Drugs That Affect The: Nervous System
Topics

• Analgesics and antagonists
• Anesthetics
• Anti-anxiety and sedative-hypnotics
• Anti-seizure / anti-convulsants
• CNS stimulators
• Psychotherapeutics
• ANS/PNS/SNS agents
But first... 

A colorful review of neurophysiology!
Nervous System

CNS

PNS

Autonomic

Somatic

Sympathetic

Parasympathetic
Analgesics

- Decrease in sensation of pain.
- Classes:
  - Opioid.
    - Agonist.
    - Antagonist.
    - Agonist-antagonist.
  - Non-opioids.
    - Salicylates.
    - NSAIDs.
    - Adjuncts.
Opioids

- Generic reference to morphine-like drugs/actions
  - Opiate: derivative of opium
- Prototype: morphine
  - Morpheus: god of dreams
- Act on endorphin receptors:
  - Mu (most important)
  - Kappa
# Actions of Opioid Receptors

<table>
<thead>
<tr>
<th>Response</th>
<th>Mu</th>
<th>Kappa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Analgesia</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Respiratory Depression</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Sedation</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Euphoria</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Physical Dependence</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>↓ GI motility</td>
<td>✓</td>
<td>✓</td>
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</table>
## Actions at Opioid Receptors

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Mu</th>
<th>Kappa</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pure Agonists</strong></td>
<td>Agonist</td>
<td>Agonist</td>
</tr>
<tr>
<td>-morphine, codeine, meperidine (Demerol®), fentanyl (Sublimaze®), remifentanil (Ultiva®), propoxyphene (Darvon®), hydrocodone (Vicodin®), oxycodone (Percocet®)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Agonist-Antagonist</strong></td>
<td>Antagonist</td>
<td>Agonist</td>
</tr>
<tr>
<td>-nalbuphine (Nubaine®), butorphanol (Stadol®)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Pure Antagonist</strong></td>
<td>Antagonist</td>
<td>Antagonist</td>
</tr>
<tr>
<td>-naloxone (Narcan®)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
General Actions of Opioids

- Analgesia
- Respiratory depression
- Constipation
- Urinary retention
- Cough suppression
- Emesis
- Increased ICP
  - Indirect through CO₂ retention
- Euphoria/Dysphoria
- Sedation
- Miosis
  - Pupil constriction
- ↓ Preload & afterload
  - Watch for hypotension!
Non-opioid Analgesics

- Salicylates
  - Aspirin (Bayer®) *(prototype for class)*

- Non-Steroidal Anti-Inflammatory Drugs
  - Ibuprofen (Motrin®, Advil®)
    - Propionic Acid derivative
  - Naproxen (Naprosyn®)
  - Naproxen sodium (Aleve®)
  - All compete with aspirin for protein binding sites
  - Ketorolac (Toradol®)
# NSAID Properties

<table>
<thead>
<tr>
<th>Drug</th>
<th>Fever</th>
<th>Inflammation</th>
<th>Pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Acetaminophen</td>
<td>✓</td>
<td></td>
<td>✓</td>
</tr>
</tbody>
</table>
Aspirin Mechanism of Action

- Inhibit synthesis of cyclooxygenase (COX)
  - Enzyme responsible for synthesis of:
    - Prostaglandins
      - Pain response
      - Suppression of gastric acid secretion
      - Promote secretion of gastric mucus and bicarbonate
      - Mediation of inflammatory response
      - Production of fever
      - Promote renal vasodilation (↑ blood flow)
      - Promote uterine contraction

- Thromboxane A₂
  - Involved in platelet aggregation
Aspirin Effects

**Good**
- Pain relief
- ↓ Fever
- ↓ Inflammation

**Bad**
- GI ulceration:
  - ↑ Gastric acidity
  - ↓ GI protection
- ↑ Bleeding
- ↓ Renal elimination
- ↓ Uterine contractions during labor
Acetaminophen (Tylenol®)

- NSAID similar to aspirin
- Only inhibits synthesis of CNS prostaglandins
  - Does not have peripheral side effects of ASA:
    - Gastric ulceration
    - Platelet aggregation
    - Renal flow
    - Uterine contractions
Acetaminophen Metabolism

**Major Pathway**

- **Acetaminophen**
  - Induced by ETOH
  - Toxic metabolites
  - Depleted by ETOH & APAP overdose
  - Non-toxic metabolites

**Minor Pathway**

- P-450
  - Toxic metabolites
  - Glutathione
  - Non-toxic metabolites
Anesthetics

• Loss of all sensation
  – Usually with loss of consciousness
  – \( \downarrow \) propagation of neural impulses

• General anesthetics
  – Gases
    • Nitrous oxide (Nitronox\textsuperscript{®}), halothane, ether
  – IV
    • Thiopental (Pentothal\textsuperscript{®}), methohexital (Brevitol\textsuperscript{®}), diazepam (valium\textsuperscript{®}), remifentanil (Ultiva\textsuperscript{®})
Anesthetics

- Local
  - Affect on area around injection
  - Usually accompanied by epinephrine
    - Lidocaine (Xylocaine ®), topical cocaine
Anti-anxiety & Sedative-hypnotic Drugs

- Sedation: ↓ anxiety & inhibitions
- Hypnosis: instigation of sleep
- Insomnia
  - ↑ Latent period
  - ↑ Wakenings
- Classes:
  - Barbiturates
  - Benzodiazepines
  - Alcohol

Chemically different, Functionally similar
Mechanism of action

• Both promote the effectiveness of GABA receptors in the CNS
  – Benzodiazepines promote only
  – Barbiturates promote and (at high doses) stimulate GABA receptors

• GABA = chief CNS inhibitory neurotransmitter
  – Promotes hyperpolarization via $\uparrow$ $\text{Cl}^-$ influx
### Benzodiazepines vs. Barbiturates

<table>
<thead>
<tr>
<th>Criteria</th>
<th>BZ</th>
<th>Barb.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relative Safety</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>Maximal CNS depression</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>Respiratory Depression</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>Suicide Potential</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>Abuse Potential</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>Antagonist Available?</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>
Benzodiazepines

• diazepam (Valium®)
• midazolam (Versed®)
• alprazolam (Xanax®)
• lorazepam (Ativan®)
• triazolam (Halcion®)

“Non-benzo benzo”

• zolpidem (Ambien®)
• buspirone (BusPar®)
## Barbiturates

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Prototype</th>
<th>Typical Indication</th>
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</thead>
<tbody>
<tr>
<td>Ultra-short acting</td>
<td>thiopental (Pentothol®)</td>
<td>Anesthesia</td>
</tr>
<tr>
<td>Short acting</td>
<td>secobarbital (Seconal®)</td>
<td>Insomnia</td>
</tr>
<tr>
<td>Long acting</td>
<td>phenobarbital (Luminal®)</td>
<td>Seizures</td>
</tr>
</tbody>
</table>
Barbiturates

- amobarbital (Amytal®)
- pentobarbital (Nembutal®)
- thiopental (Pentothal®)
- phenobarbital (Luminal ®)
- secobarbital (Seconal ®)
Anti-seizure Medications

- Seizures caused by hyperactive brain areas
- Multiple chemical classes of drugs
  - All have same approach
  - Decrease propagation of action potentials
    - ↓ Na⁺, Ca²⁺ influx (delay depolarization/prolong repolarization)
    - ↑ Cl⁻ influx (hyperpolarize membrane)
Anti-Seizure Medications

Benzodiazepines
- diazepam (Valium®)
- lorazepam (Ativan®)

Barbiturates
- phenobarbital (Luminal®)

Ion Channel Inhibitors
- carbamazepine (Tegretol®)
- phenytoin (Dilantin®)

Misc. Agents
- valproic acid (Depakote®)
Ion Diffusion

- Key to neurophysiology
- Dependent upon:
  - Concentration gradient
  - Electrical gradient
- Modified by:
  - ‘Gated ion channels’
Where Does Diffusion Take the Ion?

**Exterior**
- Na⁺: 150 mM
- K⁺: 5 mM
- Cl⁻: Low

**Interior**
- Na⁺: 15 mM
- K⁺: 150 mM
- Cl⁻: Low
Action Potential Components

- Membrane Potential (mV)
  - Threshold Potential
  - Resting Membrane Potential
  - Na$^+$ equilibrium
  - Hyperpolarized
  - Depolarization!

- Time (msec)

- Action Potential
Membrane Permeability

Membrane Potential (mV)

-70
-50
0
+30

Threshold Potential

Resting Membrane Potential

Time (msec)

Na⁺ Influx

K⁺ Efflux
What Happens to the Membrane If Cl⁻ Rushes Into the Cell During Repolarization?

It gets hyperpolarized!
What happens to the frequency of action potentials if the membrane gets hyperpolarized?

It decreases!
Clinical Correlation

- Remember that it is the rate of action potential propagation that determines neurologic function.
  - Determined by frequency of action potentials.

What is a seizure?

What would be the effect on the membrane of \( \uparrow \) Cl\(^-\) influx during a seizure?

Hyperpolarization & \( \downarrow \) seizure activity!
Gamma Amino Butyric Acid (GABA) Receptor

Hyperpolarized!
GABA+Bz Complex

Bz Receptor

GABA Receptor

Profoundly Hyperpolarized!
Are You Ready for a Big Surprise?

Many CNS drugs act on GABA receptors to effect the frequency and duration of action potentials!
SNS Stimulants

• Two general mechanisms:
  – Increase excitatory neurotransmitter release
  – Decrease inhibitory neurotransmitter release

• Three classes:
  • Amphetamines
  • Methylphendidate
  • Methylxanthines
Amphetamines

amphetamine
methamphetamine
dextroamphetamine
(Dexedrine®)

MOA:
- promote release of norepinephrine, dopamine

Indications
- Diet suppression
- ↓ Fatigue
- ↑ Concentration

Side Effects
- Tachycardia
- Hypertension
- Convulsion
- Insomnia
- Psychosis
Methylphenidate (Ritalin®)

• Different structure than other stimulants
  – Similar mechanism
  – Similar side effects
• Indication: ADHD
  – Increase ability to focus & concentrate
Methylxanthines

- Caffeine
- Theophylline (Theo-Dur®)
- Aminophylline

Mechanism of action
- Reversible blockade of adenosine receptors
A patient is taking theophylline and becomes tachycardic (SVT). You want to give her adenosine. Is there an interaction you should be aware of? How should you alter your therapy?

Methylxanthines blocks adenosine receptors. A typical dose of adenosine may not be sufficient to achieve the desired result. Double the dose!
# News You Can Use…

<table>
<thead>
<tr>
<th>Source</th>
<th>Amount of Caffeine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coffee</td>
<td></td>
</tr>
<tr>
<td>• Brewed</td>
<td>40 – 180 mg/cup</td>
</tr>
<tr>
<td>• Instant</td>
<td>30 – 120 mg/cup</td>
</tr>
<tr>
<td>Decaffeinated Coffee</td>
<td>2 - 5 mg/cup</td>
</tr>
<tr>
<td>Tea</td>
<td>20 – 110 mg/cup</td>
</tr>
<tr>
<td>Coke</td>
<td>40 – 60 mg/12 oz</td>
</tr>
</tbody>
</table>
Psychotherapeutic Medications

- Dysfunction related to neurotransmitter imbalance.
  - Norepinephrine.
  - Dopamine.
  - Serotonin.

- Goal is to regulate excitatory/inhibitory neurotransmitters.

Monoamines
**Anti-Psychotic Drugs (Neuroleptics)**

- **Schizophrenia**
  - Loss of contact with reality & disorganized thoughts
  - Probable cause: increased dopamine release
  - Tx. Aimed at decreasing dopamine activity

Two Chemical Classes:

- **Phenothiazines**
  - chlorpromazine (Thorazine®)

- **Butyrophenones**
  - haloperidol (Haldol®)
Other Uses for Antipsychotics

- Bipolar depression
- Tourette’s Syndrome
- Prevention of emesis
- Dementia (OBS)
- Temporary psychoses from other illness
Antipsychotic MOA

- Mechanism is similar
- Strength ([ ]) vs. Potency (‘oomph’)
  - Phenothiazines – low potency
  - Butyrophenones – high potency
- Receptor Antagonism
  - Dopamine$_2$ in brain
  - Muscarinic cholinergic
  - Histamine
  - Norepi at alpha$_1$

 Therapeutic effects

 Unintended effects
Antipsychotic Side Effects

- Generally short term
- Extrapyramidal symptoms (EPS)
- Anticholinergic effects (atropine-like)
  - Dry mouth, blurred vision, photophobia, tachycardia, constipation
- Orthostatic hypotension
- Sedation
- Decreased seizure threshold
- Sexual dysfunction
## Extrapyramidal Symptoms

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Onset</th>
<th>Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute dystonia</td>
<td>Hours to 5 days</td>
<td>Spasm of tongue, neck, face &amp; back</td>
</tr>
<tr>
<td>Parkinsonism</td>
<td>5 – 30 days</td>
<td>Tremor, shuffling gait, drooling, stooped posture, instability</td>
</tr>
<tr>
<td>Akathesia</td>
<td>5 – 60 days</td>
<td>Compulsive, repetitive motions; agitation</td>
</tr>
<tr>
<td>Tarditive dyskinesia</td>
<td>Months to years</td>
<td>Lip-smacking, worm-like tongue movement, ‘fly-catching’</td>
</tr>
</tbody>
</table>
Treatment of EPS

- Likely caused by blocking central dopamine$_2$ receptors responsible for movement
- Anticholinergic therapy rapidly effective
  - diphenhydramine (Benadryl®)
Antipsychotic Agents

- chlorpromazine (Thorazine®)
- thioridazine (Mellaril®)
- trifluoperazine (Stelazine®)
- haloperidol (Haldol®)
Antidepressants

• Likely cause: inadequate monoamine levels
• Treatment options:
  – Increasing NT synthesis in presynaptic end bulb
  – Increasing NT release from end bulb
  – Blocking NT ‘reuptake’ by presynaptic end bulb
Tricyclic Antidepressants (TCAs)

- Block reuptake of both NE & serotonin
  - Enhance effects
- Similar side effects to phenothiazines
TCA Side Effects

- Orthostatic hypotension
- Sedation
- Anticholinergic effects
- Cardiac toxicity
  - Ventricular dysrhythmias
Selective Serotonin Reuptake Inhibitors (SSRIs)

- Block only serotonin (not NE) reuptake
  - Elevate serotonin levels
- Fewer side effects than TCS
  - No hypotension
  - No anticholinergic effects
  - No cardiotoxicity
- Most common side effect
  - Nausea, insomnia, sexual dysfunction
Monoamine Oxidase Inhibitors (MAOIs)

- Monoamine oxidase
  - Present in liver, intestines & MA releasing neurons
  - Inactivates monoamines
  - Inactivates dietary tyramine in liver
- Foods rich in tyramine: cheese & red wine
MAOI Side Effects

- CNS Stimulation
  - Anxiety, agitation
- Orthostatic hypotension
- Hypertensive Crisis
  - From increased tyramine consumption
    - Excessive arteriole constriction, stimulation of heart
MAOI & Dietary Tyramine

Diagram showing the interaction between MAOI and dietary tyramine in the body. The diagram illustrates the metabolic pathways involving monoamine oxidase (MAO) and tyramine in various organs such as the liver, intestine, and heart. The process involves the metabolism of tyramine by MAO, leading to the formation of inactive metabolites and the subsequent release of NE (norepinephrine). The diagram also highlights the role of tyramine in the liver and intestine, showing the flow of metabolism and the potential for interactions with MAOI.
Antidepressant Mechanism

TCAs & SSRIs Block Here
Antidepressants Agents

TCAs
- imiprimine (Tofranil®)
- amitriptyline (Elavil®)
- nortriptyline (Pamelor®)

SSRIs
- fluoxetine (Prozac®)
- paroxetine (Paxil®)
- sertraline (Zoloft®)

MAOIs
- phenelzine (Nardil®)

Atypical Antidepressants
- bupropion (Wellbutrin®)
Parkinson’s Disease

- Fine motor control dependent upon balance between excitatory and inhibitory NT
  - Acetylcholine = excitatory
  - Dopamine = inhibitory

\[ \text{GABA} = \text{inhibitory} \]

Control GABA release
Parkinson’s Disease

A Normal

Substrata nigra

Striatum

DA

- +

ACh

GABA

Globus pallidus

Controlled movement

B Parkinson’s Disease

DA

- +

ACh

GABA

Disturbed movement
Parkinson’s Symptoms:

- Similar to EPS
- Dyskinesias
  - Tremors, unsteady gait, instability
- Bradykinesia
- Akinesia in severe cases
Parkinson’s Treatment

- **Dopaminergic approach**
  - ↑ Release of dopamine
  - ↑ [Dopamine]
  - ↓ Dopamine breakdown
- **Cholinergic approach**
  - ↓ Amount of ACh released
  - Directly block ACh receptors
- **All treatment is symptomatic and temporary**
Levodopa

- Sinemet ® = levodopa + carbidopa
- Increase central dopamine levels
- Side effects:
  - Nausea and vomiting
  - Dyskinesia (~80% of population)
  - Cardiovascular (dysrythmias)
Levodopa Mechanism

1. Blood-brain barrier
2. Levodopa
3. Dopamine (DA)
4. GABAergic neuron
5. Dopamine receptor
Other Agents

- amantadine (Symmetrel®)
  - ↑ release of dopamine from unaffected neurons
- bromocriptine (Parlodel®)
  - Directly stimulated dopamine receptors
- selegiline (Carbex®, Eldepryl®)
  - MAOI selective for dopamine (MAO-B)
- benztropine (Cogentin®)
  - Centrally acting anticholinergic
Drugs That Affect the Autonomic Nervous System

Word of Warning
Carefully review the A&P material & tables on pages 309 – 314 and 317 – 321!
PNS Drugs

- Cholinergic
  - Agonists & Antagonists (Anticholinergics)
  - Based on response at nicotinic \(_{(N&M)}\) & muscarinic receptors
Acetylcholine Receptors

Figure 9-8, page 313, Paramedic Care, V1
Cholinergic agents cause **SLUDGE**!

**HINT!**
These effects are predictable by knowing PNS physiology (table 9-4)

- Salivation
- Lacrimation
- Urination
- Defecation
- Gastric motility
- Emesis
Direct Acting Cholinergics

- bethanechol (Urecholine) prototype
  - Direct stimulation of ACh receptors
  - Used for urinary hesitancy and constipation
Indirect Acting Cholinergics

- Inhibit ChE (cholinesterase) to prolong the duration of ACh stimulation in synapse
- Reversible
- Irreversible
Reversible ChE Inhibitors

- neostigmine (Prostigmine®)
  - Myasthenia Gravis at nicotinic$_M$ receptors
  - Can reverse nondepolarizing neuromuscular blockade

- physostigmine (Antilirium®)
  - Shorter onset of action
  - Used for iatrogenic atropine overdoses @ muscarinic receptors
Irreversible ChE Inhibitors

- Very rarely used clinically
- Very common in insecticides & chemical weapons
  - VX and Sarin gas
  - Cause SLUDGE dammit and paralysis
- Tx: atropine and pralidoxime (2-PAM®)
  - Anticholinergics
Anticholinergics

- **Muscarinic antagonists**
  - Atropine

- **Ganglionic antagonists**
  - Block nicotinic receptors
  - *Turns off the ANS!*
  - Trimethaphan (Arfonad®)
    - Hypertensive crisis

- **Atropine Overdose**
  - Dry mouth, blurred vision, anhidrosis

- Hot as Hell
- Blind as a Bat
- Dry as a Bone
- Red as a Beet
- Mad as a Hatter
Neuromuscular Blockers

- **Nicotinic Cholinergic Antagonists**
  - Given to induce paralysis
- **Depolarizing**
  - succinylcholine (Anectin®)
- **Nondepolarizing**
  - tubocurarine from *curare*
  - rocuronium (Zemuron®)
  - vecuronium (Norcuron®)
Warning!

- Paralysis without loss of consciousness!
  - MUST also give sedative-hypnotic
  - Common agents:
    - fentanyl (Sublimaze®)
    - midazolam (Versed®)
SNS Drugs

- Predictable response based on knowledge of affects of adrenergic receptor stimulation
- HINT: Know table 9-5, page 321
- Each receptor may be:
  - Stimulated (sympathomimetic)
  - Inhibited (sympatholytic)
Alpha\textsubscript{1} Agonists

- Profound vasoconstriction
  - Increases afterload & blood pressure when given systemically
  - Decreases drug absorption & bleeding when given topically
Alpha₁ Antagonism

• Inhibits peripheral vasoconstriction
  – Used for hypertension
  – prazosin (Minipress®)
  – doxazosin (Cardura®)
  – phentolamine (Regitine®)
• Blocks alpha₁&₂ receptors
Beta$_1$ Agonists

- Increases heart rate, contractility, and conductivity
Beta Antagonists (β Blockers)

- Frequently used
- Lower Blood Pressure
- Negative chronotropes & inotropes

**Beta₁ Selective Blockade**
- atenolol (Tenormin®)
- esmolol (Brevibloc®)
- metoprolol (Lopressor®)

**Nonselective**
- propranolol (Inderal®)
- labetalol (Normodyne®, Trandate®)
- sotalol (Betapace®)
## Adrenergic Receptor Specificity

<table>
<thead>
<tr>
<th>Drug</th>
<th>$\alpha_1$</th>
<th>$\alpha_2$</th>
<th>$\beta_1$</th>
<th>$\beta_2$</th>
<th>Dopaminergic</th>
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</thead>
<tbody>
<tr>
<td>Epinephrine</td>
<td></td>
<td></td>
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<tr>
<td>Ephedrine</td>
<td></td>
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<td>Norepinephrine</td>
<td></td>
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<td>Phenylephrine</td>
<td></td>
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<td>Isoproterenol</td>
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<tr>
<td>Dopamine</td>
<td></td>
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<td>Dobutamine</td>
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</tr>
<tr>
<td>terbutaline</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>
Web Resources

- Web based synaptic transmission project
  - http://www.williams.edu/imput/index.html
Thank You!

• To Temple College EMS Professions for permission to use their materials