey of Drug Use and Health

Determined that Benzodiazepine Users

- Rarely the first drug of choice
- Have the lowest rate of abuse compared to the other commonly misused substances
- Are rarely responsible for initiation of a treatment episode
- Very rarely the specific drug used when initiating illicit drug use when compared to
 - Marijuana (56.6%)
 - Pain relievers (22.5%)
 - Inhalants (9.7%)
 - Sedatives (3.8%)
 - Tranquilizers (3.2%)

Therapeutic-dose/Medical users

- Do not drink more than social amounts of alcohol
- Do not have a history of dependence on other drugs
- Are able to successfully withdraw from BZD's without resorting to another dependence inducing drug
- Do not abuse benzodiazepines
- Do not take more than the prescribed dose
- Usually attempt to reduce dose to avoid addiction

Janicak, PG, Marder, SR, and Pavuluri, MN. Chapter 12 Treatment with Antianxiety and Sedative-Hypnotic Agents. Principles and Practice of Psychopharmacotherapy. Janicak. 5th Edition. Lippincott Williams Philadelphia 2011

Therapeutic dose/Medical users

- Females over 50
- Usually take their BZD as prescribed by a provider and supervised by a provider
- Usually do not develop tolerance and will not end up needing higher doses.
- Dislike the sedative effects
- Seldom at high risk of severe W/D
- Do not constitute a serious medical or social problem

Nonmedical Users and/or abusers

- More likely to be males between ages of 20-35 years
- Usually take doses in excesses of established therapeutic dose
- Usually abused alcohol, marijuana, cocaine, methadone
- Often develop tolerance and have to escalate the dose to obtain the desired effect
- Like and seek sedative effects
- Often at high risk of a severe withdrawal reaction
- Serious medical and/or social problems
- Take the BZD that may or may not have been obtained through a provider.

RX use behavior questionnaire...discriminated between two groups

- Use more than prescribed
- Use more often than prescribed
- Call for early refills
- Doctor shopping
- Use when feeling upset
- Use to get high or euphoria

Determining if benzo use is safe or risky

- **Green light zone:** $\frac{1}{2}$ or less of maximum dose listed in PDR: usually non-addicted patients with anxiety
- **Orange light zone:** $\frac{1}{2}$ to max of dose listed in PDR: not many anxious patients in this zone
- **Red light zone:** Above max dose listed in PDR: Addictive patients reach this zone very quickly

Total 24 hour doses for common benzos

Name	Green light zone	Orange light zone	Red light zone
lorazepam	Up to 5 mg/day	5-10 mg/day	>10 mg/day
clonazepam	Up to 2 mg/day	2-4 mg/day	>4 mg/day
diazepam	Up to 20 mg/day	20-40 mg/day	>40 mg/day
alprazolam	Up to 2 mg/day	2-4 mg/day	>4 mg/day
Alprazolam XR	Up to 3 mg/day	3-6 mg/day	>6 mg/day

Treatment considerations for patients on
benzos: primary psych disorder and NO benzo
use disorder

Psych disorders + NO benzo use disorder

- Substance use disorders rare in this group
- Take sedative-hypnotics as indicated for treatment of anxiety or insomnia
- Generally take low [therapeutic doses] for brief periods, but may use low, stable doses long term
- Source of meds: prescribed
- Tolerance rare but possible
- Withdrawal rare if used short term, but common if used >4 weeks
- Aberrant behaviors rare
- **Treatment options: continue treatment, monitor for side effects and aberrant behaviors**

Treatment considerations for patients
on benzos: primary psychiatric
disorder AND benzo use disorder

Primary psychiatric disorder AND benzo use disorder

- Current use of other substances rare, but past use possible
- Med initially prescribed for anxiety or insomnia
- Symptoms persisted despite treatment
- Symptoms exacerbated during attempted withdrawal
- Over time, patient began to rely on benzo to manage daily stress
- Doses: low to high
- Unsanctioned dose escalations
- Variable duration of treatment
- Over time, medication obtained illicitly from doctor shopping or friends/family

Primary psychiatric disorder AND benzo use disorder

- Most develop tolerance and physical dependence
- Often develop adverse physical effects
- Impairment in functioning
- Pre-occupation with securing supply
- Unable to function without it
- Often combined with alcohol

Primary psychiatric disorder AND benzo use disorder- Treatment Strategies

- In this group, rapid taper generally NOT very effective
- Re-emergence of psychiatric symptoms
- Withdrawal experience- often confused with anxiety
- Higher success rates when tapered over several months
- Complete discontinuation NOT recommended if anxiety symptoms persist despite treatment

Primary psychiatric disorder AND benzo use disorder- Treatment Strategies

Step 1: Switch to an equivalent dose of a long acting benzodiazepine [over 1-2 months]- examples: clonazepam, chlordiazepoxide, [diazepam]

Step 2: Stabilize dose over 2-4 weeks

Step 3: Taper over 6-8 weeks [at 10% a day] to clonazepam 1 mg equivalent, or 25-30% of original dose, and stabilize at that dose [often for several months]

Step 4: Final taper [Total process often 6-12 months]

Note: In many cases, an acceptable goal is to stabilize at a dose 25-30% of original dose

Primary psychiatric disorder AND benzo use disorder- Treatment Strategies

- Structure (frequent - daily/weekly - scripts, contracts, consider residential rx, family involvement, rx monitoring)
- Utox for opiate use (increased risk for OD on opiates)
- Adjunctive medications: carbamazepine, valproate, imipramine, gabapentin, pregabalin, melatonin
- Continue adjunct medications for several months post discontinuation of benzodiazepine
- Addition of psychological therapy
- CBT to recognize and manage rebound anxiety
- Therapy to promote self efficacy
- Relaxation
- Traditional modalities

Equivalency chart

Medication	Equivalent dose [mg]	Onset of effects	Duration of effects	Half life
Alprazolam	0.5	fast	3-5	6-12
Clonazepam	0.5	intermediate	10-12	18-50
Chlordiazepoxide	25	intermediate	--	7-13 [36-200]
diazepam	10	fast	4-6	20-100 [36-200]
Lorazepam	1	Fast	4-6	10-20
Oxazepam	20	Slow	--	4-15 [36-200]

Pharmacological treatment options for Anxiety in patients with SUDs

- Buspirone at high doses (45-60mg daily)
 - Improves anxiety symptoms
 - Relatively safe if patients are still drinking
 - May decrease craving and drinking outcomes
- SSRIs
 - Gold standard treatment for most anxiety disorders
 - Relatively safe in patients who are still drinking
 - Effects on alcohol outcomes is unclear
- Others?
 - Acamprosate, topiramate, carbamazepine, gabapentin, pregabalin, hydroxyzine, quetiapine

Psychopharm in patient with anxiety disorder

- TCA have most evidence for helping Social Anxiety/GAD/Panic Disorder but SE limits use
- Imipramine/paroxetine > benzodiazepine for anxiety d/o
- SSRI/SNRI first line for anxiety d/o
- MAOI' s also OK
- OCD SNRI' s >SSRIs but clomipramine is the gold standard
- Neurontin/Lyrica ? Promising for anxiety and benzodiazepine withdrawal

Psychopharm PTSD

- First line - SSRIs/SNRIs for PTSD
- Prazosin decreases NM/hyperarousal/insomnia in PTSD
- Benzos - not effective in PTSD
- Topiramate and atypicals may be helpful

Treatment considerations for patients on benzos: primary Substance Use Disorder but NO benzo use disorder

- Additional co-morbidity with psychiatric disorder
- Use benzos to reduce anxiety, but occasionally for euphoria or to potentiate the high of other substances
- Usually low, stable doses, often long term
- Usually obtained from providers unaware of substance use history; if access restricted, obtained illicitly
- Tolerance possible in chronic users
- Most develop physical dependence
- Usually few adverse effects from benzo use
- Development of drug seeking if access restricted

Treatment considerations for patients on benzos: primary Substance Use Disorder but NO benzo use disorder

- Treatment option: Continue treatment with close monitoring for aberrant behaviors; or transition to a new agent
- Treatment with benzodiazepines may stabilize psychiatric symptoms
- May decrease psychological distress
- May remove triggers for use of alcohol or other drugs
- Patients in this group receiving benzos no worse compared to patients not receiving benzos [Barlow 1997] or may even be better off [Kosten et al., 2000]!

Treatment considerations for patients on benzos: primary Substance Use Disorder AND benzo use disorder

- Low rates of mood or anxiety disorders
- Use to achieve euphoria or potentiate high of other substances
- Use to diminish adverse effects of other substances
- Very high doses possible, often with intermittent use, depending upon availability
- Obtained from multiple sources, often illicit
- Fast development of tolerance to euphoric effects
- Physical dependence with chronic use
- Adverse physical effects
- Severe behavioral problems

Treatment considerations for patients on benzos: primary Substance Use Disorder AND benzo use disorder

- Detoxification from all drugs
- Consider inpatient detoxification for patients addicted to multiple drugs
- Relapse prevention using behavioral treatment and pharmacotherapy
- Seek and treat underlying psychiatric disorders
- Consider medical treatments for other substance use disorders

Treatment considerations for patients on benzos: primary Substance Use Disorder AND benzo use disorder

- Rapid inpatient detoxification over 2-4 weeks
- Opioid dependent individuals transitioned to methadone, buprenorphine, or naltrexone maintenance
- Consider treatment with indirect GABA enhancer to prevent relapse [eg: carbamazepine, valproate]
- Other treatment options:
 - Phenobarbital substitution [Smith and Wesson 1971]
 - Crash 3 day withdrawal [Ries, 1991]:
 - Start high dose carbamazepine or valproate or gabapentin
 - Taper benzo by 1/3 each day until d/c

Clinical Pearls/Conclusions

- Benzodiazepines are
 - Effective short-term
 - Low rates of problems for short term use (2-4 wks)
 - ETOH withdrawal
- But, avoid benzodiazepines if possible
- If not, choose
 - slower-onset
 - longer acting agents such as clonazepam or librium
 - monitor use carefully