Anxiolytic drugs

**Anxiolytics**: reduce anxiety

**Sedatives**: decrease activity, calming effect

**Hypnotics**: induce sleep

Some drugs have anxiolytic and sedative/hypnotic effects.
Anxiety disorders

Excessive, severe, and prolonged anxiety that compromises normal functioning

Prevalence: 2.5-6.5% of general population

Subjective features
Apprehension
Worry
Anticipation
Fear
Hypervigilance (‘jumpiness’)
Restlessness
Impaired concentration
Depression
Physiological features
Neuromuscular e.g. tension, fatigue, tremor
Gastrointestinal e.g. dry mouth, difficulty in swallowing
Respiratory e.g. hyperventilation
Cardiovascular e.g. palpitations

**Beta-blockers**
e.g. Propranolol
Only treats physiological symptoms (palpitations, tremor and gastrointestinal upset, etc.)
Used for performance anxiety
Anxiolytic drugs

Benzodiazepines have dominated for 40 years

Alpralozam **(Xanax); Chlordiazepoxide ***
(Librium); Diazepam ***(Valium); Lorazepam **
(Ativan); Chlorazepate * (Tranxene)
*Short-acting (3-8 hours)
**Intermediate (10-20 hours)
*** Long-acting (1-3 days)

Azapirones:

Buspirone (Buspar) - partial 5-HT1A agonist
### Sedative/hypnotic drugs

#### Benzodiazepines:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Brand Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clonazepam</td>
<td>Klonopin</td>
</tr>
<tr>
<td>Diazepam</td>
<td>Valium</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>Ativan</td>
</tr>
<tr>
<td>Oxazepam</td>
<td>Serax</td>
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<td>Triazolam</td>
<td>Halcion</td>
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<td>Temazepam</td>
<td>Restoril</td>
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<tr>
<td>Flurazepam</td>
<td>Dalmane</td>
</tr>
<tr>
<td>Quazepam</td>
<td>Doral</td>
</tr>
<tr>
<td>Midazolam</td>
<td>Versed</td>
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</tbody>
</table>

#### Benzodiazepine binding site agonists (but not benzodiazepines): Z drugs

- Zaleplon (Sonata)
- Zolpidem (Ambien)
Sedative/hypnotic drugs

Barbiturates
- Amobarbital **(Amytal); Aprobarbital (Alurate);
- Butabarbital (Butisol); Mephobarbital (Mebaral);
- Methohexital * (Brevital); Pentobarbital**
  (Nembutal); Phenobarbital ***(Luminal);
- Secobarbital **(Seconal); Thiopental* (Pentothal)

*Ultrashort (5-15 min)/induction of anesthesia
**Short acting (3-8 hrs)/insomnia/preoperative sedation
***Long acting (days) treatment of seizures

Newer GABA receptor activators are also used for anesthesia
OTHERS

Alpha₂ adrenergic agonist sedation/analgesia/anxiolytic
Dexmedetomididine (Precedex)

Ramelteon MT1/MT2 melatonin agonist - insomnia
(targtes a nucleus in the hypothalamus)

Meprobamate (Miltown) - used as an anxiolytic appears
to have a barbiturate like effect but can also directly
activate the GABAₐ receptor

Chloral hydrate (Noctec) - older sedative/hypnotic
Flunitrazepam (Rohypnol) fast-acting BDZ causes
amnesia “date rape”
Classifying anxiety disorders

• Generalized anxiety disorder
• Phobic anxiety disorder (e.g. agoraphobia, social phobia etc)
• Panic disorder
• Obsessive-compulsive disorder (OCD)
• Post-traumatic stress disorder
• Adjustment disorder with anxiety (and sometimes depression), also known as acute stress disorder
• Comorbid depression and anxiety
Generalized anxiety disorder (GAD)
excessive anxiety and worry most of the time

Phobic anxiety disorders
an irrational fear that interferes with normal behavior

Panic disorder
discrete periods of intense fear

Obsessive-compulsive disorder (OCD)
*Obsessions*: persistent thoughts, ideas, or images that intrude into conscious awareness
*Compulsions* are urges or impulses for repetitive intentional behaviors
Post-traumatic stress disorder
recurrent anxiety precipitated by exposure to an exceptionally stressful or life threatening event

Acute stress disorder
a reaction to a recent identifiable stress;
lasts less than six months

Comorbid depression and anxiety
Depression and anxiety occurring together at the same time in the same patient
Higher cortical function (consciousness, cognition, mood)

Psychological treatment

Drug treatment

Molecules
(neurotransmitters, receptors, ion channels)
‘Fear’ vs ‘Anxiety’

**Fear**: reaction to immediate perceived threat/critical to survival

**Conditioned fear**: reaction to a stimulus that is associated with a threat

**Anxiety**: anticipatory response to an uncertain, potential threat
Functional neuroanatomy of anxiety and fear

The amygdala is central

Limbic System
(Greatly simplified)

Sensory input

thalamus

hippocampus

hypothalamus

amygdala

brainstem

/striatum

“experience”

cortex

“expression”

‘fight or flight’

Motor response

Autonomic responses

hormonal stress response

(Greatly simplified)
Neurochemistry of anxiety and fear

Corticotropin-releasing hormone/factor (CRH/F)
  Glutamate
  Norepinephrine
  Acetylcholine
  Serotonin (5-HT)
  Dopamine
  Gamma-aminobutyric acid (GABA)
Cholecystokinin (CCK; neuroactive peptide)
neuropeptides
**GABA_A receptors**
Infusion of benzodiazepines into amygdala has anxiolytic effect (animal studies)

Benzodiazepine antagonists and inverse agonists cause anxiety

**Serotonergic system**
Serotonin released in amygdala during anxiety?
5-HT\textsubscript{2A}, 5-HT\textsubscript{2C}, 5-HT\textsubscript{1A} and 5-HT\textsubscript{1B} receptors

**Noradrenergic system**
Hyperactive response in anxiety disorders
Panic disorder - hypersensitive to anxiogenic alpha2 antagonists
Ascending arousal system
Buspirone full agonist

Inhibitory autoreceptor

Buspirone

Buspirone metabolite: 1-2-pyrimidinylpiperazine (1-PP)
**Buspirone**

Partial agonist at postsynaptic 5HT$_{1A}$ receptors

Full agonist at presynaptic 5HT$_{1A}$ receptors

Hippocampus site of anxiolytic action?

Chronic buspirone -> desensitize presynaptic 5-HT$_{1A}$ -> increased serotonergic activity

Can exacerbate panic attacks in patients with panic disorder (1-PP alpha2 antagonist effect?)

No dependency
Antidepressants

Monoamine oxidase inhibitors
Tricyclic antidepressants
Selective serotonin reuptake inhibitors

Take several weeks to have beneficial effect - desensitization of presynaptic autoreceptors - mechanism will be covered in detail

Can initially make anxiety symptoms worse
Effective in treating anxiety and comorbid depression
Mechanism for $\alpha_2$-Induced Sedation/Hypnosis in the Rat Locus Coeruleus
Benzodiazepines

Modulate GABA$_A$ receptor  
Increase potency but not efficacy of GABA  
No intrinsic agonist activity - can not open the Cl- channel  
Amygdala site of anxiolytic action?

• Risk of **classic tolerance** and dependence  
• Sedative, hypnotic, muscle relaxants, anticonvulsant and anxiolytic  
• Hypnosis and stupor at high doses  
• Preferred over barbiturates - **when used alone** - rarely cause fatal CNS depression (additive depression with ethanol)  
• **Flumazenil** is a competitive BDZ antagonist - no clinical effect alone
GABA$_A$ receptors

GABA-gated Cl$^-$ channel
(GABA$_A$ receptor)
**GABA\textsubscript{A} receptors**

Anxiolytics/sedatives/hypnotics that bind to GABA\textsubscript{A} receptors:

- Benzodiazepines (BZD)  
- Barbiturates (BRB)  
- Zolpidem (Zol)  
- Zaleplon (Zal)  
- Meprobamate (Mep)  
- chloral hydrate (ChH)

Increase GABA\textsubscript{A} receptor activity

‘agonists’ / positive allosteric modulators
Sedative/hypnotics

- death
- surgical anesthesia
- coma
- sleep
- sedation

Drug dose

Most non-benzodiazepine sedative/hypnotics

Benzodiazepines, Zolpidem, Zaleplon
<table>
<thead>
<tr>
<th></th>
<th>Anxiolytic?</th>
<th>Sedative/hypnotic?</th>
<th>Tolerance/dependence?</th>
<th>Lethal in overdose?</th>
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</thead>
<tbody>
<tr>
<td>BZD</td>
<td>Yes (variable)</td>
<td>Yes (variable)</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>BRB</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Zol</td>
<td>No</td>
<td>Yes</td>
<td>Not supposed to</td>
<td>No</td>
</tr>
<tr>
<td>Zal</td>
<td>No</td>
<td>Yes</td>
<td>Not supposed to</td>
<td>No</td>
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<tr>
<td>Mep</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>ChH</td>
<td>?</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>
**GABA**<sub>A</sub> receptor subtypes

**GABA**<sub>A</sub> receptors are heteropentamers

Five subunits combine to form a channel through the membrane

Individual subunit

- Plasma membrane
- Extracellular
- Intracellular
- Hyperpolarization

Cl⁻ ions
## Subunit composition

<table>
<thead>
<tr>
<th>Subunit class</th>
<th>isoforms</th>
</tr>
</thead>
<tbody>
<tr>
<td>alpha</td>
<td>1-6</td>
</tr>
<tr>
<td>beta</td>
<td>1-4</td>
</tr>
<tr>
<td>gamma</td>
<td>1-4</td>
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<td>epsilon</td>
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</tr>
<tr>
<td>pi</td>
<td>1</td>
</tr>
<tr>
<td>rho</td>
<td>1-3</td>
</tr>
</tbody>
</table>
Subunit composition

preferred pentameric combination:
2 alpha, 2 gamma, 1 beta, or
2 alpha, 2 beta, 1 gamma
Distribution of subunits in the brain

Different subunits have distinctive patterns of distribution in the brain

For example:

alpha-1 subunit predominantly in the cerebellum

gamma-1 subunit predominantly in amygdala and septum

The stoichiometry (subunit combination) of GABA$_A$ receptor subtype probably varies among different brain regions
Differential drug sensitivity

The sensitivity profile of a GABA$_A$ receptor to different benzodiazepenes depends on the identity of its alpha subunits.

For example:

The **common benzodiazepines** bind to GABA$_A$ receptors that contain alpha-1, alpha-2, alpha-3 or alpha-5 subunits (not alpha-4 or alpha-6)

Zolpidem and zaleplon are specific for receptors containing the alpha-1 subunit

Receptors containing the gamma-1 subunit have low affinity for most of the benzodiazepine site ligands
Different drug actions may be mediated by different GABA$_A$ receptor subtypes

The benzodiazepine binding site is made up with residues from the $\alpha$ and $\gamma$ subunits

Not all GABA$_A$ receptors bind benzodiazepines

**Transgenic - ‘knock-in’ mouse**

GABA$_A$ receptor with 'wild-type' alpha-1 subunit \[\xrightarrow{\text{Diazepam-sensitive}}\] GABA$_A$ receptor with mutant alpha-1 subunit

Diazepam-sensitive \[\xrightarrow{\text{Diazepam-insensitive}}\]
Effects of Diazepam

Sedation

Memory impairment

Anticonvulsant activity (suppress tonic seizures)

Myorelaxant activity (muscle-relaxing effect)

Motor impairment (uncoordinated movement)

Potentiates the sedative effects of ethanol

Anxiolytic effect
Summary

Knock-in mice resistant to sedative and amnesic effects, and partially resistant to anticonvulsant effects of diazepam.

Myorelaxant, motor control impairment, ethanol-potentiating and anxiolytic actions of diazepam not changed in knock-in mice.
Conclusion

The sedative, amnesic and some of the anticonvulsivive effects of diazepam are mediated by GABA$_A$ receptors that contain the alpha-1 subunit.

The other effects of diazepam are mediated by GABA$_A$ receptors that contain the alpha-2, alpha-3 or alpha-5 subunits.

The selective sedative effect of zolpidem and zaleplon may be due to their specificity for GABA$_A$ receptors that contain the alpha-1 subunit.
Another mechanism of selective drug effects: partial BZD agonists (newer agents)
Benzodiazepine receptor partial agonists

Anxiolytic, but less sedation, motor impairment, dependence, tolerance than diazepam

Abecarnil
Alpidem – withdrawn in Europe – hepatotoxicity
Bretazenil
Suridone
Imidazenil

None available clinically in USA
Main points

Many anxiolytics and sedative/hypnotics act at GABA<sub>A</sub> receptors

Different GABA<sub>A</sub> drugs have different spectra of effects

Mode of action

Selectivity

Receptor subtypes, stoichiometry

Partial agonists