Antidepressants and Sedatives

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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
A stricter standard for the 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 HT $\xrightarrow{AADC}$ serotonin
  – Origin: raphe nuclei
  – Targets: cortex, basal ganglia, hippocampus, brainstem
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
Tricyclics and heterocyclics - pharmokinetics 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.
- Overdose of tricyclics (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.
Some commonly used tricyclics 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 tricyclic compounds
- Also do not have the anticholinergic side effects of the tricyclics
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

- Both drugs bind to GABA<sub>A</sub> 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
More than a dozen benzodiazepines are marketed in the US. They are distinguished primarily by their profiles of distribution and half-life. Toxicity is mainly excessive sedation. After chronic use, withdrawal seizures may occur, especially with short half-life agents.

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

| Brain | Blood | Muscle, adipose tissue and other organs |

Diagram showing the redistribution process.
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 a 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.