We are starting psychotherapeutics
In this lecture we will look at drugs with lots of overlapping indications.

GABA-A agonists

GABA is a neurotransmitter that acts upon the GABA-A receptor to negatively modulate the activity of other neurons. That means it inhibits their activity, slows them down, dampens their actions. It should be easy to see then, how a drug that mimics this neurotransmitter should have calming, sedating, hypnotic effects.

Alcohol (ethanol) is a GABA-A agonist. If you can remember the effects of alcohol and that they are dose-related, it will help you with all the other GABA-A agonists. The effects of alcohol include:

**At a low dose:** euphoria, decreased anxiety, increased sociability, impaired judgment and shortened attention span.

**At a moderate dose:** sedation, impaired memory and understanding, delayed reactions, impaired muscle coordination (ataxia, blurred vision), dizziness, impaired speech.

**At high doses:** Lapses of consciousness, respiratory depression, anterograde amnesia, vomiting, incontinence, depressed reflexes, decreased heart rate, severe CNS depression, coma...

GABA-A agonists are not the only ones with sedating effects. Anticholinergics, including 1st generation antihistamines, β blockers, antidepressants and antipsychotics, among others, may too.

GABA-A agonists

- Benzodiazepines
  - Alprazolam
  - Diazepam
  - Lorazepam
  - Midazolam
- Non-benzodiazepine hypnotics
  - Zolpidem
  - Eszopiclone
- Barbiturates
  - Phenobarbital
- Certain antiepileptic drugs
  - Pregabalin
- Certain general anesthetics
  - Propofol
Sedative Hypnotic Drugs

Benzodiazepines, BZD (all C-IV)

**Alprazolam** (Xanax) is used orally as an anxiolytic. It has active metabolites.

**Lorazepam** (Ativan) does not have active metabolites. It is now a drug of choice for status epilepticus. Lorazepam is currently on the FDA drug shortage list (as of Nov 2012).

**Diazepam** (Valium) has active metabolites and unpredictable kinetics. Genetic differences in metabolism make this drug interesting. It is still used for many purposes on and off label, including acute alcohol withdrawal.

**Midazolam** (Versed, Hypnovel) has active metabolites, but has a very short duration of action, for hypnosis, only about 2 hours. Midazolam is used in surgery as part of the anesthetic cocktail, to promote anxiolysis, sedation and memory loss. It is very dangerous due to respiratory depression, though.

All BZD and non-BZD hypnotics are on the Beer's List.

Non-BZD hypnotics

These drugs act just like BZD and are all C-IV.

**Zolpidem** (Ambien, Intermezzo, Zolpimist) and **Eszopiclone** (Lunesta) are used for short-term treatment of insomnia. The doses should be halved in women, the elderly and for eszopiclone, liver patients.

Both are associated with somnambulism, or “sleepwalking.” Patients exhibiting this behavior may appear to be completely awake and talk or carry out other seemingly normal activities (like cooking, or driving).
Other Sedatives and Hypnotics

The barbiturates are also GABA-A agonists. All of the barbiturates induce P450s, some, like phenobarbital, very strongly so. The barbiturates fall into two basic classes, those that are highly lipid soluble, like thiopental (also known as pentothal), and the more polar barbiturates like phenobarbital (luminal). The lipid soluble drugs tend to have a more rapid onset and are C-III. The polar drugs often last longer and are C-IV.

In subhypnotic doses, phenobarbital is antiepileptic. Unfortunately, the long duration of action typically causes considerable drowsiness, or drug-hangover, until the patient becomes tolerant to the drug.

Thiopental, a drug used in states with “death-by-lethal-injection” sentences in their judicial system, is becoming very difficult to get.

Sedating antihistamines like diphenhydramine (Benadryl, Sominex) are often used OTC as a short-term hypnotic.

The type of sleep induced by all the sedative hypnotic drugs differs from physiologic sleep. Patients should be advised to not suddenly discontinue their medications if used regularly as they may experience markedly increased dreaming, nightmares and often, insomnia. Therefore, patients taking hypnotics should be gradually weaned off their medication over several days to a week.

Non Sedating Anxiolytics

Buspirone (BuSpar) is indicated for anxiety disorders. It isn’t understood how Buspirone works. It has a high affinity for 5-HT1a receptors and moderate affinity for dopamine (D2) receptors.

Propranolol (Inderal) is anxiolytic because it interrupts the sympathetic nervous system response to stress. Because of this, propranolol has great promise in actually curing (in some people) post-traumatic stress disorder (PTSD).

Other anxiolytics include AEDs like Topiramate, Pregabalin and Gabapentin and antidepressants including the SSRIs.
Mood Stabilizers

Mood stabilizers are used in the treatment of bipolar disorder. There are a number of unrelated drugs used, which share a number of warnings, including increased risk of:

- Suicide (especially the antidepressants) NOT lithium, which decreases the risk of suicide;
- Psychosis (a risk with bipolar anyway)
- Arrhythmias or seizures
- Discontinuation syndrome
- Significant weight gain

Lithium (Lithane, Happy Happy, Eskalith, Lithobid) was used in the 1800’s to treat gout because it increases the water solubility of uric acid. In the 1940’s an Australian psychiatrist accidentally discovered that lithium had a calming effect.

Lithium has a very narrow therapeutic margin. Therapeutic levels are usually between 0.6-1.2 mEq/L, while toxicity begins at 1.5 mEq/L. Many patients were poisoned before a reliable blood test was developed to monitor lithium levels. Patients taking lithium must be monitored every 3-6 months once levels are stable. For information on the test and additional monitoring, click HERE.

Carbamazepine (Equetro, Tegretol) is an antiepileptic drug (AED) indicated to treat epilepsy, mania associated with bipolar disorder and trigeminal neuralgia. It is used for many other purposes. It has a number of boxed warnings, including a risk of Steven Johnson’s syndrome (SJS).

http://www.drugs.com/monograph/carbamazepine.html
Divalproex (Depakote) is a 50:50 mixture of valproate and valproic acid. Valproate (Depacon) is a Prodrug converted to valproic acid (Depakene) in the stomach. They are AEDs with many other uses including mania associated with bipolar disorder, migraine, and as an adjunct to schizophrenia treatment in patients with agitated, aggressive or violent behavior.

Lamotrigine (Lamictal) is another AED with many uses. It is indicated for epilepsy and for maintenance treatment of bipolar 1 disorder.

Other drugs used in bipolar therapeutics

Doxepin (Sinequan) an antidepressant, is used to treat bipolar depression as is the mixture of Fluoxetine, another antidepressant, with Olanzapine, an antipsychotic, which are formulated into the popular fixed-dose combination Symbyax.

A number of antipsychotics are used, alone or in combination therapy, including Olanzapine (Zyprexa), Risperidone (Risperdal), Quetiapine (Seroquel), Ziprasidone (Geodon) and Aripiprazole (Abilify).
Lithium side effects

- Substantial weight gain – 30% become obese
- Tremors – up to 60% of patients develop tremors
- Goiter – up to 90% of patients develop thyroid problems
- Alopecia – 20% will lose their hair
- Teratogenic in 1st trimester
- Loss of visual accommodation
- Memory loss
- Skin effects – especially acne and rashes

The risk of toxicity and side effects is increased by:

- NSAIDs
- Thiazide diuretics
- Dehydration

Homework and Exercises

1. Read the “START HERE” announcement in Laulima for updates and instructions.
3. Review the Powerpoints and listen to the audio from the face-to-face lecture. You may opt to watch the appropriate videos for this lecture. Review any handouts available for this lecture in the Course Index.
5. Use “Chat,” “Discussions and Private Messages” or the lecture “Forum” to ask questions and find answers or to seek assistance.
6. Complete the online quiz in Laulima, Tasks, Tests and Surveys.

If you have any questions, email me at abeale@hawaii.edu