Neuropharmacology II
Antidepressants and Sedatives

Depression

- A frequent problem, affecting up to 5% of the population
- Common presentations include low mood, loss of energy, disinterest in activities
- May also include weight loss, sleep disturbance, or psychosis
- Should be considered in patients with atypical dementia and chronic pain

Diagnosis of Depression - DSM-IV

- Five of the following present during the same 2-week period and represent a change from previous functioning:
    - depressed mood
    - markedly diminished interest or pleasure in all, or almost all, activities
    - significant weight loss when not dieting or weight gain
    - insomnia or hypersomnia
    - psychomotor agitation or retardation
    - fatigue or loss of energy
    - feelings of worthlessness or excessive or inappropriate guilt
    - diminished ability to think or concentrate, or indecisiveness
    - recurrent thoughts of death, recurrent suicidal ideation or a suicide attempt
- The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
- The symptoms are not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition (e.g., hypothyroidism).
- The symptoms are not better accounted for by Bereavement

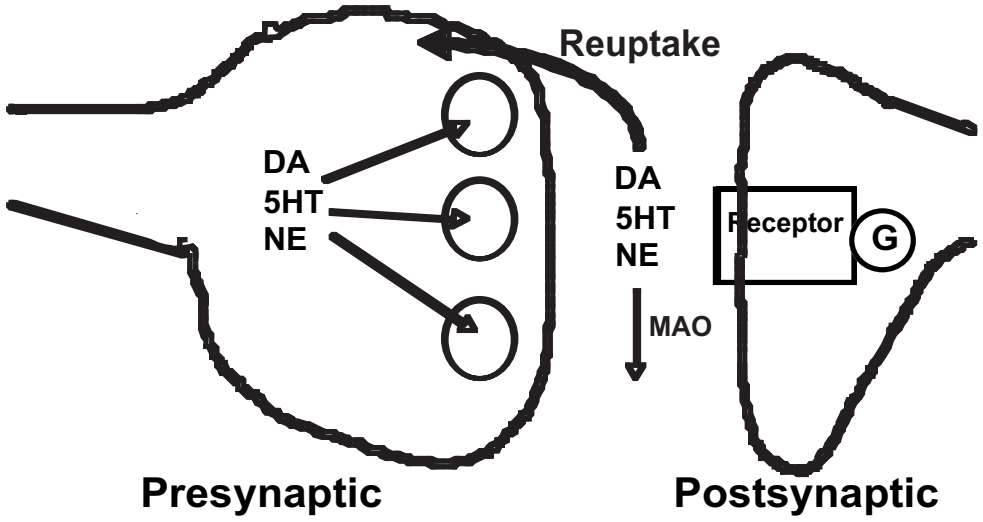
Pathophysiology of depression

- At present, mechanism is unknown - may be more than one mechanism.
- No useful biomarkers or imaging abnormality during life
- Study of postmortem brain has not revealed any consistent structural or neurochemical abnormality
- Majority of the currently available medications were discovered empirically
- Most current theories are based on “amine hypothesis”

Biogenic amines

- **Dopamine**
  - Synthesis: tyrosine $\xrightarrow{TH}$ L-DOPA $\xrightarrow{AADC}$ dopamine
  - Origin: substantia nigra, ventral tegmental area
  - Targets: basal ganglia, cerebral cortex
- **Norepinephrine**
  - Synthesis: dopamine $\xrightarrow{D\beta H}$ Norepinephrine
  - Origin: locus ceruleus
  - Targets: cerebral cortex
- **Serotonin**
  - Synthesis: tryptophan $\xrightarrow{TPH}$ 5-HTP $\xrightarrow{AADC}$ serotonin
  - Origin: raphe nuclei
  - Targets: cortex, basal ganglia, hippocampus, brainstem

Turnover of Biogenic Amines



Classes of Antidepressants

- Tricyclics and heterocyclics
- Selective serotonin reuptake inhibitors (SSRI's)
- Bupropion
- Nonselective MAO inhibitors
- Non-pharmacological therapy
    - ECT
    - Psychotherapy

Tricyclics and heterocyclics - Clinical pharmacology

- Large family of structurally related compounds
- Multiple pharmacological actions
- Therapeutic effect probably due to ability to block reuptake of serotonin and/or norepinephrine
- All may be sedating, although some much more than others
- Many of these drugs have anticholinergic (anti-muscarinic) actions - leads to somnolence, dry mouth, urinary retention

Tricylics and heterocyclics - pharmacokinetics and toxicity

- All are primarily metabolized by the liver, and undergo first pass metabolism
- Biochemical half-lives range from 4 to more than 24 hours, but clinical response is much slower - typically several weeks of therapy is required to observe any clinical improvement
- <u>Overdose of tricylics (more than 1 gram) is often lethal due to cardiac conduction disturbances. Great care must be taken when these drugs are prescribed for potentially suicidal patients.</u>

Some commonly used tricylics and heterocyclics

- Amitriptiline (Elavil®)
    - Inhibits serotonin & NE reuptake
    - Prominent anticholinergic effects
    - Metabolite is nortriptyline
- Desipramine (Norpramine®)
    - Inhibits NE reuptake
    - Mild anticholinergic effects
- Trazodone (Desyrel®)
    - Heterocyclic
    - Inhibits serotonin reuptake
    - Minimal anticholinergic effects
    - Sedating

Selective Serotonin Reuptake Inhibitors (SSRI's)

- Act by inhibition of presynaptic reuptake of serotonin in central synapses.
- Not as sedating as many of the tricylic compounds
- Also do not have the anticholinergic side effects of the tricyclics
- Some are potent inhibitors of P450 enzyme systems, and may lead to drug interactions

Some commonly used SSRI's

- Fluoxetine (Prozac®)
- Sertaline (Zoloft®)
- Citalopam (Celexa®)
- Paroxetine (Paxil®)
    - All are potent inhibitors of serotonin reuptake
    - Adverse effects: anxiety, tremor
    - Overdose of SSRI alone is rarely lethal
    - Should not be administered with nonselective MAO inhibitors
    - Suicide as an adverse effect?

Bupropion

- Structurally related to the tricyclics, but seems to have a different therapeutic mechanism, related to altered release of NE
- Not sedating or anticholinergic, but does sometime induce hallucinations or seizures
- Also effective in treating tobacco addiction

MAO Inhibitors

- Non-selective, irreversible enzyme inhibitors - long duration of action
- Therapeutic effect is due to is enhancement of CNS amine levels
- Major adverse effects are due to excessive accumulation of amines in the circulation
    - Tyramine: the "cheese effect."
    - Drug interactions: SSRI's, sympathomimetics
- Safe in carefully controlled circumstances, but "real world" use may lead to serious adverse effects.

Treatment of depression

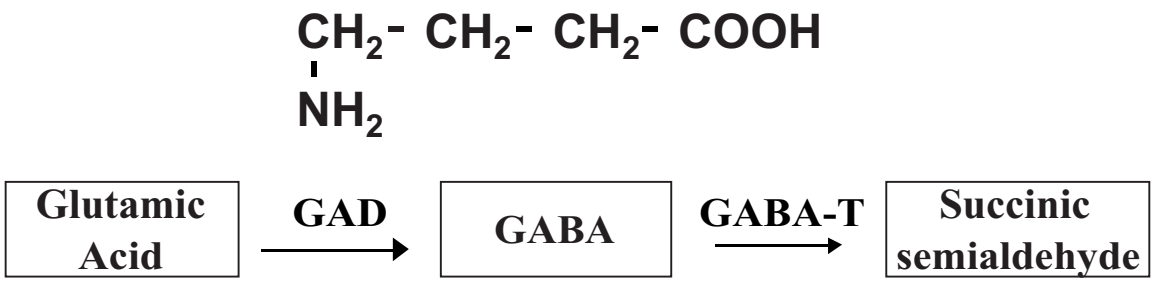
- Many patients will not report symptoms of depression unless asked specifically
- Patients who are depressed may be suicidal - it is essential to inquiry about their intentions
- The response of an individual patient to a particular antidepressant cannot be predicted, and treatment often requires sequential trials of several drugs

- In severely depressed patients, ECT often produces a rapid improvement and may be the best initial treatment

Sedatives and hypnotics

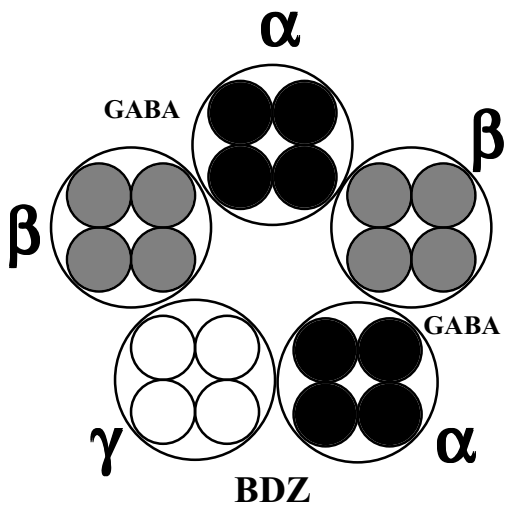
- Used to reduce anxiety, or induce sleep
- Very commonly prescribed
- Two principal chemical classes:
  - Benzodiazepines
  - Barbiturates
- Both work by enhancing activity of the inhibitory neurotransmitter, GABA

GABA (γ-aminobutyric acid)



- Principal inhibitory transmitter of the mammalian brain
- Receptors:
  - $GABA_A$: ligand gated ion channels, regulate chloride ion, at least 15 different subunit proteins
  - $GABA_B$: G-protein coupled receptors

Effects of benzodiazepines and barbiturates on GABA Receptors



- Both drugs bind to $GABA_A$ receptor subunits, but at different sites.
- Neither one binds to the agonist site
- Benzodiazepines increase the frequency of channel opening, but do not alter conductance or duration of opening
- Barbiturates prolong the duration of channel opening

Benzodiazepines

- More than a dozen benzodiazepines are marketed in the US
- They are distinguished primarily by their profiles of distribution and half-life.

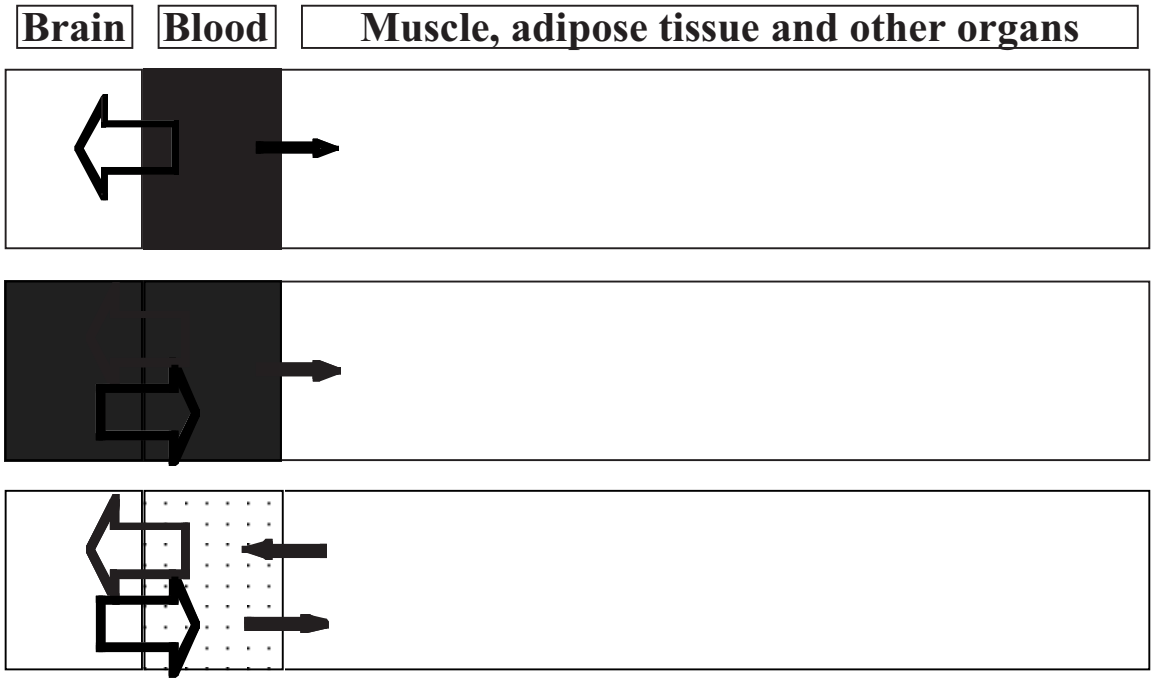
Examples of some benzodiazepines			
	trade name	**t1/2 - hours**	**typical application**
midazolam	*Versed*	1 - 3	IV - brief sedation for procedure
triazolam	*Halcion*	2 - 4	hypnotic - may produce amnestic syndrome
temazepam	*Restoril*	10 - 17	hypnotic
lorazepam	*Ativan*	10 - 20	hypnotic, sedative
diazepam	*Valium*	30 - 60	hypnotic, sedative
flurazepam	*Dalmane*	50 - 100	old hypnotic - not recommended

- Toxicity is mainly excessive sedation.
- After chronic use, withdrawal seizures may occur, especially with short half-life agents
- Flumazenil: a benzodiazepine antagonist, blocks effects of other benzodiazepines

Barbiturates

- Also distinguished largely by half-life and duration of action.
- Toxicity is excessive sedation, but unlike benzodiazepines, often leads to respiratory depression which may be fatal.
- Biochemical half lives range from 3 hours (methohexital) to 100 hours (phenobarbital)
- Redistribution is a key mechanism regulating duration of the biological effect of barbiturates (and benzodiazepines) when administered rapidly.

Redistribution



- Redistribution is a mechanism which limits the duration of action
- Effect is greatest when:
    - Agent is administered rapidly (e.g., intravenous)
    - Agent is highly lipophilic
- Can lead to very short duration of action (minutes) even though biochemical half life is longer (hours).

Clinical use of sedatives

- Anxiolytic use
    - Usually a medium to long acting benzodiazepine, such as diazepam, administered orally.
- Hypnotic use
    - Usually a short to medium acting benzodiazepine, such as temazepam, administered orally - but note that all hypnotics lose efficacy if taken daily.

- Sedative use (for surgical procedures)
    - A short acting benzodiazepine, such as midazolam
    - A short acting barbiturate, such as thiopental
    - Administered intravenously, and action terminated by redistribution.

Tolerance, cross-tolerance, and addiction

- Chronic use of sedatives of either class (benzodiazepine or barbiturate) induces tolerance to all members of the class, and cross-tolerance to members of the other class.
- Both also induce tolerance to ethanol, which acts in part through GABA receptors.
- Both benzodiazepines and barbiturates may produce dependence and are susceptible to abuse. Potentially lethal actions of the barbiturates makes them particularly problematic when abused.
- Rapid withdrawal from either class of sedatives may lead to anxiety, agitation, and seizures