Anxiety Pharmacology

UNIVERSITY OF HAWAI‘I HILO PRE-NURSING PROGRAM
NURS 203 – GENERAL PHARMACOLOGY
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Learning Objectives

- Understand the normal processing of fear vs fear processing in the anxious individual
- Know the classes of medications used to treat anxiety
- Know the agents within the individual classes that have properties outside the class in general
### What is anxiety?

A state or feeling of apprehension, uneasiness, agitation, uncertainty, and fear resulting from the anticipation of some threat or danger, usually of psychic origin, whose source is generally unknown or unrecognized.

<table>
<thead>
<tr>
<th>Mental Symptoms</th>
<th>Physical Symptoms</th>
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<tbody>
<tr>
<td>◦ Fear</td>
<td>◦ Shortness of breath</td>
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<tr>
<td>◦ Difficulty concentrating</td>
<td>◦ Chest pain</td>
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<tr>
<td>◦ Worry</td>
<td>◦ Restlessness</td>
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<tr>
<td>◦ Irritability</td>
<td>◦ Nausea</td>
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<tr>
<td>◦ Sleep disturbances</td>
<td>◦ Trembling</td>
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<tr>
<td>◦ Etc.</td>
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</tbody>
</table>
Causes of Anxiety

Medical conditions
- Cardiovascular conditions
  - Angina
  - Heart failure
  - Arrhythmias
- Gastrointestinal
  - IBS
  - Other inflammatory bowel conditions
- Endocrine
  - Diabetes – hypoglycemia
  - Hyperthyroidism
  - Cushing’s
- Other
  - Pain
  - Migraine
  - Asthma

Drugs
- Pseudoephedrine
- SSRIs
- TCAs
- Caffeine
- Ginseng
- Ephedra
- Cocaine
- Levothyroxine
- Prednisone
- Albuterol
- Etc.
Types of Anxiety Disorders

Panic disorder
Generalized anxiety disorder
Obsessive compulsive disorder
Specific phobias
Posttraumatic stress disorder

Page 311 in the book
- Treatment alternatives
  - SSRIs
  - SNRI
  - TCAs
  - Prazosin (PTSD)
  - Antipsychotics
Under Normal Circumstances – creating/remembering fear

Locus Coeruleus NE

B₁

Amygdala: Consolidation of Fear

GR

HPA axis activity Cortisol
Under Normal Circumstances – fear extinction

Inhibitory signal from GABAergic interneurons

Amygdala: Fear Extinction

Central nucleus

Fear Expression

Rationalize Fear
Anxious Individuals

Inhibitory signal from GABAergic interneurons

Amygdala: Fear Extinction

Central nucleus

Rationalize Fear

Fear Expression
Benzodiazepines

MOA - GABA channels work by allowing the flow of chloride into the neuron. This **HYPERPOLARIZES** the cell – making the neuron less likely to fire (**inhibitory**).

Benzodiazepines increases the frequency of GABA channel opening as well as the affinity of GABA to its receptor.

**Drugs in the class –**

- **Short-Acting**
  - Alprazolam
  - Midazolam
  - Oxazepam

- **Intermediate-Acting**
  - Lorazepam
  - Temazepam

- **Lone-Acting**
  - Chlordiazepoxide
  - Clonazepam
  - Diazepam
GABA & Benzodiazepine Receptors/Effects

GABA –
- Main neurotransmitter of the CNS (located throughout)
- GABA is an inhibitory NT
- Activation of GABA receptors
  - Anxiolytic
  - Anti-spasmodic
  - Hypnotic
  - Amnesia
  - Anesthesia
- ****NO PAIN RELIEF
- GABA receptor have a BZD binding site located on them

GABA channels work by allowing the flow of chloride into the neuron. This HYPERPOLARIZES the cell – making the neuron less likely to fire (inhibitory).

Benzodiazepines increases the frequency of GABA channel opening.
# Benzodiazepines

<table>
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<tr>
<th>Uses</th>
<th>ADRs</th>
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<tr>
<td>◦ Anxiolytic</td>
<td>◦ Sedation, depression, disorientation, respiratory depression, ataxia, retrograde amnesia,</td>
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<tr>
<td>◦ Antiemetic</td>
<td></td>
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<tr>
<td>◦ Sedative</td>
<td></td>
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<tr>
<td>◦ Anti-seizure</td>
<td></td>
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<td>◦ Muscle relaxant</td>
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<td>◦ Substance abuse (withdrawal)</td>
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Benzodiazepines - General

Kinetics
- Vary with individual agents
- See following slides

Notes
- Taper – rebound anxiety
- Withdrawal can precipitate seizures
- Watch for dependence and tolerance
- Should be used short term in anxiety or acute treatment of panic attack

ADRs
- Sedation, depression, disorientation, respiratory depression, ataxia, retrograde amnesia, paradoxical excitation

Interactions
- CNS depressants, alcohol, barbiturates, SSRIs, TCAs, antihistamine, anticonvulsants, opioids
- CYP3A4 inhibitors/inducers (except LOT)
- CYP1A2 – fluvoxamine (diazepam)
- Pregnancy
  - Not considered safe
  - Concentrated in breast milk
Benzodiazepines -

Short-Acting
- Alprazolam
- Midazolam
- Oxazepam

Onset – rapid (<15 mins)
Duration – 6-24 hrs.
Metabolized – CYP3A4 – short lived metabolite

Onset – rapid (<15 mins)
Duration – < 6 hours (anesthesia)
Metabolized – Extensive CYP3A4 – active metabolite

Onset – Slow (30-60 mins)
Duration – 6-24 hours
Metabolized – Glucuronidation – NO CYP
Benzodiazepines -

**Intermediate-Acting**
- Lorazepam
- Temazepam

Onset – 15-30 mins
Duration – 6-24 hours
Metabolism – Glucuronidation (NO CYP)

Onset – 30-60 mins
Duration – 6-24 hours
Metabolism – Glucuronidation (NO CYP)
Benzodiazepines -

Long-Acting
• Chlordiazepoxide
• Clonazepam
• Diazepam

Onset: 15-30 mins
Duration: Long (>24 hours)
Metabolism: Metabolized by CYP3A4 into long lived active metabolites

Onset: Slow (30-60 mins)
Duration: Long (>24 hours)
Metabolism: CYP3A4 into an inactive metabolite

Onset: Rapid (<15 mins)
Duration: Long (>24 hours)
Metabolism: CYP3A4 & 2C19 into long lived active metabolites
Flumazenil – BZD Antidote

MOA – Competes with BZDs at the GABA-benzodiazepine receptor (antagonist)

Reversal
○ Over-sedation
○ Respiratory depression

Kinetics
○ Onset – 1-2 minutes
○ Peak – 6-10 minutes
○ Duration – 1-3 hours
○ Metabolized – Liver
○ Excreted - Kidneys

ADRs
○ Seizures
○ HA, visual disturbances, pain at injection site, sweating, nausea, lightheadedness, arrhythmia
Buspirone

MOA – Unknown, high affinity for serotonin receptors 5-HT$_{1A}$&$2$ & moderate affinity for dopamine D$_2$ receptor

Kinetics
- Absorption – rapid
- Onset – slow, days-weeks
- Protein binding – 86%
- Metabolism – CYP3A4, extensive 1$^{st}$ pass effect
- Half life – 2-3 hours
- Time to peak – 40-90 minutes
- Excretion – urine (29-63% as metabolites), 18-38% in feces

ADRs
- Dizziness, drowsiness, nervousness, HA, confusion, excitement, nausea, diarrhea, weakness, blurred vision

Interactions
- Alcohol, other serotonergic/dopaminergic drugs, CYP3A4 inducer/inhibitors (grapefruit juice)
- Pregnancy – category B
  - Not known if secreted in breast milk

Notes
- Less sedating than BZD, less abuse, less tolerance
- May be safer in alcoholic, elderly, and pregnancy
Beta Blockers - Propranolol

Beta blockers (like propranolol) that are active in the CNS can inhibit fear consolidation.

Effects:
- Decrease tremor in skeletal muscles
- Decrease heart rate
- Decrease force of contractility
Questions