1. Read chapter

2. Review: (A) antidepressants, (B) anxiolytics, (C) opioid analgesics

**Antidepressants**

3. Antidepressants are primarily used to reduce unpleasant or sad feelings but they have other applications as well (e.g., smoking cessation). There are at least three theories that antidepressants might be useful in smoking cessation. Firstly, nicotine withdrawal may produce unpleasant symptoms or precipitate a major depressive episode. Use of antidepressants may relieve these symptoms. Secondly, nicotine may produce antidepressant effects that leads the patient to continue to smoke. Antidepressants may substitute for this effect during smoking cessation. Finally, some antidepressants such as bupropion and nortriptyline may have a specific beneficial effect on (A) neural pathways (e.g. inhibiting monoamine oxidase or monoamine oxidase inhibitor) or (B) receptors (e.g. blockade of nicotinic-cholinergic receptors) underlying nicotine addiction.

(A) Monoamine produces effects that are “high, alert, pleasant.” Monoamine oxidase is an enzyme that metabolizes monoamine. One of the effects of nicotine is inhibition of monoamine oxidase, thus producing the high, alert, or pleasant feeling for tobacco smokers.

(B) By blocking the nicotine-cholinergic receptors, the adrenergic responses (alert, pleasant feeling) become predominant.

[Reference: Antidepressants for smoking cessation by Hughes JR et al.]

4. Two antidepressants have been found to be equally effective in smoking cessation: bupropion (Zyban, Wellbutrin); nortriptyline (Aventyl, Pamelor).
5. Common antidepressants and use for smoking cessation

<table>
<thead>
<tr>
<th>Antidepressant</th>
<th>Use</th>
<th>Side Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bupropion (Zyban, Wellbutrin)</td>
<td>Depression</td>
<td>Nausea</td>
</tr>
<tr>
<td></td>
<td>ADHD</td>
<td>Vomiting</td>
</tr>
<tr>
<td></td>
<td>Seasonal affective disorder</td>
<td>Dry mouth</td>
</tr>
<tr>
<td></td>
<td><strong>Smoking cessation</strong></td>
<td>Headache</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Constipation or diarrhea</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dizziness</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Blurred vision</td>
</tr>
<tr>
<td>Nortriptyline (Aventyl, Pamelor)</td>
<td>Depression</td>
<td>Drowsiness</td>
</tr>
<tr>
<td></td>
<td>Anxiety</td>
<td>Dizziness</td>
</tr>
<tr>
<td></td>
<td>Nerve pain</td>
<td>Dry mouth</td>
</tr>
<tr>
<td></td>
<td><strong>Smoking cessation</strong></td>
<td>Blurred vision</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Constipation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Weight gain</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Trouble urinating</td>
</tr>
</tbody>
</table>

**Anxiolytics, sedatives, and hypnotics**

6. Anxiolytics, sedatives and hypnotics (amnestic) are drugs that provide different degrees of anxiety reducing effects. Anxiolytics offer the lightest anxiety reduction and hypnotics provide the strongest anxiety reduction. All three classes of drugs work on the central nervous system to provide the desired effects. The main drugs are **benzodiazepines** and **barbiturates**.

7. Anxiety is a feeling perceived by the central nervous system (CNS). **Benzodiazepines** are agents that inhibit the central nervous system, acting selectively on gamma-aminobutyric acid-A (GABA-A) receptors. GABA-A is a major central nervous system inhibitory transmitter. Normally the GABA transmitters opening the chloride channels and _______ (blocking, allowing) an influx of chloride ions into the cells. Over time, the chloride level subsides and the same cycles repeat. Besides the normal GABA-A, benzodiazepines also open the chloride channel.

8. When the GABA-A receptors are activated by _______ (GABA-A, benzodiazepines, GABA-A or benzodiazepines), the chloride channels open leading to an influx of *large amount* of chloride ions (Cl⁻) into the cells. This highly _______ (positive, negative) ionic environment causes a hyperpolarized state. Prolonged hyperpolarization causes _______ (excitation, inhibition) of the neurons due to the elevated inhibitory post-synaptic potential (IPSP) inside the cell. In other words, hyperpolarization prolongs the repolarization recovery period, thus blocking the normal CNS activities (e.g., anxiety).
9. _______ (Excitation, Inhibition) of the neurons causes sedation because the neurons become unable to perceive normal or abnormal sensations. The duration and intensity of the neuron inhibition are directly related to the benzodiazepine type and dose.

10 Benzodiazepines are similar in pharmacological action but have different potencies, and some benzodiazepine work better in treatment of particular conditions. Benzodiazepines at different formulations and doses may be effective as sedatives, hypnotics, anxiolytics, anticonvulsants and muscle relaxants (for muscle spasms).

11. Common benzodiazepines and similar agents

<table>
<thead>
<tr>
<th>Class / Type</th>
<th>Name</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzodiazepine (GABA mechanism)</td>
<td>Diazepam (Valium)</td>
<td>+ ETOH overdose or abuse</td>
</tr>
<tr>
<td></td>
<td>Alprazolam (Xanax)</td>
<td>+ BP neutral</td>
</tr>
<tr>
<td></td>
<td>Lorazepam (Ativan)</td>
<td>+ IVP or drip</td>
</tr>
<tr>
<td></td>
<td>Midazolam (Versed)</td>
<td>- cumulative effects in prolonged drip use</td>
</tr>
<tr>
<td>Alpha2-adrenergic agonist</td>
<td>Dexmedetomidine (Precedex)</td>
<td>+ short acting</td>
</tr>
<tr>
<td>(inhibits release of norepinephrine)</td>
<td></td>
<td>+ delirium</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- hypotension</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- bradycardia</td>
</tr>
<tr>
<td>GABA mechanism (aka milk of amnesia)</td>
<td>Propofol (Diprivan)</td>
<td>+ short acting</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- continuous infusion in ICU</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- hypotension</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- bradycardia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- hyperlipidemia</td>
</tr>
<tr>
<td>Antipsychotic</td>
<td>Haloperidol (Haldol)</td>
<td>+ short acting</td>
</tr>
<tr>
<td></td>
<td></td>
<td>+ RR/BP neutral</td>
</tr>
<tr>
<td></td>
<td></td>
<td>+ delirium</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- QT interval change (may cause arrhythmia)</td>
</tr>
</tbody>
</table>

References:
http://www.vhpharmsci.com/vhformulary/tools/benzodiazepines-comparison.htm

12. Access the link below and review the drugs under “Alternative Agents and Management”
Sedation Scale

13. Review RASS (Richmond Agitation-Sedation Scale) below for assessment of sedation. Sedation target +1 to -2

4  Combative  Overtly combative or violent; immediate danger to staff
3  Very agitated Pulls on or removes tube(s) or catheter(s) or has aggressive behavior toward staff
2  Agitated  Frequent nonpurposeful movement or patient-ventilator dyssynchrony
1  Restless  Anxious or apprehensive but movements not aggressive or vigorous
0  Alert and calm
-1  Drowsy  Not fully alert, but has sustained (more than 10 seconds) awakening, with eye contact, to voice
-2  Light sedation  Briefly (less than 10 seconds) awakens with eye contact to voice
-3  Moderate sedation  Any movement (but no eye contact) to voice
-4  Deep sedation  No response to voice, but any movement to physical stimulation
-5  Unarousable  No response to voice or physical stimulation

14. What is the primary purpose of sedating mechanically ventilated or critically ill patients?

15. What are the main purposes of sedative vacation?

16. What is the indication for flumazenil (Romazicon)? p.335

Opioid Analgesics

17. Review Table below for adverse patient outcomes associated with uncontrolled pain.

<table>
<thead>
<tr>
<th>Reaction Induced by Pain</th>
<th>Adverse Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tissue initiated stress hormone response</td>
<td>Breakdown of body tissue</td>
</tr>
<tr>
<td></td>
<td>Increased blood clotting</td>
</tr>
<tr>
<td></td>
<td>Increased metabolic rate</td>
</tr>
<tr>
<td></td>
<td>Increased water retention</td>
</tr>
<tr>
<td></td>
<td>Decreased immune function</td>
</tr>
<tr>
<td>Activation of autonomic functions</td>
<td>Increased blood pressure</td>
</tr>
<tr>
<td></td>
<td>Increased heart rate</td>
</tr>
<tr>
<td>Muscle splinting</td>
<td>Decreased tidal volume</td>
</tr>
<tr>
<td></td>
<td>Decreased respiratory rate</td>
</tr>
<tr>
<td></td>
<td>Decreased minute ventilation</td>
</tr>
<tr>
<td>Immobility</td>
<td>Formation of deep vein thrombosis and pulmonary embolism</td>
</tr>
<tr>
<td>Diminished gastrointestinal function</td>
<td>Delay of bowel and gastric function</td>
</tr>
</tbody>
</table>
18. Common opioid analgesics

<table>
<thead>
<tr>
<th>Drug</th>
<th>Notes</th>
</tr>
</thead>
</table>
| Fentanyl (Duragesic, Sublimaze) | + IVP or drip  
+ short acting  
+ BP neutral |
| Morphine                    | + IVP or drip  
+ myocardial infarction  
- constipation  
- RR  
- hypotension |
| Hydromorphone (Dilaudid)    | + IVP or drip  
- opioid dependence |

19. Opioids are one of the most abused drugs. Since October 6, 2014, hydrocodone combination products have been up-regulated from Schedule III to Schedule II (e.g., morphine) controlled drugs.

20. What are the primary functions or responses of activated \textit{mu} receptors?

<table>
<thead>
<tr>
<th>Physical Parameter</th>
<th>Narcotic Receptor Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mu</td>
</tr>
<tr>
<td>Pain sensation</td>
<td>↓</td>
</tr>
<tr>
<td>Body Temperature</td>
<td>↓</td>
</tr>
<tr>
<td>HR</td>
<td>↓</td>
</tr>
<tr>
<td>RR</td>
<td>↓</td>
</tr>
<tr>
<td>CNS</td>
<td>Sedation</td>
</tr>
<tr>
<td>Pupil</td>
<td>Constricted</td>
</tr>
</tbody>
</table>

↑ Increased effect when receptor is stimulated  
↓ Decreased effect when receptor is stimulated  
n/a No effect

Note: Opioids such as morphine, meperidine (Demerol), and fentanyl (Sublimaze) are \textbf{agonists} to the \textit{mu} and \textit{kappa} receptors and no effects on the \textit{sigma} receptor. Naloxone (Narcan) is \textbf{antagonist} to all three nacortic receptors.
21. Adverse effects of narcotic analgesis (opioids and synthetic analgesics)

<table>
<thead>
<tr>
<th>CNS</th>
<th>Sedation</th>
<th>Respiratory depression</th>
<th>Shallow breathing and atelectasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muscle group</td>
<td>Myoclonus (twitching or spasm)</td>
<td>Convulsions</td>
<td>Chest wall rigidity</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Direct vasodilation</td>
<td>Vagally mediated bradycardia</td>
<td>Hypotension</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Delayed gastric emptying</td>
<td>Constipation</td>
<td>Nausea</td>
</tr>
<tr>
<td>Others</td>
<td>Miosis (pupil constriction)</td>
<td>Altered levels of stress hormone</td>
<td>Uncommon allergic reactions</td>
</tr>
</tbody>
</table>

22. What is code brown.

23. Is opioids reversible? If yes, by what? If no, what should be done to the patient?

24. Review 0.4 mg auto-injector at evzio.com
Note: Naloxone is also available in 4 mg nasal spray.

25. When opioids are used as pain controlling agents, Narcan can cause excessive bowel activities and pain. Explain.

26. Review the list of opioid agonists and antagonists in Table 20-9. (p.338-340)