Benzodiazepines: Risks, Benefits and Accidental Deaths

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November, 2014
Disclosures

• Sub-Investigator, Alkermes
Objectives

To understand...

1. Benefits of benzodiazepines
2. Short and long-term risks with benzodiazepines
3. The role of benzodiazepines in unintended overdose
4. Historical, cultural and legislative factors relevant to benzodiazepines
History

Benzodiazepines Part I
Sedatives Before Benzos

1903  Barbiturates seen as a safer replacement for opioids, bromides, and chloral hydrate

1940-60  Barbiturate use peaks, 24 pills per U.S. citizen; overdoses rise

Deaths from barbiturate overdose

- Judy Garland
- Marilyn Monroe
- Jimi Hendrix
- Bruce Lee
Benzos 1960-1980

1960  Chlordiazepoxide (Librium) released, followed by diazepam (Valium) in 1963
1963  Benzodiazepine withdrawal identified
1970-4 Usage peaks: 10-20% of US adults take benzos
1975-9 Abuse recognized, moved to schedule-IV
1981  Alprazolam (Xanax) released

1977  Accidental overdose on: **Diazepam**, Opioids (Codeine, Morphine, Meperidine), Barbiturates (Amobarbital, Pentobarbital), Other Sedatives (Methaqualone, Ethchlorvynol, Ethinamate, Carbromal), Amitriptyline

His physician’s medical license was suspended for 3 months and later revoked in 1995 for overprescribing to Jerry Lee Lewis and others.

Elvis Presley, Singer
Benzos 1980-present

1980-90s  Use in elderly rises
1989     Triplicate scripts required in NY
2003     Medicare withdraws, then reinstates (2013) coverage of benzos
2000-10  Rate of accidental death triples from sedatives
2007     Controlled Substance Reporting System in NC

1983

Admitted to a 35-year addiction to: Diazepam and alcohol.

Her physicians were reprimanded in 1994.
Risk & Benefits
Benzodiazepines Part II
Benefits of Benzos

Appropriate for short-term (1-3 months) treatment of:

- Anxiety
- Insomnia
- Seizures
- Muscle relaxant
- Disorders of slow-wave sleep (sleep walking, night terrors)

Robert McFarland, National Security Adviser to Ronald Reagan

WHO Guidelines, 1996

1987

Non-fatal suicide attempt on: 
Diazepam (during Iran-Contra Affair).

Robert McFarland, National Security Adviser to Ronald Reagan
Ideal Use in Anxiety

- Severe, disabling anxiety that is expected to resolve quickly (1-3 mth) as stress lowers or treatment (e.g. antidepressant, therapy) takes effect.
- Intermittent use (e.g. rare use for panic/phobia).
- Best evidence is for use in panic disorder.

1994

Suicide during intoxication with: 
**Diazepam** and heroin.

Kurt Cobain, Lead Singer of Nirvana
Use in Substance Abuse Population

• Benzo abuse occurs with other drug abuse 80% of the time (e.g. to enhance highs of opioids or treat side effects of cocaine/amphetamines).

Prescribed benzos were associated with:

• 2-fold increase in other substance abuse over 6 years, but not poorer outcome, in dual-diagnosed patients.
• Poorer outcomes in patients on methadone maintenance.

1996

Accidental overdose on:
Several **benzodiazepines** and cocaine.

He had doctor-shopped 15,000 medications from 15 doctors, one of whom lost her license.

**Don Simpson**, Producer (Top Gun, Flashdance)
Use in Psychotherapy

• May impair learning in exposure-based psychotherapy (e.g. Cognitive Behavioral Therapy, CBT).
• In contrast, cycloserine enhances learning in psychotherapy.
• Unlike slow-acting psychiatric medications, benzos are not neuroprotective may be neurotoxic.

Effects of stress / depression on brain cell vs. Neuroprotective effects of treatment
Neuroprotection occurs with medications (antidepressant, lithium, valproate), ECT and exercise
Side effects

- Memory loss
- Sedation (usually improves with time)
- Motor impairment
- Abuse, tolerance, withdrawal
- Disinhibition
- Impairment of learning in psychotherapy
- Long-term worsening of anxiety (e.g. PTSD)

1996

1996

Fatal suicide by overdose on: Clonazepam and Phenobarbital.

Margaux Hemingway, Actress (grand-daughter of Ernest)
Benzos and Cognition

- Impair formation of new memories, and spatial/temporal
- Motor impairment: 10mg diazepam = DWI level of alcohol. Patients are unaware of the impairment; does not improve with time.
- Dementia risk: Increased by 50% in elderly users of benzos (confirmed in 6/8 uncontrolled studies adjusted for confounders; worse with duration of use)

2007

Anna Nicole Smith, Model

Accidental overdose on: Diazepam, Clonazepam, Lorazepam, Chlora hydrate.

Her physician’s medical license was revoked.
Mortality Increases with Hypnotic Exposure

Hypnotic use and age: effects on survival

Kripke, 2012
Major Contraindications

- Disorders prone to respiratory impairment:
  Sleep apnea, myasthenia gravis, lung disease
- Active alcohol, sedative or opioid abuse
- Delirium
- History of disinhibition on benzos

Accidental overdose on:
Diazepam, Temazepam, Alprazolam, Opioids
(Oxycodone, Hydrocodone), Antihistamine (Doxylamine).

Heath Ledger, Actor
Relative Contraindications

- In recovery from past sedative, alcohol or opioid abuse
- Elderly
- Dementia
- Recent trauma or post-traumatic stress
- Traumatic Brain Injury (TBI)

Overdose (ruled a homicide) on: **Diazepam, lorazepam, midazolam** and propofol.

His physician served a two-year prison sentence for involuntary manslaughter (2011-2013)
Risks in the Elderly

Changes in drug-metabolism elevate these risks:

• Dependence, falls, memory, sedation, coordination, motor vehicle accidents
• Progressively worsening syndrome resembling dementia, depression, or anxiety
• Long-acting agents, and those with metabolites, more prone to accumulate

2008

Amy Winehouse, Singer

Accidental overdose on: Chlordiazepoxide and alcohol.
Long-term Use of Benzos

Practice patterns are the reverse of practice guidelines:

• Most often used in the elderly, former substance abusers, and chronic anxiety disorders
• 60-70% of benzo scripts are for long-term use
• However, dose escalation is rare in those without a substance abuse history, and chronic (12 yr) use in anxiety disorders did not increase risk of alcohol abuse.

2009

Brittany Murphy, Actress

Accidental overdose on: Two Benzodiazepines and Hydrocodone during Pneumonia.
Withdrawal Syndrome

- Occurs in 40% of users (5-75%); worse with longer use and higher doses
- Peaks at 1-3 weeks
- Insomnia, anxiety, irritability, depression, heightened or abnormal perception, paranoia, nightmares
- Seizures, headache, tremor, tinnitus, dizziness, muscle twitching, racing heart, GI distress

Accidental overdose on: **Diazepam**, hydrocodone and carisoprodol (Soma) during pneumonia.

He had doctor-shopped 7 physicians, obtaining 553 pills in the month before his death.
Benzodiazepine Discontinuation

• 50% succeed, 30% lower their dose, 20% don’t change.
• After a letter from their PCP, 22% stopped on their own.
• Those who came off reported greater self-esteem
• Faster in the beginning, then slow down:
  First Week: 50% reduction
  Next Month: 25% reduction
  Next ½ Year: final 25% reduction
• Or convert to diazepam and reduce by 2mg every 1-2 weeks (Ashton manual: www.benzo.org.uk)
# Benzos of Distinction

<table>
<thead>
<tr>
<th>Category</th>
<th>Medications</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rapid onset, brief action</strong></td>
<td>Diazepam, Alprazolam, Lorazepam, Triazolam, Midazolam</td>
</tr>
<tr>
<td><strong>Slowest onset</strong></td>
<td>Oxazepam, Clorazepate, Chlordiazepoxide</td>
</tr>
<tr>
<td><strong>Most likely to accumulate</strong></td>
<td>Diazepam, Flurazepam, Chlordiazepoxide, Clorazepate, Quazepam</td>
</tr>
<tr>
<td><strong>No hepatic interactions</strong></td>
<td>Lorazepam, Oxazepam, Temazepam (ideal in elderly, liver impairment)</td>
</tr>
<tr>
<td><strong>Worst withdrawal</strong></td>
<td>Alprazolam</td>
</tr>
<tr>
<td><strong>Best for withdrawal</strong></td>
<td>Diazepam, Chlordiazepoxide</td>
</tr>
<tr>
<td><strong>Best for sleep</strong></td>
<td>Temazepam, Estazolam, Lorazepam, Oxazepam</td>
</tr>
<tr>
<td><strong>Most notorious</strong></td>
<td>Flunitrazepam (date-rape drug)</td>
</tr>
<tr>
<td><strong>Highest fatality index</strong></td>
<td>Flurazepam, Temazepam</td>
</tr>
<tr>
<td><strong>Lowest fatality index</strong></td>
<td>Oxazepam</td>
</tr>
<tr>
<td><strong>Best overall?</strong></td>
<td>Oxazepam</td>
</tr>
</tbody>
</table>
You can’t set her free. But you can help her feel less anxious.

You know this woman.

She’s anxious, tense, irritable. She’s felt this way for months.

Beset by the seemingly insurmountable problems of raising a young family, and confined to the home most of the time, her symptoms reflect a sense of inadequacy and isolation. Your reassurance and guidance may have helped some, but not enough.

Serax (oxazepam) cannot change her environment, of course. But it can help relieve anxiety, tension, agitation and irritability, thus strengthening her ability to cope with day-to-day problems. Eventually—as she regains confidence and composure—your counsel may be all the support she needs.

Indicated in anxiety, tension, agitation, irritability, and anxiety associated with depression.

May be used in a broad range of patients, generally with considerable dosage flexibility.

Contraindications: History of previous hypersensitivity to oxazepam. Oxazepam is not indicated in psychosis.

Precautions: Hypersensitive reactions are rare, but use with caution where complications could result from a fall in blood pressure, especially in the elderly. One patient exhibiting drug dependency by taking a chronic overdose developed symptoms resembling withdrawal symptoms. Carefully supervise dosage and amounts prescribed, especially for patients prone to overdose; excessive prolonged use in susceptible patients (alcoholics, ex-addicts, etc.) may result in dependence or habituation. Reduce dosage gradually after prolonged excessive dosage to avoid possible epileptiform seizures. Caution patients against driving or operating machinery until absence of drowsiness or dizziness is ascertained. Warn patients of possible reduction in alcohol tolerance. Safety for use in pregnancy has not been established.

Not indicated in children under 16 years; absolute dosage for 5 to 12 year-olds not established.

Side Effects: Therapy-interrupting side effects are rare. Transient mild drowsiness is common initially; if persistent, reduce dosage. Dizziness, vertigo and headache have also occurred infrequently; syncope, rarely. Mild paradoxical reactions (excitement, stimulation of affect) are reported in psychiatric patients. Minor diffuse rashes (morbilliform, urticarial and maculopapular) are rare. Nausea, lethargy, edema, slurred speech, tremor and altered libido are rare and generally controllable by dosage reduction. Although rare, leukopenia and hepatic dysfunction including jaundice have been reported during therapy. Periodic blood counts and liver function tests are advised. Ataxia, reported rarely, does not appear related to dose or age.

These side reactions, noted with related compounds, are not yet reported: paradoxical excitation with overuse, hallucinations, emotional lability, change in EEG pattern, blood dyscrasias (including agranulocytosis), blurred vision, diplopia, incontinence, stupor, disinhibition, fever, euphoria and dysmetria.

Availability: Capsules of 10, 15 and 30 mg, oxazepam.

To help you relieve anxiety and tension

Serax

Oxazepam

Wyeth Laboratories
Benzodiazepines by frequency of diversion in the U.S., 2011-2012 (source: DEA)
Accidental Deaths
Benzodiazepines Part III
A New Epidemic

- 15-20% of PCP visits result in an opioid prescription.
- Robust increases in pain expenditures from 1997 to 2005 did not translate into improvements in self-assessed health status and pain (Martin BI, JAMA 2008).
- Accidental drug overdose is currently the leading cause of injury-related death among Americans age 35-54.

2012

Accidental overdose on: Alprazolam, Marijuana, Benadryl, and Cyclobenzaprine.

Whitney Houston, Singer
Deaths from Barbiturates Overdose (UK)
Overdose Deaths by Intent (NC, 1999-2012)
Accidental Deaths by Year & OD type

- 4,030 opioid deaths in 1999
- 16,651 opioid deaths in 2010

Opioid Painkillers

Benzodiazepines

Heroin

Cocaine

National Vital Statistics System, 1999-2010
Benzos with Opioids

• Death from benzo OD alone is rare; more common when combined with alcohol or opioids.
• Benzos may play a role in up to 80% of unintentional deaths involving opioids.
• Benzo + Opioid = enhanced euphoria and respiratory depression.
• 40% of those on opioids for chronic pain also take benzos.

2014

Accidental overdose on: Diazepam, Alprazolam and Heroin.

Philip Seymour Hoffman, Actor
# ED visits for non-medical Rx use

<table>
<thead>
<tr>
<th>Drug category and selected drug</th>
<th>ED visits</th>
<th>Percent of ED visits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sedatives-hypnotics</td>
<td>363,270</td>
<td>33.6</td>
</tr>
<tr>
<td>Barbiturates</td>
<td>11,824</td>
<td>1.1</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>312,931</td>
<td>29.0</td>
</tr>
<tr>
<td>Alprazolam</td>
<td>112,552</td>
<td>10.4</td>
</tr>
<tr>
<td>Clonazepam</td>
<td>57,633</td>
<td>5.3</td>
</tr>
<tr>
<td>Diazepam</td>
<td>25,150</td>
<td>2.3</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>36,582</td>
<td>3.4</td>
</tr>
<tr>
<td>Zolpidem</td>
<td>29,127</td>
<td>2.7</td>
</tr>
<tr>
<td>Muscle relaxants</td>
<td>50,878</td>
<td>4.7</td>
</tr>
<tr>
<td>Carisoprodol</td>
<td>29,980</td>
<td>2.8</td>
</tr>
<tr>
<td>Cyclobenzaprine</td>
<td>11,178</td>
<td>1.0</td>
</tr>
</tbody>
</table>

- Alprazolam ED visits increased by 142% from 2004-2009
- Clonazepam ED visits increased by 105% from 2004-2009
- Lorazepam ED visits increased by 107% from 2004-2009

Dawn, 2009: National ED Estimates
# ED Visits for suicide attempt by OD

<table>
<thead>
<tr>
<th>Drug category and selected drugs</th>
<th>ED visits</th>
<th>Percent of ED visits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total ED visits, suicide attempts</td>
<td>198,403</td>
<td>100.0</td>
</tr>
<tr>
<td>Alcohol (all ages)</td>
<td>61,827</td>
<td>31.2</td>
</tr>
<tr>
<td>Illicit drugs</td>
<td>35,586</td>
<td>17.9</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>36,154</td>
<td>94.2</td>
</tr>
<tr>
<td>Antipsychotics</td>
<td>23,910</td>
<td>12.1</td>
</tr>
<tr>
<td>Pain relievers</td>
<td>75,545</td>
<td>38.1</td>
</tr>
<tr>
<td>Anxiolytics, sedatives, hypnotics</td>
<td>77,623</td>
<td>39.1</td>
</tr>
</tbody>
</table>

Dawn, 2009: National ED Estimates
Map of Deaths by Unintentional Poisoning in NC, 2013
Predicted Age-Adjusted Death Rates due to Drug Poisoning:

1999-2000
2004-2005
2008-2009

Rossen et al, 2013, AJPM
Opioids
16,651 deaths

Antidepressants
3,889 deaths
57.6% involved an opioid

Benzodiazepines
6,497 deaths
77.2% involved an opioid

Antiepileptics
1,717 deaths
66.5% involved an opioid

Opioids + Benzos + Antidepressants
936 deaths

Opioids + Benzos + Antiepileptics
545 deaths
Opioid deaths, sales, and treatment admissions rise in lock-step

Opioid Sales (kg per 10k)

Opioid Deaths (per 100k)

Opioid Treatment Admissions (per 10k)

National Vital Statistics System, DEA’s Automation of Reports and Consolidated Orders System, SAMHSA’s TEDS
Risk of Prescription Drug Overdose by Age

Death rates by age

Highest in white men age 25-55 and in mountain-regions

CDC/NCHS, National Vital Statistics System
Most common causes of drug-related deaths in 2009 (n=8,653)

- Oxycodone: 14% (n=1,185)
- BZD: 13% (n=1,099)
- Methadone: 8% (n=720)
- Ethyl alcohol: 6.5% (n=559)
- Cocaine: 6% (n=529)
- Morphine: 3.5% (n=302)
- Hydrocodone: 3% (n=265)

BZD: benzodiazepine.
"Physicians should be aware that there is very little data to support the use of long term opioid therapy for common causes of chronic pain such as fibromyalgia, low back pain, pelvic pain, functional bowel disorders and chronic headache.

Opioids should be tapered or discontinued when a patient's pain is poorly controlled on appropriate doses of medication or if there is no physical, functional, and psychosocial improvement with opioid treatment."

—NC Medical Board policy on opioids (6/2014 update)
NC Controlled Substance Reporting System

"Information from the NCCSRS should be part of every patient's initial evaluation and subsequent monitoring program.

Physicians should register with the NCCSRS and become familiar with analyzing and using NCCSRS data.

Relevant information from the NCCSRS should become part of the patient's medical record."

—NC Medical Board policy on opioids (6/2014 update)
NC Controlled Substance Reporting System

Started in 2007. Updates to legislation in 2013:

• DHHS may notify MDs of suspected of doctor-shopping.
• DHHS may notify NCMB of potentially improper prescribing patterns.
• MDs may designate office staff to check CSRS.
• Pharmacies must report within 3 days. Small dispensions (≤2 days worth) are not reported.
• Register at: www.ncdhhs.gov/mhddasas/controlledsubstance