Understanding Medications Used in the Treatment of Traumatic Brain Injury

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Outline
- Basic principles
- Neurotransmitter systems
- Evidence for treating common behaviors with medications
- Specific medication considerations (in handout)
- Summary & case examples

Medication as a Treatment
- Correct diagnosis
- Look for and treat possible causes
- Medications as the problem
- Pharm Vs. Non-pharm approaches
  - Medications are not always the right answer
  - Combining pharma with non-pharma treatments
    • Individual, family, cognitive, behavioral, environmental

Assessment for Treatment
- Timeline, type, frequency, severity, impact, precipitators, relieving factors
- Other symptoms, daily function and activities
- Use objective rating scales, feedback
- Notice effect of missed doses
- Complete list of past & current medications
  - dosages, reasons prescribed, responses on and off agent(s)

Common Problems With Past Treatments
- Misdiagnosis
- Not properly applied
- Duration too short
- Dose too low
- Dose too high
- Not actually taken
- Some treatments not tried
- Not combined with other treatments
- Contribute to/cause problem

Look for and Treat Other Causes
- Phase of recovery
- Sleep disturbance
- Pain
- Occult fracture
- Substance withdrawal
- Dehydration
- Hypoxemia / Pulmonary embolism
- Infection / sepsis
- Seizure / temporal lobe seizure
  - Need to specify “temporal or nasopharyngeal leads” when EEG ordered
- Autonomic instability
- Neuroendocrine or metabolic dysfunction
  - Electrolyte imbalance, thyroid, adrenal insufficiency, testosterone
  - Hypoglycemia, hepatic
- Depression
- Anxiety
- Stress / environment
- Substance use
- Musculoskeletal injury
- Medication side effects or toxicity or drug interaction
**Medications as the Problem**

- **Aggression**
  - Bromocriptine, tranquilizers, hypnotics, levodopa, phenelzine, digitals
- **Depression**
  - Antidepressants, anticonvulsants, propranolol, narcotics, levodopa, metoclopramide, oral contraceptives, benzodiazepines
- **Hallucinations**
  - Anticonvulsants, propranolol, bromocriptine, amantadine
- **Paranoia**
  - Bromocriptine, amphetamines, propranolol, corticosteroids, NSAIDS
- **Cognitive decline**
  - Anticonvulsants, propranolol
- **Sedation**
  - Benzodiazepines, Anticholinergics, narcotics, benzodiazepines, phenergan, metoclopramide, antipsychotics
- **Slowed motor recovery**
  - NA blockade

**Function Susceptible to Alpha-1 NA Blockade**

- Prazosin, haloperidol, risperdone, clonidine, tizanidine, phenoxylbenzamine, & other drugs reducing NA levels, reinstates deficits

**Eliminate Medications**

- Eliminate meds that are unnecessary, potential for causation, or hinder arousal, cognitive function, recovery
  - Anticholinergics
  - Benzodiazepines
  - Narcotics
  - GI proph & reflux (metoclopramide, H2 blockers), phenergan
  - Catecholamine antagonists (haloperidol, risperidol, lorazepam, seroquel)
  - Antiepileptic Drugs
  - Antihypertensives (clonidine)
- If not needed: discontinue
- If needed: substitute

**Pharmacologic Selection**

- Add agents targeted to improve function with minimal-no risk
- Choices ...  
  - Limited evidence base → Largely physician preference & experience
  - Consider context of occurrence of the behavior
    - Depression, anxiety, psychosis
  - Consider likely injury location, symptoms, evidence for effect in BI and other diagnoses
  - Consider Risk : Benefit
    - Consider drug-drug interactions, side effects & contraindications
  - Choose agents that accomplish >1 need
    - (e.g., tachycardia, headache, seizure mgmt, pain, insomnia, arousal, cognition, processing speed, depression, anxiety)

**Role of Mechanism**

- Consider using different mechanisms
  - Neurotransmitter
  - Location of action
- Augment partial responses thru similar mechanisms
- Likely need more than 1 medication for optimal response & multiple symptoms

**Go 1, Go Low, Go Slow**

- Start low
- Give enough time
- Gradually increase
- Try to make one change at a time
- Don’t give up too early
- Follow progress
### Duration of Treatment

- Remission / carry-over effect vs. ongoing need
- Relapse risk?
- Depends on treatment purpose?
  - Seizure / Anticonvulsants
    - Depends on reason for use
      - Prophylaxis: No risk after 1 week post-injury
      - Treatment: 2 years seizure free; negative EEG; risk of vs.
  - Depression / Antidepressants
    - American Psychiatric Assn for major depression: Minimum 16-20 weeks after complete remission of symptoms
  - Other purposes
    - Have you noticed worsening if skipped dose(s)
    - Trial off

### Neurotransmitters (nt)

- Carry messages to control arousal, cognition & behavior
  - Some hinder function
  - Some enhance function (arousal, memory, initiation, self control)
- BI ➔ Changes in nt availability & function
- Modulation (via medications) may help
- Medications often influence more than one nt

### Neurotransmitters

- **Catecholamine**
  - Dopamine
  - Norepinephrine
- Serotonin
- Acetylcholine
- GABA

### Dopamine (DA)

- Predominant location & action
  - Subcortex, including basal ganglia, frontal lobe & hypothalamus
- Actions
  - Screening out information, arousal, apathy, initiation, attention, memory, hypothalamic function/autonomic stability, pleasure, extrapyramidal / motor movements
- TBI changes
  - Acutely elevated
  - Chronically decreased?
- Medication Examples
  - Amantadine, bromocriptine, sinemet, methylphenidate, modafinil

### Catecholaminergic Augmentation

- Dopaminergic (DA)
  - bromocriptine
  - carbidopa/levodopa
- Mixed dopaminergic (DA) & noradrenergic (NA)
  - methylphenidate
  - dextroamphetamine
  - other amphetamine salts
- Indirect dopaminergic effects via:
  - uncompetitive NMDA receptor antagonism
  - amantadine
  - memantine
  - ? modafinil
  - ? lamotrigine
**Norepinephrine (NE)**
- **Predominant location & action**
  - Brainstem (locus Ceruleus), frontal lobe
- **Actions**
  - Arousal, attention, memory, initiation, executive function, behavior, motor function
- **TBI changes**
  - Acutely elevated
  - Chronically decreased?
- **Medication Examples**
  - Dexedrine, Tricyclic antidepressants

**Serotonin (5E)**
- **Predominant location & action**
  - Brainstem (caudal linear nucleus, nucleus raphe, reticular formation), frontal lobe, hippocampus, substantia nigra
- **Actions**
  - Arousal, depression, anxiety, emotional liability, obsessive-compulsive disorder, appetite suppression, aggression, motor control, memory
- **TBI changes**
  - Acutely: site of injury may dictate
  - Unsure chronically
- **Medication Examples**
  - Prozac, Paxil, Seroxat, Effexor, Buspar

**Acetylcholine (Ach)**
- **Predominant location & action**
  - Medial temporal lobe, thalamus, amygdala, hippocampus, basal ganglia, olfactory bulb, cerebral cortex, brainstem
- **Actions**
  - Declarative memory, learning, executive function, attention, mood, motivation, aggression, reward, cortical arousal, motor coordination, social intelligence, induction of REM sleep, sensory gating, EEG fast wave activity
- **TBI changes**
  - Acutely elevated
  - Chronically decreased
- **Medication Examples**
  - Ach: Physostigmine
  - Inhibit Ach Esterase: Aricept, Exelon, Cognex/Tacrine

**Cholinergic Deficiency and Delirium**
- **Anticholinergic activity may cause delirium**
- **Anticholinergic activity in common drugs**
  - Significant anticholinergic: amitriptyline, desipramine, diphenhydramine, nortriptyline, oxybutinin
  - Moderate anticholinergic: amantadine, CBZ
  - Mild anticholinergic: alprazolam, atenolol, bupropion, captopril, codeine, diazepam, digoxin, fentanyl, furosemide, haloperidol, lorazepam, metoprolol, morphine, prednisone, ranitidine, trazodone, warfarin

**GABA**
- **Main CNS inhibitory neurotransmitter**
  - Including: hypothalamus, hippocampus, cerebral cortex & cerebellar cortex
- **Sedation, confusion, long-term cognitive deficits, n/v, dryness of mouth, abnormal eye movements, fatigue, immunosuppression**
- **Examples**
  - Benzodiazepines, non-benzodiazepine hypnotics (e.g.: zolpidem, badodan, barbiturates, progabide [gabazine], tiagabine [gabatril], ethanol
- **Glutamate-GABA balance**
  - Glutamate increases aggression GABA decreases aggression
  - Thought to play a role in Alzheimer’s behavior

**Anticholinergic Effects in Commonly Used Medications**

**Anticholinergic Burden Scale**
- Score of >3 is considered clinically significant
  - Severe (3 points): amitriptyline, desipramine, diphenhydramine, nortriptyline, oxybutinin
  - Mod (2 points): amantadine, CBZ
  - Mild (1 points): alprazolam, atenolol, bupropion, captopril, codeine, diazepam, digoxin, fentanyl, furosemide, haloperidol, lorazepam, metoprolol, morphine, prednisone, ranitidine, trazodone, warfarin
**Biology of Cognition**

- Catecholamines (DA, NE) may improve arousal, speed of processing, sustained attention/vigilance, possibly executive aspects of attention
- Signal-to-noise ratio
  - Too much DA and/or NE: Increased cognitive “noise” (i.e., irrelevant task / distractions)
  - Deficient DA and/or NE: “signal” misses target

**Brain Circuitry & Neuromodulators of Non-TBI Aggression**


<table>
<thead>
<tr>
<th>Brain Circuitry</th>
<th>Reduced serotonin</th>
<th>Increased DA &amp; NE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cortical:</td>
<td>Cortical lesion (trauma, tumor)</td>
<td>Decreased cortical volume</td>
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<tr>
<td></td>
<td>Orbitofrontal/cingulate cortex processing inefficiency</td>
<td></td>
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<tr>
<td>Limbic:</td>
<td>Hyperactivity of amygdala/limbic system</td>
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<td></td>
<td>Emotional hypersensitivity</td>
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<tr>
<td>Kindling</td>
<td>Reduced GABA / Increased glutamate</td>
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<tr>
<td></td>
<td>Increased Ach</td>
<td></td>
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</tbody>
</table>

**Implications for Pharmacotherapy of Aggression**

<table>
<thead>
<tr>
<th>Pharmacological Class</th>
<th>Target</th>
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<tbody>
<tr>
<td>Antidepressants</td>
<td>Drive</td>
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<tr>
<td>Serotonergic reuptake</td>
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<tr>
<td>Subcortical dopaminergic stimulation</td>
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<tr>
<td>Stimulants</td>
<td>Brake</td>
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<tr>
<td>Opiate antagonists</td>
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</tr>
</tbody>
</table>

- Side effect profiles should be considered, especially relevant to brain injury

**Evidence for Medication Treatment**

- Little research to support or refute
  - Case studies
  - Open-label case series
  - Few randomized, controlled trials (RCTs), & thus, most evidence at level of options
- Trial and error
  - Clinician experience
  - Literature in other diagnostic populations
### Summary of Literature: Cognition

<table>
<thead>
<tr>
<th>Problem</th>
<th>Standards</th>
<th>Guidelines</th>
<th>Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>General cognition</td>
<td>-</td>
<td>Avoid phénytoin</td>
<td>Methylphenidate (DA) Amantadine (DA)</td>
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<tr>
<td>Attention &amp; Processing Speed</td>
<td>-</td>
<td>Methylphenidate (DA) Dextroamphetamine (DA/NE) Amantadine (DA) Physostigmine (Ach)</td>
<td></td>
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<tr>
<td>Memory</td>
<td>-</td>
<td>Donepezil (Ach)</td>
<td>Methylphenidate (DA) CDP Choline 1 gram (cytidine diphosphate choline)</td>
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<tr>
<td>Executive Function</td>
<td>-</td>
<td>Bromocriptine (DA)</td>
<td>-</td>
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</tbody>
</table>

### Summary of Literature: Mood & Behavior

<table>
<thead>
<tr>
<th>Problem</th>
<th>Standards</th>
<th>Guidelines</th>
<th>Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depression</td>
<td>-</td>
<td>-</td>
<td>TCA (amitriptyline, desipramine) (NE &amp; SE) Sertraline (SE) Watch out for side effects (attn, conc, mem, arousal, seizures)</td>
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<tr>
<td>Anxiety</td>
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<tr>
<td>Psychosis</td>
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<td>-</td>
<td>Abnormal antipsychotics (watch for weight gain &amp; sedation)</td>
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<tr>
<td>Apathy</td>
<td>-</td>
<td>-</td>
<td>SSRI (SE) If part of depression, could make worse if not part of depression Stimulants &amp; DA enhancers</td>
</tr>
<tr>
<td>Irritability</td>
<td>-</td>
<td>Beta-Blockers</td>
<td>Methylphenidate (DA), SSRI (SE), valproate, lithium, TCA (amitriptyline &amp; desipramine) (NE &amp; SE), buspirone (SE), amantadine (DA), carbamazepine</td>
</tr>
</tbody>
</table>

### Physician Preferences: Francisco 2007

<table>
<thead>
<tr>
<th>Drug</th>
<th>Depressed</th>
<th>Lab/Inn.</th>
<th>Mood</th>
<th>Psychosis</th>
<th>Agitation/Aggressions</th>
<th>Anxiety</th>
<th>Apathy</th>
<th>Cognition</th>
<th>NE Risk</th>
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<tr>
<td>Nortriptyline</td>
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<td>Amantadine</td>
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<td>Valproate</td>
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<td>Buspirone</td>
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<td>Atypical antipsychotic</td>
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<td>Methylphenidate</td>
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<td>Amantadine</td>
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<td>Bromocriptine</td>
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<td>Modafinil</td>
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### Irritability & Aggression

- **Standards:** Insufficient
- **Guidelines:**
  - Beta Blockers:
    - Propranolol (420-520 mg/day max)
    - Pindolol (40-100 mg/day)
  - BEERs: n=27, peak, post-acute, 150-200 mg daily, 12 wks, improved behavior
  - Hammond n=76
  - Hammond n=168
- **Options:**
  - Methylphenidate, SSRI, valproate, lithium, TCA (amitriptyline & desipramine), buspirone, CES, homeopathy
- **RCTs in progress**
  - Hammond: CBZ & Buspirone
- **7 published RCTs**
  - Amantadine (3), Methylphenidate (2), Beta blockers (4)

### Physician Preferences: Francisco 2007

<table>
<thead>
<tr>
<th>Problem</th>
<th>&quot;Expert&quot; PMR</th>
<th>Not &quot;expert&quot; PMR</th>
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<tbody>
<tr>
<td>Insomnia</td>
<td>Traazdione (23) Zolpidem (15) Nortriptyline (9)</td>
<td>Traazdione (16) Zolpidem (9) Nortriptyline (2) Benzoazepams (7)</td>
</tr>
<tr>
<td>Hypoaressel</td>
<td>Methylphenidate (13) Amantadine (10) Modafinil (6)</td>
<td>Methylphenidate (13) Amantadine (5)</td>
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<tr>
<td>Apathy</td>
<td>Methylphenidate (14)</td>
<td>Amantadine (13)</td>
</tr>
<tr>
<td>Inattention</td>
<td>Methylphenidate (17) Amantadine (10) Modafinil (9)</td>
<td>Methylphenidate (18) Amantadine (10)</td>
</tr>
<tr>
<td>Slow mental processing</td>
<td>Methylphenidate (17) Amantadine (9) Modafinil (2)</td>
<td>Methylphenidate (14) Modafinil (4)</td>
</tr>
<tr>
<td>Memory Deficit</td>
<td>Nothing (8) Donepezil (9) Galantamine (9) Bromocriptine (6)</td>
<td>Nothing (9) Galantamine (8) Amantadine (4)</td>
</tr>
</tbody>
</table>
Summary

• Misdiagnosis is common
• Look for & treat other causes
• Multi-faceted approach is needed
• History of meds tried and reactions are important
• Trial & error
• 1 at a time, start low, gradually increase, reach max.
typical dose before giving up, augment response, try
other mechanisms, combine strategies for best results,
monitor for drug-drug interactions and side effects
• Often need more than 1 approach

Summary of BI Cognitive & Behavioral Pharmacotherapies

• Critical variables for treatment selection
  - Injury severity
  - Time post-injury and phase
  - Cognitive & behavioral
  - Impact on life functions

• Cognition
  - catecholaminergic
  - augmentation / balance
  - cholinergic augmentation
  - mixed catecholamine and
  - cholinergic augmentation

• Behavior
  - catecholaminergic
  - augmentation / balance
  - cholinergic augmentation
  - Anticonvulsants
  - Mixed

SPECIFIC MEDICATIONS

Amantadine (Dopaminergic)

• Trade name: Symmetrel
• Mechanism of action: Dopamine agonist & NMDA receptor antagonist
• Literature:
  - Irritability, First RCT for TBI irritability & aggression completed finding substantial improvement for amantadine group (Hammond, et al)
• Other uses:
  - Vegetative State/Minimally Conscious State, arousal, disinhibition, hypersexual, lability, impulsivity, poor initiation, cognitive impairment, irritability, general cognitive function
• Side effects:
  - Hypotension, confusion, hallucinations, seizure, coma, death
  - Dose-related!
  - Creatinine Clearance is critical
  - 30-50: 100 mg/day
  - 15-29: 100 mg every 48 hours
  - <15: 200 mg every 7 days

Bromocriptine (Dopaminergic)

• Trade name: Parlodel
• Mechanism of action: Stimulates Dopamine receptors
• Literature:
  - Executive function & initiation (RCT)
• Other uses: Coma/VS/MCS emergence
• Dose:
  - 2.5 – 7.5 mg / day (increasing gradually up to 12.5 – 15 mg bid for coma)
• Side effects:
  - Dizziness, drowsiness, faintness, syncope, nausea, vomiting, constipation, diarrhea, hallucinations

Methylphenidate (Dopaminergic)

• Trade name: Ritalin
• Mechanism of action:
  - Inhibits the postsynaptic reuptake of dopamine
  - Thought to act on the brainstem reticular activating system and cortex
  - Cognitive & behavioral effects are not fully understood
  - MP may improve post-TBI behavior through effects on attention, arousal, and initiation
• Literature:
  - Arousal, and processing speed, and aggression
    - Reduces aggression in ADHD & TBI populations (RCT)
• Other uses:
  - Initiation, attention, distractibility, vigilance, memory, ADHD, motor impairment, apathy, fatigue, agitation, depression
• Contraindications:
  - MAOI (monamine oxidase inhibitors)
  - Don’t use with Linezolid (Zyvox) or until 2 weeks off
  - May increase drug levels of other meds
  - Can worsen psychosis
Serotonin Reuptake Inhibitors (Serotonergic)

- **Examples:** Sertraline (Zoloft), citalopram (Celexa), paroxetine (Paxil), fluoxetine (Prozac) (Antidepressant agent)
- **Literature:**
  - Depression: Sertraline (Case series, 1 RCT); Fluoxetine
  - Irritability: Sertraline (Case study)
- **Uses:** Depression and anxiety
- **Side effects:**
  - H/A, nausea, vomiting, diarrhea, constipation, insomnia, sedation, abnormal dreams, anxiety, tremors, diziness, fatigue, impaired concentration, agitation, anorexia, weight gain, rash, sexual dysfunction
- **Contraindications:** Monoamine Oxidase Inhibitors (MAOI)

Acetylcholine Esterase Inhibitors (Cholinergic)

- **Examples:** Donepezil (Aricept), Exelon (Rivastigmine)
- **Mechanism of action:**
  - Reversible inhibitor of the enzyme acetylcholinesterase
- **Literature:** Attention and memory, speed of processing (post-hoc analysis)
- **Uses:** Deficits in executive function
- **Dosing considerations:**
  - Dose at night
  - Steady state is not achieved for 15 days
  - Side effects related to rate of dose escalation & generally temporary
  - Start at 5 mg and then wait 4-6 weeks to increase to 10 mg
- **Side effects:**
  - Most common: Nausea, diarrhea, insomnia, vomiting, muscle cramps, fatigue, anorexia
  - Influenza, chest pain, urinary incontinence or retention, orthostatic hypotension, hallucinations, nightmares, anxiety, vertigo, ataxia, syncope, increased or decreased blood pressure, depression, suicidal ideation, delusions, tremor, dry mouth, increased or decreased appetite, weight gain or loss, nausea, vomiting, diarrhea, constipation, insomnia, sedation, fatigue, impotence, loss of libido, cold hands, hyperesthesia, numbness, blurred vision, syncope, cholinergic crisis
- **Contraindications:** Known hypersensitivity to donepezil, history of cholinergic crisis, COPD

Summary of Cholinesterase Inhibitor Studies

- **Physostigmine**
  - Evidence: single case (1) w/double-blind (1), open-label case series (1), single-site double-blind placebo-controlled (2)
- **Donepezil**
  - Single-case report (1), open-label case series (3), single-site double-blind placebo-controlled (1)
- **Rivastigmine**
  - Multicenter RCT (1) with open-label extension (1), single-site double-blind placebo-controlled (1)
- **Galantamine**
  - Open-label case series (1)

Tricyclic Antidepressants (NE & SE)

- **Examples:**
  - Elavil (amitriptyline) (insomnia, neuropathic pain, lability, depression)
  - Norpramin (Sinequan, Aventyl, Permaflex, Norprin, Amiflone and Norprin) (chronic fatigue syndrome, chronic pain, migraine, labile affect)
  - Desipramine (Norpramin, Pertofrane) (ADHD, arousal)
- **Mechanism of action:** (poorly understood)
  - Inhibits re-uptake of norepinephrine and serotonin
  - Also possesses affinity for muscarinic & histamine H1 receptors to varying degrees
- **Literature:**
  - Acute agitation: Amitriptyline 150 mg
  - Depression: Amitriptyline, desipramine
  - Other uses: Poor sleep maintenance and neurogenic pain
  - Side effects: (differing profiles)
    - Sedation, seizure, lethargy, overdose, dysrhythmias, myocardial infarction, hepatic dysfunction, hypertension, worsened depression, suicidal thoughts, leukopenia, agranulocytosis, weight gain, decrease of thyroid
  - Levels may be increased by Selective Serotonin Reuptake Inhibitors
- **Contraindications:** Acute myocardial infarction

Zhang 2004, Silver 2006
Buspirone (Dopamine & Serotonin)
- **Trade name:** BuSpar (anxiolytic agent)
- **Mechanism of action:**
  - Affinity for brain D2 dopamine receptors (both an antagonist and agonist) and for the 5-HT1A receptors (agonist)
  - Buspirone does not block the neuronal uptake of monoamines and, on chronic administration, it does not lead to changes in receptor density in the models investigated
- **Contraindications:**
  - Asthma, poor circulation, diabetes, thioridazine
- **Side effects:**
  - Headache, dizziness, nausea, insomnia
- **Dosing:** 15 mg three times daily
- **Expect lag of 2-3 weeks; allow 4 weeks to know if dose is effective**
- **Other uses:** anxiety, depression, somatic preoccupation, inattention, distractibility
- **Contraindications:**
  - May increase antipsychotic (haloperidol) levels
  - Monoamine Oxidase Inhibitors (MAOI)

Anticonvulsants
- **Evidence:** Aggression: Case reports, Case series
- **Uses:** Seizure, aggression, disinhibition, impulsivity, neuropathic pain
- **Carbamazepine** (Tegretol): 3 case studies/series; RCT in progress
  - Side effects: drowsiness, cognitive impairment, SJS, aplastic anemia, hyponatremia, hepatic dysfunction
- **Valproic acid** (Depakote): Case reports
  - Side effects: Weight gain, hemolytic anemia, leukopenia, thrombocytopenia, neural tube defect risk, hepatic dysfunction
- **Newer anticonvulsants:** limited literature
  - Oxcarbazepine (trihydropyrimidine), lamotrigine/Lamictal, gabapentin
  - Avoid phenytoin & phenobarbital which are more sedating
  - Lab monitoring

Benzodiazepines (GABA)
- **Examples:** lorazepam (Ativan), diazepam (Valium)
- **Mechanism of action:** Enhance GABA receptor function
- **Uses:**
  - Agitation: Generally reserve use if imminent danger
  - Anxiety: Avoid use of BuSpar instead
- **Lots of drug interactions!**
- **Side effects particularly common in TBI!**
  - Side effects: drowsiness, dizziness, ataxia, slurred speech, memory impairment, agitation, akathisia, psychomotor impairment (including diving)
- **Contraindications:**
  - Severe liver disease, Chronic Obstructive Pulmonary Disease (COPD), sleep apnea

Beta-Blockers
- **Literature:**
  - Agitation & aggression
  - Pindolol (behavior issues in general population)
  - Nalidixic acid (agression, non-koemic RE)
- **Other uses:** Hyperadrenergic state, migraine headache
- **Use lipophilic B-blockers for agitation**
  - Lopressor, Propranolol, Metoprolol
  - CNS effect appears beneficial for agitation
  - Hydrophilic: Atenolol, nadolol
  - Lower incidence of CNS-related side effects in general population
- **Consider if patient is sedated on lipophilic agent**
  - **Side effects:**
    - Sedation, dizziness, light-headed, clinical depression, lower HDL, increased BP & pulse (switch to propranolol)
    - Drug interactions: Increased plasma levels of antipsychotics & AED
- **Contraindications:** Asthma, poor circulation, diabetes, thioridazine

Lithium
- **Consider for:**
  - Severe aggression, associated major depression, bipolar disorder
- **Side effects:**
  - Toxicity, H/A, nausea, vomiting, diarrhea, polyuria, weight gain, tremor, dizziness, sedation, rash, leukopenia, dyspepsia, hypo- or hyperthyroidism
- **Contraindications:**
  - Renal failure, severe renal disease, dehydration, significant cardiac disease, pregnancy, lactation, under 12 years of age, caution with diuretics
  - Many drug interactions:
    - NSAIDs, ACE, diuretics, thyroid agents
  - Lab monitoring required

Antipsychotics (Dopamine Blocking)
- **1st generation vs. 2nd generation**
  - 1st generation: Haloperidol (Haldol)
  - 2nd generation: risperidone (Risperdal), olanzapine (Zyprexa), quetiapine (Seroquel)
  - Atypicals have less propensity for extrapyramidal symptoms
  - Both tend to block receptors to brain’s dopamine pathways, but encompass a wide range of receptor targets
- **AVOID:** If needed, use short-acting. Use sparingly for:
  - Imminent danger; psychotic features (hallucinations or delusions)
  - Generally don’t solve the problem
  - Exclude other causes for psychosis
- **Side effects**
  - Tardive dyskinesia, neuroleptic syndrome, weight gain, priapism, prolonged QT/PRA, tardive dyskinesia, akathisia, tardive dystonia, akinesia, emesis, enuresis, cardiac arrhythmia, thrombocytopenia

Antipsychotics
- **Mechanism of action:**
  - Dopamine & serotonin (DHT1/2 receptor antagonists)
- **Uses:**
  - Seizure, aggression, disinhibition, impulsivity, neuropathic pain
  - **Carbamazepine** (Trigrelot): 3 case studies/series; RCT in progress
  - **Valproic acid** (Depakote): Case reports
  - **Newer anticonvulsants:** limited literature
  - Oxcarbazepine (trihydropyrimidine), lamotrigine/Lamictal, gabapentin
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Cases

Case 1

- 28 yo male
- Mild TBI
- Frequent irritability and occasional aggressive behaviors
  - Mostly aimed towards spouse
- Headaches – migraine characteristics

Case 1: Considerations for Treatment

- Consider treatments that may help both the headaches and the behavior
  - Beta-blocker
  - Anticonvulsant: carbemazepine or valproate
  - Catecholaminergic augmentation
  - Cholinergic augmentation

Case 2

- 44 yo female
- Severe TBI
- Frequent irritability and occasional aggressive behaviors
  - Mostly aimed towards spouse and children
- Depressed mood
- Poor sleep

Case 2: Considerations for Treatment

- Treat sleep disturbance
- High level cognitive impairment
- Treat depression
  - Serotonergic augmentation
  - Catecholaminergic augmentation
  - Cholinergic augmentation

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Questions?

Injury Location & Vulnerability

- **Frontal lobe**
  - Emotions, reasoning, planning, problem solving, judgment, creativity, parts of speech, movement
- **Temporal lobe**
  - Emotion, learning, meaning, memory, language, hearing, interpreting & processing auditory stimuli
- **Parietal lobe**
  - Senses, language functions
- **Occipital lobe**
  - Vision, ability to recognize objects
- **Midbrain**
  - Amygdala
  - Emotions
  - Hippocampus
  - Memory
  - Thalamus
  - Receives and relays information to cortex, brain, brainstem

A Cholinergic Synapse

Pre-Injury Factors:
Genetic Variations in Neurotransmitter Metabolism

- Genetic variations in
  - Catechol-O-Methyltransferase (COMT)
    - Influence DA & NE metabolism
      - Met/Met – slow
      - Met/Val – intermediate
      - Val/Val – fast
    - May influence neurobehavioral functions that are catecholaminergically-dependent

Cholinergic Augmentation:
Acetylcholine Improves Cerebral Processing Efficiency

- Improves efficiency of cerebral signaling:
  - Increases excitatory tone in reticulothalamic systems
  - Improves information gating in the hippocampus and thalamus
  - Increases the strength of signals co-processed with glutamate in the hippocampus so as to facilitate long-term potentiation
  - Facilitates the effects of other neurotransmitters: glutamate, GABA, dopamine, norepinephrine, and serotonin on information processing in frontal, temporal, parietal, and cerebellar areas