Benzodiazepines
2015

Dual Disorders Ward
Lev-Hasharon Mental Health Medical Center
Netanya
Israel
050-626-7912
alerner@lev-hasharon.co.il

State of Israel
Ministry of Health
Lev-Hasharon
Mental Health Medical Center
Affiliated to
Sackler School of Medicine
Tel-Aviv University
Israel
This talk will cover and analyze some, but not all the aspects of the topic.

This conversation will probably place and produce more questions than answers.
Substances may be classified by at least, four cellular mechanisms of action that have been described to cause an acute dopamine increase (representative, not exhaustive list).

- **Group I** consists of opioids, cannabinoids and γ-hydroxybutyrate (GHB). They decrease the release of GABA from VTA interneurons and thereby remove the inhibitory transmission “brake” onto DA neurons. This indirect increase of DA cells’ activity is known as dis-inhibition, and is possible due to either cell-type specific expression of their respective receptor to the substance like in opioids, cannabinoids or higher affinity of the drug for the receptor located on GABA neurons (GHB).

- **Group II** consists of Nicotine which directly activates DA neurons.

- **Group III** consists of stimulants like cocaine and amphetamines which target and perturb the DA transporter (DAT) either by blocking it (cocaine) or reversing its activity (amphetamines).

- **Group IV** consists of alcohol and BZ which release B-endorphins that reduces the inhibitory effect on VTA allowing DA release.

*Arnaud L. Lalive, Uwe Rudolph, Christian Lüscher, Kelly R. Tan.*  
*Is there a way to curb benzodiazepine addiction?*  
*Swiss Med Wkly. 2011;141:w13277*
BZ (like alcohol) appears to produce its effects by *intercalating* itself into membranes and thus increasing fluidity of the membranes, increasing chloride channel activity and enhancing GABA$_A$ receptor affinity to GABA neurotransmitter.

- BZs bind at the interface of the $\alpha$ and $\gamma$ subunits on the GABA$_A$ receptor.
- Barbiturates mainly bind to the GABA$_A$ receptor at the alpha subunit.

The GABA$_A$ receptor is a protein complex located in the synapses of neurons.

All GABA$_A$ receptors contain an ion channel that conducts chloride ions across neuronal cell membranes and two binding sites for the neurotransmitter gamma-aminobutyric acid (GABA).

A subset of GABA$_A$ receptor complexes also contain a single binding site for benzodiazepines.

The subset of GABA$_A$ receptors that also bind benzodiazepines are referred to as benzodiazepine receptors (BzR).

The GABA$_A$ receptor is a heteromer composed of *five subunits*, most commonly two $\alpha$'s, two $\beta$'s and one $\gamma$ ($\alpha2\beta2\gamma$). For each subunit, many subtypes exist ($\alpha1$-$6$, $\beta1$-$3$ and $\gamma1$-$3$).

GABA$_A$ receptors that are made up of different combinations of subunit subtypes have different properties, different distributions in the brain and different activities relative to pharmacological and clinical effects.
BZ

Diagram showing the components of a GABA receptor, including α1, β2, γ2, and Cl⁻ pore sites, as well as GABA and BZD binding sites.
BZ is a GABA agonist and NMDA (glutamate) receptor antagonist.

BZ enhances the inhibitory action of GABA-ergic neurotransmitters by increasing the response (super-sensitivity: number, affinity and efficiency) of GABA receptors.

BZ reduces the excitatory action of GLUTAMAT-ergic neurotransmitters by altering the response (sub-sensitivity) of NMDA receptors.
BZ and alcohol

- Alcohol appears to behave like BZ on BZ receptors
- GABA, the major inhibitory neurotransmitter, interacts with GABA type A complex.
- BZ receptors (two central and one peripheral) are contiguous to the GABA type A receptor.
- DBI diazepam binding inhibitor is a protein that modulates GABA receptors.
- Endozepines are endogenous compounds with benzodiazepine like effects. They have been linked to hepatic encephalopathy and have controversially been linked to some cases of recurrent stupor.
- Occupation of BZ receptor changes the conformation of the GABA receptor to increase its affinity to GABA neurotransmitter, enhances chloride ion influx and hyper-polarization.

BZ use disorders

Common BZ associated clinical syndromes (non DSM - 5) 
(representative non exhaustive)

- Acute BZ intoxication
- Idiosyncratic BZ intoxication
- BZ Paradoxical Intoxication
- BZ associated Blackouts
- Uncomplicated BZ withdrawal
- BZ delirium
- BZ DT
- BZ associated withdrawal seizures
- BZ- like Wernicke – Korsakoff syndrome
Benzodiazepines receptors agonists

- BZs bind to GABA A complex enhancing the effect of the neurotransmitter GABA which results in sedative, hypnotic, anticonvulsant, muscle relaxant and amnestic action.

- After stabilization is achieved BZ should be gradually and wisely reduced.

- Every BZs appear to be effective in controlling in-progress narcotic withdrawal syndrome.

- Diazepam (available and easy to manage), lorazepam, oxazepam, clorazepate and alprazolam.
Clinical aspects of adjunctive medications

*Approximate Therapeutic Equivalent Doses of Benzodiazepines*

<table>
<thead>
<tr>
<th>Generic name</th>
<th>Dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alprazolam</td>
<td>1</td>
</tr>
<tr>
<td>Alprazolam XR</td>
<td>1</td>
</tr>
<tr>
<td>Chlordiazepoxide</td>
<td>25</td>
</tr>
<tr>
<td>Clonazepam</td>
<td>0.5-1</td>
</tr>
<tr>
<td>Clorazepate</td>
<td>15</td>
</tr>
<tr>
<td>Diazepam</td>
<td>10</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>2</td>
</tr>
<tr>
<td>Oxazepam</td>
<td>30</td>
</tr>
<tr>
<td>Triazolam</td>
<td>0.25</td>
</tr>
<tr>
<td>Estazolam</td>
<td>1</td>
</tr>
<tr>
<td>Flurazepam</td>
<td>30</td>
</tr>
<tr>
<td>Prazepam</td>
<td>80</td>
</tr>
<tr>
<td>Temazepam</td>
<td>20</td>
</tr>
<tr>
<td>Quazepam</td>
<td>15</td>
</tr>
<tr>
<td>Zolpidem</td>
<td>10</td>
</tr>
</tbody>
</table>
Clinical aspects of adjunctive medications
Benzodiazepines

Generic name

- Alprazolam
- Alprazolam XR
- Chlordiazepoxide (Nirvaxal)
- Clonazepam
- Clorazepate (Tranxal)
- Diazepam
- Lorazepam
- Oxazepam
- Flunitrazepam
- Nitrazepam
Z-Drugs

**Mechanism of action of sleeping pills**

Zolpidem (Stilnox and Zodorm 10 mg)
Zopiclone (Nocturno and Imovane 7.5 mg)

- They work on the benzodiazepine site on the GABA\textsubscript{A} receptor complex similarly to BZ.
- Some but not all of the non-BZ are selective for the $\alpha_1$ subunit on GABA\textsubscript{A} receptors, which is responsible for inducing sleep and may therefore have a cleaner side-effect profile than the older benzodiazepines.
- Zopiclone like benzodiazepine drugs bind unselectively to $\alpha_1$, $\alpha_2$, $\alpha_3$ and $\alpha_5$ GABA\textsubscript{A} complex.
- Zolpidem is more selective and is highly selective for the $\alpha_1$ subunit, thus giving them an advantage over benzodiazepines in terms of sleep architecture and a reduction in side-effects.
- The non-BZ drugs have milder activity at the $\alpha_1$ subunit on GABA\textsubscript{A} receptors compared to most benzodiazepines, rendering them ineffective for moderately severe to severe insomnia.
- Z-drugs and BZ decrease time to fall asleep, increase total sleep time (depending on half-life) and enhance GABA function through allosteric modulation (*regulation of an enzyme or other protein by binding an effector molecule at the protein's allosteric site that is, a site other than the protein's active site*).
- These drugs appear to cause both psychological dependence and physical dependence, though less than traditional benzodiazepines and can also cause the same memory and cognitive disturbances along with morning sedation.

- Trazodone and mirtazapine increase total sleep time and blocks 5HT receptors.
- Olanzapine and quetiapine decrease awakening.
- Ramelteon decreases time to fall asleep. Is a melatonin agonist.
- Promethazine increases total sleep time and decreases awakening. Blocks H1 receptors.
More Z-Drugs.....

Z –Drugs

- Zolpidem: Stilnox, Ambien, Zodorm
- Zopiclone: Nocturno
- Zaleplone (Sonata)
- Eszopiclone: Lunesta
Eszopiclone

- Eszopiclone is active the dextrorotatory stereoisomer of zopiclone, and belongs to the class of drugs known as cyclopyrrolones.
- Eszopiclone is effective in the treatment of insomnia where difficulty in falling asleep is the primary complaint.
- It is not recommended for chronic use in the elderly due to Sundown Syndrome:
  - Increased general confusion as natural light begins to fade and increased shadows appear.
  - Agitation and mood swings.
  - Patients may become fairly frustrated with their own confusion as well as aggravated by noise.
  - Patients found yelling and becoming increasingly upset with their caregiver is not uncommon.
  - Mental and physical fatigue increase with the setting of the sun. This fatigue can play a role in the patient's irritability.
  - Tremors may increase and become uncontrollable.
  - A patient may experience an increase in their restlessness while trying to sleep.
  - Restlessness can often lead to pacing and or wandering which can be potentially harmful for a patient in a confused state.
Eszopiclone acts on benzodiazepine binding site situated on GABAA neurons as an agonist.

Eszopiclone is rapidly absorbed after oral administration, with serum levels peaking between 1 and 1.3 hours.

The elimination half-life of eszopiclone is approximately 6 hours and it is extensively metabolized by oxidation and demethylation.

Approximately 52% to 59% of a dose is weakly bound to plasma protein.

Cytochrome P450 (CYP) isozymes CYP3A4 and CYP2E1 are involved in the biotransformation of eszopiclone thus, drugs that induce or inhibit these CYP isozymes may affect the metabolism of eszopiclone.

Less than 10% of the orally administered dose is excreted in the urine as racemic zopiclone.

In terms of benzodiazepine receptor binding and relevant potency, 3 mg of eszopiclone is equivalent to 10 mg of diazepam.
**Melatonin and melatonin agonists**

- The hormone melatonin is effective in several types of insomnia. Melatonin has demonstrated effectiveness in inducing sleep and regulating the sleep/waking cycle. One particular benefit of melatonin is that it can treat insomnia without altering the sleep pattern, which is altered by many prescription sleeping tablets. Another benefit is it does not impair performance related skills.

- Melatonin OTC: 2 and 4 mg.

- **Melatonin (Circadin prolonged-release 2 mg)**
  - Circadin is indicated as monotherapy for the short-term treatment of primary insomnia characterized by poor quality of sleep in patients who are aged 55 or over.
  - The recommended dose is 2 mg once daily, 1-2 hours before bedtime and after food. This dosage may be continued for up to thirteen weeks.
  - Caution should be exercised in patients on fluvoxamine, which increases melatonin levels (by 17-fold higher AUC and a 12-fold higher serum C\text{max}) by inhibiting its metabolism by hepatic cytochrome P450 (CYP) isozymes CYP1A2 and CYP2C19.
  - Caution should be exercised in patients on contraceptive or hormone replacement therapy and cimetidine a CYP2D inhibitor, which increases plasma melatonin levels, by inhibiting its metabolism
  - CYP1A2 inducers such as carbamazepine and rifampicin may give rise to reduced plasma concentrations of melatonin.
  - Alcohol should not be taken with Circadin, because it reduces the effectiveness of Circadin on sleep.
  - Circadin may enhance the sedative properties of benzodiazepines and nonbenzodiazepine hypnotics, such as zolpidem and zopiclone.
BZ & Basic Withdrawal Management

- **Diazepam**: 40 mg – 60 mg (Golden Dosage)
- **Loading of Anti-Seizure Medication**:
  - **Immediate release Carbamazepine**
    1. First day 400 mg
    2. Second day 600 mg
    3. Third day 800 mg
  - **Immediate release Valproate**
    1. First day 400 mg
    2. Second day 600 mg
    3. Third day 800 mg
- **Propanolol**: 30 mg – 60 mg
- **Clonidine**: 0.15 mg – 0.45 mg
- **Symptomatic Management**: Antidepressant Tranquilizers, Second Generation Antipsychotics......
BZ & Basic Withdrawal Management

Replacement..
Stabilization..
Taper Down..

Basic Long term medication:
Mood Stabilizers: Lamotrigine (400 mg – 600 mg)
Two Antidepressants: **Morning** (SSRI or NSRI) and **Evening** (Tranquilizer)
Types

- **Agonists**: bind to the main receptor site (the site where GABA normally binds, also referred to as the "active" or "orthosteric" site) and activate it, resulting in increased Cl⁻ conductance.

- **Antagonists**: bind to the main receptor site but do not activate it. Though they have no effect on their own, antagonists compete with GABA for binding and thereby inhibit its action, resulting in decreased Cl⁻ conductance.

- **Positive allosteric modulators**: bind to allosteric sites on the receptor complex and affect it in a positive manner, causing increased efficiency of the main site and therefore an indirect increase in Cl⁻ conductance.

- **Negative allosteric modulators**: bind to an allosteric site on the receptor complex and affect it in a negative manner, causing decreased efficiency of the main site and therefore an indirect decrease in Cl⁻ conductance.

- **Open channel blockers**: prolong ligand-receptor occupancy, activation kinetics and Cl⁻ ion flux in a subunit configuration-dependent and sensitization-state dependent manner.

- **Non-competitive channel blockers**: bind to or near the central pore of the receptor complex and directly block Cl⁻ (chloride) conductance through the ion channel.

*Source: WIKI*
New Medications

- A useful property of the many benzodiazepine site allosteric modulators is that they may display selective binding to particular subsets of receptors comprising specific subunits.
- This allows one to determine which GABA_A receptor subunit combinations are prevalent in particular brain areas and provides a clue as to which subunit combinations may be responsible for behavioral effects of drugs acting at GABA_A receptors.
- These selective ligands may have pharmacological advantages in that they may allow dissociation of desired therapeutic effects from undesirable side effects.
- Few subtype selective ligands have gone into clinical use as yet, with the exception of zolpidem which is reasonably selective for α_1, but several more selective compounds are in development such as the α_3-selective drug adipoiplon.
- There are many examples of subtype-selective compounds which are widely used in scientific research, including:
  - CL-218,872 (highly α_1-selective agonist)
  - Bretazenil (subtype-selective partial agonist)
  - imidazenil and L-838,417 (both partial agonists at some subtypes, but weak antagonists at others)
  - QH-ii-066 (full agonist highly selective for α_5 subtype)
  - α_3IA (selective inverse agonist for α_5 subtype)
  - SL-651,498 (full agonist at α_2 and α_3 subtypes, and as a partial agonist at α_1 and α_5
  - 3-acyl-4-quinolones: selective for α_1 over α_3

Source: WIKI
Thanks for your attention