Benzodiazepines Revisited

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Director, Treatment Resistant Depression Program
New York University School of Medicine

[Chemical structure diagram]
Benzodiazepines
Benzodiazepine Use

- 5.2% of adults aged 18-80 years use benzodiazepines*
- In 65-80 years group, it’s 8.7%
- This older group has the highest proportion of long-term use—31.4%
- The proportion of long-term prescriptions by psychiatrists decrease by patient age
- Roughly 25% of patients receive long-acting benzodiazepines

*The percentage of those 12 and over taking antidepressants is 11%

Benzodiazepines approved for use in the United States

- alprazolam (Xanax)
- chlordiazepoxide (Librium)
- clonazepam (Klonopin)
- clorazepate (Tranxene)
- diazepam (Valium)
- estazolam (ProSom)
- flurazepam (Dalmane)
- lorazepam (Ativan)
- oxazepam (Serax)
- temazepam (Restoril)
- triazolam (Halcion)
- quazepam (Doral)
Benzodiazepine Use in the United States

Percentage of Population in the United States in 2008 With Any Benzodiazepine Use by Sex and Age. The data source was 2008 IMS LifeLink Information Assets–LRx Longitudinal Prescription Database (IMS Health Inc).
Classification of “Long-Acting” and “Short-Acting” Benzodiazepines

**Long-Acting Agents**
- chlordiazepoxide (Librium)
- clorazepate (Tranxene)
- diazepam (Valium)
- flurazepam (Dalmane)
- quazepam (Doral)
- halazepam
- prazepam

**Short-Acting Agents**
- alprazolam (Xanax)
- clonazepam (Klonopin)
- lorazepam (Ativan)
- temazepam (Restoril)
- triazolam (Halcion)
- estazolam (ProSom)
- oxazepam (Serax)
- midazolam (Versed)
Long “Acting” vs. Short “Acting”

• Long-half-life BZs are first degraded to active intermediates, and both the parent drug and the intermediate are long-lasting/acting
• Short-half-life BZs are not converted to active intermediates; they are metabolized directly into inactive products
• The elderly have a reduced ability to metabolize long-half-life BZs (and their active metabolites)
• Pharmacokinetics are not drastically altered with the short-half-life BZs
Benzodiazepine Use in the United States

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

The data source was 2008 IMS LifeLink Information Assets–LRx Longitudinal Prescription Database (IMS Health Inc).

## Benzodiazepine Use in the United States

### Table 2. Prescriptions From Psychiatrists Among Persons With Any Benzodiazepine Use, Long-term Benzodiazepine Use, and Use of Long-Acting Benzodiazepines by Sex and Age Group in the United States in 2008<sup>a</sup>

<table>
<thead>
<tr>
<th>Variable</th>
<th>18-35</th>
<th>36-50</th>
<th>51-64</th>
<th>65-80</th>
</tr>
</thead>
<tbody>
<tr>
<td>Among Persons With Any Benzodiazepine Use</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>With at least 1 prescription from psychiatrist</td>
<td>15.0</td>
<td>12.8</td>
<td>11.3</td>
<td>5.7</td>
</tr>
<tr>
<td>Among men</td>
<td>15.1</td>
<td>12.4</td>
<td>10.8</td>
<td>5.3</td>
</tr>
<tr>
<td>Among women</td>
<td>14.9</td>
<td>13.1</td>
<td>11.5</td>
<td>5.9</td>
</tr>
<tr>
<td>Among Persons With Long-term Benzodiazepine Use&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>With at least 1 prescription from psychiatrist</td>
<td>32.6</td>
<td>25.0</td>
<td>20.4</td>
<td>9.8</td>
</tr>
<tr>
<td>Among men</td>
<td>31.9</td>
<td>23.5</td>
<td>19.0</td>
<td>9.4</td>
</tr>
<tr>
<td>Among women</td>
<td>33.0</td>
<td>25.8</td>
<td>21.1</td>
<td>10.0</td>
</tr>
<tr>
<td>Among Persons With Long-Acting Benzodiazepine Use</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>With at least 1 prescription from psychiatrist</td>
<td>6.2</td>
<td>6.8</td>
<td>7.0</td>
<td>3.6</td>
</tr>
<tr>
<td>Among men</td>
<td>6.4</td>
<td>6.5</td>
<td>6.6</td>
<td>3.2</td>
</tr>
<tr>
<td>Among women</td>
<td>6.0</td>
<td>7.0</td>
<td>7.2</td>
<td>3.9</td>
</tr>
<tr>
<td>Among Persons With Long-Acting Benzodiazepine Use and at Least 1 Prescription From a Psychiatrist</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>With long-term benzodiazepine use&lt;sup&gt;b&lt;/sup&gt;</td>
<td>33.5</td>
<td>44.8</td>
<td>50.9</td>
<td>53.5</td>
</tr>
<tr>
<td>Among men</td>
<td>33.3</td>
<td>44.1</td>
<td>51.1</td>
<td>50.6</td>
</tr>
<tr>
<td>Among women</td>
<td>33.7</td>
<td>45.2</td>
<td>50.8</td>
<td>54.8</td>
</tr>
</tbody>
</table>

<sup>a</sup> The data source was 2008 LifeLink Information Assets-LRx Longitudinal Prescription Database (IMS Health Inc).

<sup>b</sup> Long-term use defined as 120 days or more supply of benzodiazepines during 2008.
Table 1. Prevalence of Any Benzodiazepine Use, Long-term Benzodiazepine Use, and Use of Long-Acting Benzodiazepines by Sex and Age Group in the United States in 2008a

<table>
<thead>
<tr>
<th>Variable</th>
<th>18-35</th>
<th>36-50</th>
<th>51-64</th>
<th>65-80</th>
</tr>
</thead>
<tbody>
<tr>
<td>US Population</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>With any benzodiazepine use, y</td>
<td>2.6</td>
<td>5.4</td>
<td>7.4</td>
<td>8.7</td>
</tr>
<tr>
<td>Among men</td>
<td>1.7</td>
<td>3.7</td>
<td>5.3</td>
<td>6.1</td>
</tr>
<tr>
<td>Among women</td>
<td>3.6</td>
<td>7.1</td>
<td>9.2</td>
<td>10.8</td>
</tr>
</tbody>
</table>

| Among Persons With Any Benzodiazepine Use |       |       |       |       |
| With long-term benzodiazepine useb | 14.7  | 22.4  | 28.0  | 31.4  |
| Among men | 15.6  | 22.8  | 28.4  | 28.8  |
| Among women | 14.2  | 22.2  | 27.8  | 32.6  |
| With any long-acting benzodiazepine use, y | 24.1  | 25.4  | 25.4  | 23.8  |
| Among men | 26.9  | 29.5  | 29.4  | 27.1  |
| Among women | 22.7  | 23.3  | 23.4  | 22.4  |

a The data source was 2008 LifeLink Information Assets–LRx Longitudinal Prescription Database, 2008 (IMS Health Inc).

b Long-term use defined as 120 days’ or more supply of benzodiazepine during 2008.
CNS Effects

Increasing dose

Coma

Barbiturates

Medullary depression

Benzodiazepines

Anesthesia

Sedation, disinhibition, anxiolysis

Possible selective anticonvulsant & muscle-relaxing activity

Hypnosis

Dose Response Relationships
# Benzodiazepines: Benefits and Risks

<table>
<thead>
<tr>
<th>Benefits</th>
<th>Drawbacks</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Sedation</td>
<td>• Potential for abuse</td>
</tr>
<tr>
<td>• Rapid onset of action</td>
<td>• Unwanted sedation</td>
</tr>
<tr>
<td>• Can be used PRN</td>
<td>• Cognitive impairment</td>
</tr>
<tr>
<td>• Few and mild subjective adverse-effects</td>
<td>• Interaction with CNS depressants</td>
</tr>
<tr>
<td>• Safety in overdose</td>
<td>• Psychomotor impairment</td>
</tr>
<tr>
<td>• Address anxiety symptoms</td>
<td>• Dependence</td>
</tr>
<tr>
<td></td>
<td>• Withdrawal</td>
</tr>
</tbody>
</table>
# Benzodiazepines: The Controversies

<table>
<thead>
<tr>
<th>Con (Moore N, et al)</th>
<th>Pro (Salzman and Shader)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Use only for very short periods or avoid altogether in elderly.</td>
<td>• Therapeutically very effective</td>
</tr>
<tr>
<td>• Restrict the prescription of benzodiazepines to psychiatrists.</td>
<td>• Remarkably safe with relatively minor side effects</td>
</tr>
<tr>
<td>• Consider them the same as other dangerous addictive substances and put them on</td>
<td>• Discontinuation syndrome relatively mild</td>
</tr>
<tr>
<td>a tight dispensation schedule using limited-duration prescriptions with no refills.</td>
<td>• When triplicate prescriptions were introduced in NYS, BZ use declined, but alcohol</td>
</tr>
<tr>
<td></td>
<td>and other sedative/hypnotic use increased</td>
</tr>
</tbody>
</table>
The GABA\textsubscript{A} receptor is a complex with 7 subunit families comprising at least 18 subunits in the CNS:

$\alpha_{1-6}, \beta_{1-3}, \gamma_{1-3}, \delta, \varepsilon, \theta, \rho_{1-3}$

The major subtype combination (60% of all GABA-A receptors) consist of $\alpha_1\beta_2\gamma_2$
The GABAA—benzodiazepine receptor complex, visualised by electron microscopy, showing five protein sub-units arranged around a central core (from Nayeem et al (1994), with permission).
The most important and most prevalent GABAA—benzodiazepine receptor in the brain is made up from α1, β2 and γ2 sub-units, encoded by the same cluster of genes on chromosome 5.
Schematic representation of the binding sites on the GABAA—benzodiazepine receptor complex.
Benzodiazepines Do Alter Brain Structures

- 60 - 75% of all brain synapses are GABAergic
- Chronic BZ use decreases the number of GABA receptors
- The number of GABA receptors is slowly restored in response to benzodiazepine cessation or dose reduction.
- In time, GABA receptors regenerate
How Long Does it Take for GABA Receptors to Normalize

- No evidence that downregulation from benzodiazepine use can be permanent
- But, it can take 18-24 months for complete reversal to occur
The GABA$_A$ receptor is a complex with 7 subunit families comprising at least 18 subunits in the CNS:

$$\alpha_{1-6}, \beta_{1-3}, \gamma_{1-3}, \delta, \varepsilon, \theta, \rho_{1-3}$$

Benzodiazepines increase the affinity of the receptor for GABA, and thus increase Cl$^-$ conductance and hyperpolarizing current.

Therefore, benzodiazepines are *indirect agonists* of the GABA receptor.

The major subtype combination (60% of all GABA-A receptors) consist of $\alpha_1\beta_2\gamma_2$.
Benzodiazepines and Dementia

• A large prospective population based study showed that new use of benzodiazepines is associated with an approximately 50% increase in the risk of dementia.

• Mean age of population = 78.2

• Considering the extent to which benzodiazepines are now prescribed, physicians and regulatory agencies should consider the increasing evidence of the potential adverse effects of this drug class for the general population.

Billoti S et al BMJ 2015
“Not Again: Benzodiazepines Once More Under Attack”

- Problems with conclusions of Canadian study
- Actually, there is evidence that BZs may decrease the risk of development of AD by decreasing the toxic effect of chronic stress on the CNS
- “In our view, it is poor medical practice that deprives a patient of a useful and therapeutic class of drugs.”

Benzodiazepine Use

- 5.2% of adults aged 18-80 years use benzodiazepines
- In 65-80 years group, it’s 8.7%
- This older group has the highest proportion of long-term use—31.4%
- The proportion of long-term prescriptions by psychiatrists decrease by patient age
- Roughly 25% of patients receive long-acting benzodiazepines

Benzodiazepines and Dementia

- Database from the Quebec health insurance program identified nearly 2,000 men and women over age 66 who had been diagnosed with Alzheimer’s disease.
- People who had taken a benzodiazepine for three months or less had about the same dementia risk as those who had never taken one.
- Taking the drug for three to six months raised the risk of developing Alzheimer’s by 32%, and taking it for more than six months boosted the risk by 84%.
- The type of drug taken also mattered. People who were on a long-acting benzodiazepine like diazepam (Valium) and flurazepam (Dalmane) were at greater risk than those on a short-acting one like triazolam (Halcion), lorazepam (Ativan), alprazolam (Xanax), and temazepam (Restoril).
Probability of participants not having dementia

Follow-up (years)

Benzodiazepine new users
95 54 26 10

Benzodiazepine non-users
968 535 319 147

Source: BMJ © 2012 BMJ Publishing Group Ltd
Limitations

- The researchers acknowledge that the use of benzodiazepines could be just a signal that people are trying to cope with anxiety and sleep disruption—two common symptoms of early Alzheimer’s disease. If that’s true, their use of a benzodiazepine may not be a factor in causing dementia but an indication it is already in progress.
- Lack of data on young adults.
- It remains unclear whether benzodiazepines increase the risk of dementia or are prescribed to combat pre-clinical symptoms.
Cautionary comment from Dr. Anne Fabiny, chief of geriatrics at Harvard-affiliated Cambridge Health Alliance.

The association [with Alzheimer's] isn’t surprising given past research on the subject, but it still should be viewed with caution. Benzodiazepines are risky to use in older people because they can cause confusion and slow down mental processes. However, although there is an association, we still can’t say that benzodiazepines actually cause Alzheimer’s.
Benzodiazepines and Dementia

- Benzodiazepine use could be seen as an early risk marker for dementia that might highlight a particular at risk background in patients, but without playing any causal role in the occurrence of the disease.

- Persistent anxiety in middle age has been shown to be associated with a greater risk of dementia in elderly people.

- Hence, benzodiazepine use may be a marker of this scenario and might help to identify people at increased risk of, and not already on the causal pathway leading to, dementia.
“Benzodiazepines Not Linked to Dementia” Study

- 3,434 adults age 65 and older
- Followed on average for 7 years
- By study end, 23% developed dementia
- Found no link between highest level of BZ use (on average, 1 year of daily use) and dementia and cognitive decline
- Found small increased risk with moderate and low use

Fig 3 | Hazard ratios for all cause dementia and Alzheimer’s disease for each level of cumulative benzodiazepine exposure compared with no use. Multivariable models adjusted for study cohort, age at study entry, sex, educational level, hypertension, diabetes mellitus, current smoking, stroke, coronary heart disease, BMI, regular exercise, self rated health, and depressive symptoms.
Fig 4 | Association between cumulative benzodiazepine use modeled as spline and risk of incident dementia or Alzheimer's disease
Decreased Brain GABA-A-Benzodiazepine Receptor Binding in Panic Disorder: Preliminary Results From a Quantitative PET Study

Middle brain (12 mm above the anterior commissure–posterior commissure plane) median volume of distribution map for controls (left) and patients with panic disorder (right). Note the generalized decrease in volume of distribution affecting the thalami and the heads of the caudate nucleus. FC indicates frontal cortex; CN, caudate nucleus; Th, thalamus; Ins, insula; TC, temporal cortex; and OC, occipital cortex.

Decreased Brain GABAA-Benzodiazepine Receptor Binding in Panic Disorder: Preliminary Results From a Quantitative PET Study

Volume of distribution values for the panic disorder and control groups at the voxels with the greatest (left, \( z=4.22 \)) and least (right, \( z=1.96 \)) significant difference within the gray matter.
Decreased Brain GABA<sub>A</sub>-Benzodiazepine Receptor Binding in Panic Disorder: Preliminary Results From a Quantitative PET Study

- The major finding was that there is a global reduction in benzodiazepine site binding throughout the brain in patients with panic disorder compared with controls.

- This decreased binding at the brain GABA<sub>A</sub>-benzodiazepine site in panic disorder suggests that abnormalities in basal or adaptive inhibitory neuromodulation are of pathologic significance in this condition.

- Loci with the largest regional decrease in binding (right orbitofrontal cortex and right insula) were areas thought to be essential in the central mediation of anxiety.
Endogenous Benzodiazepines

- Benzodiazepines are found in the (paraffin-preserved) brains of individuals who died long before the first laboratory synthesis of benzodiazepines (Sangameswaran et al, 1986).

- Endogenous benzodiazepine agonists (endozapines) are found in the rare familial condition, idiopathic recurrent stupor (Tinuper et al, 1994) and possibly in hepatic encephalopathy (Cossar et al, 1997).

- Plants, notably Aspergillus fungi, can make a range of benzodiazepines, and these naturally occurring benzodiazepines can also be stored in human brains after being eaten — so it is possible that the receptors evolved to take advantage of these naturally occurring anxiolytics.
Position emission tomography (PET) scans of the brains of patients with panic disorder (right) show a significant global reduction in binding to the benzodiazepine antagonist flumazenil compared with ‘normal’ brains (left).

DAVID J. NUTT, and ANDREA L. MALIZIA BJP
2001;179:390-396
Benzodiazepines Withdrawal

- Tachycardia – increase in heart rate
- Severe headaches
- Panic attacks Tremors
- Changes in perception – not fully in tune with, or aware of, everything going on around you
- Weight loss
- Parasthesias
Predictors of Severe Benzodiazepine Withdrawal

- High-potency-quickly eliminated
  - (e.g. alprazolam, lorazepam, triazolam)
- Higher daily dose
- More rapid rate of taper (esp last 50%)
- Diagnosis of panic disorder (not GAD)
- High pre-taper levels of anxiety and depression
- ETOH or other substance dependence/abuse
- Personality pathology - e.g. neurotic or dependent
- Poor motivation to discontinue use
Protracted Withdrawal From Benzodiazepines: The Post-Withdrawal Syndrome

School of Neurosciences
Division of Psychiatry
The Royal Victoria Infirmary
Queen Victoria Road
Newcastle upon Tyne NE1 4LP

Professor C Heather Ashton, DM, FRCP

First published in:
<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Usual Course</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anxiety</td>
<td>Gradually diminishing over a year</td>
</tr>
<tr>
<td>Insomnia</td>
<td>Gradually diminishing over 6 to 12 months</td>
</tr>
<tr>
<td>Depression</td>
<td>A few months; responds to antidepressants</td>
</tr>
<tr>
<td>Perceptual symptoms: tinnitus, paraesthesiae — tingling, numbness, pain usually in limbs, extremities</td>
<td>Gradually receding, but may last at least a year and occasionally permanent</td>
</tr>
<tr>
<td>Motor symptoms: muscle pain, weakness, tension, painful cramps, tremor, shaking attacks, jerks, blepharospasm</td>
<td>Gradually receding, but may last at least a year and occasionally permanent</td>
</tr>
<tr>
<td>Gastro-intestinal symptoms</td>
<td>Gradually receding, but may last at least a year and occasionally permanent</td>
</tr>
<tr>
<td>Mechanisms for protracted symptoms not known, but may include both psychological and pharmacological factors, and possibly structural brain damage.</td>
<td></td>
</tr>
</tbody>
</table>
Protracted withdrawal from benzodiazepines: The post-withdrawal syndrome

- The question of permanent damage is discussed in "Psychiatric Annals 25, 174-179.
- The article clearly states that the evidence about permanent (structural) brain damage due to benzodiazepines is equivocal and there is at present no definite proof of this although some evidence is suggestive. However, occasionally people do have "withdrawal" symptoms which appear to be permanent and may persist till death. This has been reported in the medical literature by others and also observed by myself.