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**Outline**

- **Common Medical Problems**
  - Post-traumatic Seizures/Epilepsy
  - Spasticity
  - Depression/Anxiety
  - Agitation/Aggression
  - Sleep disorders
  - Attention deficits
- **Medications and side effects for each**

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**Medication Management Philosophy**

- Start low and go slow
- Change one medication at a time
  - Adding medications
  - Removing medications
  - Changing doses
- Look for medications that can be eliminated before adding others
- Give adequate time for therapeutic effect
- Educate patients and families on reasonable outcomes, targeted effects, side effects

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**Post-traumatic Seizures**

- **Post-traumatic Seizures**
  - Immediate: first 24 hours
  - Early: 1 – 7 days
  - Late: after 7 days
- **Post-traumatic Epilepsy**
  - Two or more late onset seizures separated by at least 24 hours that is not attributable to other causes (Infections, Electrolytes, Medications)

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**Post-traumatic Seizures**

- Generalized
  - Bilateral hemisphere involvement
  - Previously known as “Grand Mal”
  - Nearly all involve loss of consciousness (LOC)
- Partial
  - Unilateral involvement
  - Complex or Simple
    - Complex: (+) LOC
    - Simple: (-) LOC
  - **Most common form found in TBI**

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**Post-traumatic Seizures**

- **Generalizations**
  - 80% of seizures will develop in first 2 years
  - Neuro-imaging is NOT helpful in predicting PTS
  - EEG is NOT helpful in predicting PTS
    - False positives and negatives are common

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### Post-traumatic Seizures

- Treatment
  - Only treat late-onset seizures
  - Tegretol, Depakote, Lamictal, Topamax, Vimpat, Trileptal, Keppra
  - Duration is physician dependent
    - 1<sup>st</sup> seizure: 18 months
      - Goal is to limit potentially cognitive sedating meds as much as possible
    - 2<sup>nd</sup> Seizure: 2 years
    - 3<sup>rd</sup> seizure: lifetime
  - Seizures lasting greater than 5 minutes have a high risk of developing status epilepticus
    - ER evaluation and treatment

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### Post-traumatic Seizures

- Medications
  - Tegretol (Carbamazepine)
  - Depakote (Valproic Acid)
  - Lamictal (Lamotrigine)
  - Topamax (Topiramate)
  - Keppra (Levetiracetam)
  - Vimpat (Lacosamide)
  - Trileptal (Oxcarbazepine)

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### Post-traumatic Seizures

- Mechanism of Action
  - Stabilizes cell membranes to decrease frequency of spontaneous firing
- Common Side effects
  - Lethargy
  - Confusion
  - Dizziness/Gait unsteadiness
  - Hepatotoxicity
  - Pancytopenia

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### Post-traumatic Seizures

- Monitoring levels
  - Can get levels on any anti-seizure medication to assure therapeutic range, however.....
  - Only clinically useful for Tegretol and Depakote
  - CBC, CMP and drug levels every 3 months
- Toxicity effects
  - Marked lethargy/somnolence
  - Hallucinations/Paranoid delusions
  - Fever
  - Depression

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### Spasticity

- Definition: Velocity dependent increase in muscle tone with resistance to stretch
- Occurs due to deficiency or absent of descending inhibitory pathways
  - Gamma Amino Butyric Acid (GABA) is the primary inhibitory neurotransmitter that turns off the spinal reflex

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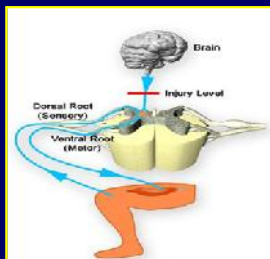
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### Spasticity



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### Spasticity

- **Treatments**
  - PT/OT for stretching, splinting/casting and modalities (heat, ice, ultrasound, E-Stim)
  - Oral Medications
    - Baclofen, Dantrium, Zanaflex
  - Injections
    - Botulinum toxin, Phenol
  - Invasive treatments
    - Intrathecal Baclofen pump
    - Tendon lengthening procedures

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### Spasticity

- **Medications**
  - **Baclofen**
    - 5-20mg TID
    - enhances effect of GABA in the CNS in effort to “turn off” the spinal reflex pathway
    - Side effects: weakness, lethargy, confusion, dizziness, respiratory distress
    - Withdrawal: increase muscle tone, itching (without presence of a rash), hallucinations (usually visual), seizures, fever, death
    - Oral or Intra-theal preparations

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### Spasticity

- **Medications (cont.)**
  - **Dantrium (Dantrolene Sodium)**
    - 50-100mg BID or TID
    - Inhibits muscle activity at the muscle itself (only agent that works at the muscle level). Inhibits Calcium release from the sarcoplasmic reticulum.
    - Side effects: **Hepatotoxicity**, weakness, lethargy
    - Monitoring: CBC, CMP every 3 months

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## Spasticity

- Medications (cont.)
  - Zanaflex (Tizanidine)
    - 2-8mg TID
    - Inhibits descending excitatory pathways both at the brain and spinal cord levels
    - Usually used as an adjunct to other medications
    - Side effects: hypotension, sedation, fatigue, dizziness, hepatotoxicity

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## Spasticity

- Injectable treatments
  - Botulinum toxin (Botox, Myobloc, Dysport)
    - Inhibit the release of Acetylcholine into the synapse to prevent muscle contraction
    - Best if localization measures are used
      - EMG, Electrical stimulation, Ultrasound
    - Side effects: Muscle irritation, localized pain, fever, nausea, dysphagia (if used close to the neck)
    - FDA approved for upper extremity spasticity only

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## Depression

- Definition: psychological disorder that presents as a depressed mood, lost of interest or pleasure, feelings of guilt or low self-worth
  - Not just feeling “sad”
- Patients often claim to feel “lost in the world”
- Pathophysiology
  - deficiency in serotonin, norepinephrine and/or dopamine in the Central Nervous System

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### Depression

- Medications should be used in conjunction with psychotherapy and counseling
- Medication classes
  - SSRI
  - SNRI
  - TCA
  - MAOI
  - “Novel”

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### Depression

- SSRI's
  - Selectively inhibits the reuptake of Serotonin in the synapse making it more available to the post-synaptic membrane

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### Depression

SSRI Mechanism of Action



The diagram illustrates the mechanism of action of a Selective Serotonin Reuptake Inhibitor (SSRI) in a synapse. It shows a presynaptic terminal containing vesicles of serotonin (5-HT) and the enzyme MAO. The process of serotonin release is triggered by an action potential (AP) arriving at the nerve terminal. Inside the terminal, MAO is involved in the metabolism of 5-HT. The serotonin transporter (SERT) is shown on the presynaptic membrane, normally responsible for reuptaking 5-HT into the terminal. An SSRI is shown binding to and inhibiting SERT, preventing the reuptake of 5-HT. This results in an increased concentration of 5-HT in the synaptic cleft. The diagram also shows 5-HT being metabolized by COMT in the cleft and binding to 5-HT receptors on the postsynaptic membrane. Labels include: AP (action potential), nerve terminal, MAO, SERT, SSRI, COMT, 5-HT, postsynaptic membrane, and 5-HT receptor.

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### Depression

- SSRI's (cont.)
  - **Zoloft** (Sertraline) 50-150mg daily
  - **Paxil** (Paroxetine) 20-50mg daily
  - **Celexa** (Citalopram) 10-40mg daily
  - **Lexapro** (Escitalopram) 10-20mg daily
  - **Prozac** (Fluoxetine) 20-80mg daily

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### Depression

- SSRI's (cont.)
  - Side effects: Nausea, Vomiting, Diarrhea, Dry mouth, sedation (esp with Paxil), delayed ejaculation, decreased libido, serotonin syndrome (especially when used with other SSRI's)
  - Must give 3-4 weeks trial before changing dose or switching medications

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### Depression

- SNRI's
  - Inhibits the reuptake of serotonin and norepinephrine in the nerve synapse

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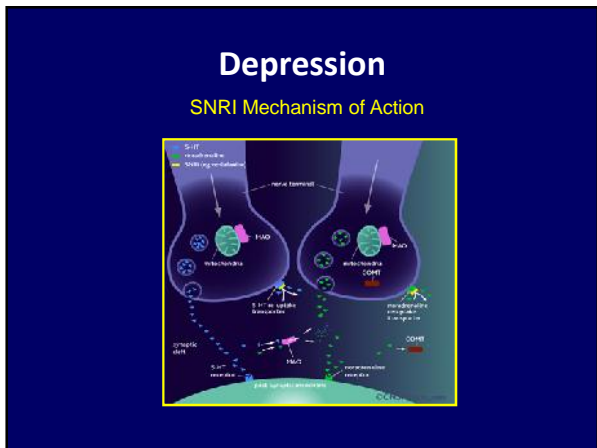
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- ### Depression
- SNRI's (cont.)
    - **Cymbalta** (Duloxetine) 30-60mg daily
    - **Effexor** (Venlafaxine) 37.5-75mg BID or TID
    - **Pristiq** (Desvenlafaxine) 50mg daily
    - Side effects: Insomnia, nausea, vomiting, diarrhea, seizures, HTN, heart arrhythmias, anxiety, agitation/aggression

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- ### Depression
- TCA's (Tricyclic/Tetracyclic Antidepressants)
    - Inhibits re-uptake of norepinephrine, serotonin and histamine at the synapse.
    - Anticholinergic effects which limit use in TBI population and is cause for most common side effects

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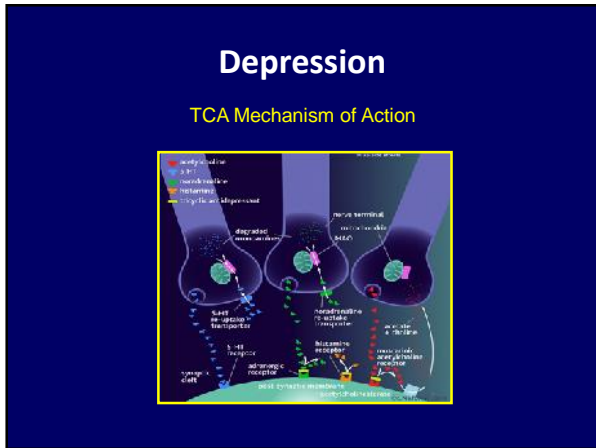
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- ### Depression
- TCA's (Tricyclic/Tetracyclic Antidepressants)
    - **Elavil** (Amitriptyline) 50-150mg qhs
    - **Pamelor** (Nortriptyline) 50-150mg qhs
    - **Anafranil** (Clomipramine) 50-250mg qhs

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- ### Depression
- TCA's (Tricyclic/Tetracyclic Antidepressants)
    - **Side effects:** Memory loss, attention and concentration deficits, sedation, confusion, delirium, hypotension, urine retention, constipation
    - Used mostly in TBI population for sleep disorders, not depression

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**Depression**

- MAOI (MonoAmine Oxidase Inhibitors)
  - **Emsam** (Selegiline), **Marplan** (Isocarboxacid), **Nardil** (Phenelzine), **Parnate** (Tranlycypromine)
- Inhibits the enzyme Monoamine Oxidase which leads to increase in blood levels of serotonin, melatonin, epinephrine, norepinephrine and dopamine
- Not used in TBI patients due to adverse side effects

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**Depression**

- MAOI (cont.)
  - Side effects: Orthostatic hypotension, dizziness, drowsiness, insomnia, confusion, tremors, hallucinations

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**Depression**

- “Novel” Group
  - **Wellbutrin** (Bupropion) 50-150mg BID
    - Inhibits reuptake of serotonin, norepinephrine and dopamine at nerve synapse
    - Useful for depression and attention/concentration deficits
    - Side effects: anxiety, insomnia, seizures, hallucinations
  - **Remeron** (Mirtazapine) 15-30mg qhs
    - Used mostly for sleep disorders and poor appetite
  - **Trazodone**
    - Used predominately for sleep disorders

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### Anxiety

- **Definition:** psychological disorder presenting as feelings of fear, uneasiness and/or restlessness
  - Situational or Generalized
- Commonly accompanies depression as a clinical syndrome

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### Anxiety

- **Situational**
  - Panic disorder usually triggered by an external stimulus
  - Crowded areas such as malls, grocery stores, events, etc...
  - Includes social phobias, OCD and PTSD
- **Generalized**
  - Constant feeling of tension, uneasiness, fear

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### Anxiety

- **Situational**
  - **Anxiolytics**
    - Short Acting (half-life 8-10 hours)
      - **Xanax** (Alprazolam) 0.25-1mg TID prn
      - **Serax** (Oxazepam) 10-30mg TID
    - Medium acting (half-life 10-14 hours)
      - **Ativan** (Lorazepam) 2-6mg/day divided BID or TID prn
      - **Estazolam** 1-2mg qhs prn

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## Anxiety

- Situational
  - Anxiolytics (cont.)
    - Long Acting (half-life 20-40 hours)
      - Klonopin (Clonazepam) 0.5-5mg TID
      - Valium (Diazepam) 2-10mg BID to TID
      - Dalmane (Flurazepam) 10-30mg qhs
    - Non-Benzodiazepine
      - Vistaril (Hydroxazine) 25-50mg TID
      - Inderal (Propranolol) 10-30mg TID
  - Used mostly on an as needed basis

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## Anxiety

- Side effects
  - Benzodiazepines (all classes)
    - Lethargy, Drowsiness, Dizziness, Confusion, Delerium, Ataxia, Potential for abuse/addiction, Respiratory depression
  - Vistaril
    - Dry mouth, dizziness, lethargy, drowsiness
  - Inderal
    - Drowsiness, hypotension, bradycardia, depression

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## Agitation

- A psychological state manifested by verbal and/or physical aggression or rage
- Usually caused by an external trigger, but not always
- **Must identify what is causing the agitation in order to treat it effectively**
  - Commonly not mood instability but rather an underlying anxiety disorder, sleep disorder or depression
- Physiologically is a state of sympathetic overdrive and/or excessive dopamine
- Treatments are aimed at controlling these physiologic changes

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## Agitation

- **Treatments**
  - **Acutely**
    - **Oral or IM Benzodiazepines**
      - Ativan works best for acute agitation or aggression
      - Typical Antipsychotics should NEVER be used in the TBI patient (Haldol, e.g.)
        - » Evidence of incomplete or delayed cognitive recovery and higher incidence of tardive dyskinesia
  - **Maintenance therapy**
    - **Mood Stabilizers**
      - Depakote 250-1500mg BID
      - Tegretol 100-400mg BID

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## Agitation

- **Treatments**
  - **Maintenance therapy (cont.)**
    - **Atypical Antipsychotics**
      - Seroquel 50-200mg BID
      - Geodon 20-80mg BID
      - Zyprexa 5-20mg daily
      - Risperdal 1-3mg BID

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## Agitation

- **Treatments**
  - **Maintenance therapy (cont.)**
    - **Beta-blockers**
      - Inderal
    - **Anxiolytics**
      - Vistaril, Clonazepam
    - **Antidepressants**
      - SSRI's
    - **Neurostimulants**
      - Ritalin, Adderall, Concerta, Strattera

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### Sleep disorders

- Difficulty with initiation, maintenance or both
- Must take a thorough history in order to treat sleep problems effectively
  - Night time routines
  - Caffeine intake
  - Napping during the day
  - Headaches
  - Awakening due to other medical problems
    - Pain, Urination, muscle spasms

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### Sleep disorders

- Treatment
  - First line is environmental changes
    - “Settling down” period at night
    - Relative dark environment with little/no noises
    - No caffeine after 7pm
  - If headaches are associated, may need to get a sleep study
    - Also if a spouse/significant other can confirm that patient snores excessively
  - Treat any underlying medical problem that is contributing

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### Sleep disorders

- Treatment
  - Initiation only problem
  - Brain can’t “shut down” at night
  - Once patient can get to sleep they can stay asleep for 6-8 hours
    - Melatonin
      - 3-6mg at night about an hour prior to wanting to go to sleep
    - Trazodone
      - 50-150mg at night

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### Sleep disorders

- Treatment
  - Maintenance or Combined problem
    - Patients have difficulty with getting to sleep and staying asleep....OR....can get to sleep fine, but have trouble staying asleep
    - Awaken 5-7 times per night
    - Again....must treat any underlying medical cause
    - Medications
      - Restoril (Temazepam) 15-30mg at night
      - Ambien 5-10mg at night

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### Sleep disorders

- Side effects
  - **Melatonin**: sleepiness (duh!!), nightmares, sleepwalking, headaches
  - **Trazodone**: headaches, dizziness, nausea/vomiting, dry mouth
  - **Restoril**: drowsiness, fatigue, “hangover” effect, dizziness
  - **Ambien**: sleepwalking, night terrors, hallucinations, dizziness, lethargy, “hangover” effect

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### Attention Deficits

- Inability to maintain focus and concentration on visual or auditory tasks
- Common with Frontal and/or Temporal lobe injuries
- Physiologically is a deficiency in the dopaminergic and/or noradrenergic pathways
- Can be associated with or without a hyperactivity component
- Again, a thorough history needs to be taken before any agent should be started
  - Heart disease (personal or family), seizures, sleep disorders, psychosis

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### Attention Deficits

- Clinical presentations
  - Poor memory
  - Agitation
  - Frustration
  - Irritability
  - Tangential speech
  - Restlessness (hyperactive)

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### Attention deficits

- Treatment
  - Neurostimulants
    - **Ritalin** – blocks the re-uptake and increases the release of Norepinephrine (and some Dopamine) at the synaptic terminal
      - 5-20mg every morning and noon
      - Side effects: Agitation, hallucinations, mania, hypertension, tachycardia, anorexia. Anxiety, insomnia
    - **Adderall** – same as Ritalin but with less Dopamine effects
      - 10-20mg every morning and noon
      - Side effects: Same as Ritalin

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### Attention deficits

- Treatment
  - Dopaminergics
    - **Amantadine**: Increases the release of dopamine from the pre-synaptic membrane
      - 100-200mg every morning and noon (should not be taken after 3pm)
      - Side effects: Hallucinations, Seizures, Irritability, Anxiety, Insomnia
    - **Bromocryptine**: Blocks the re-uptake of dopamine from the synapse
      - 2.5-10mg every morning and noon (should not be taken after 3 pm)
      - Side effects: Same as Amantadine

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### Attention deficits

- Treatment (cont.)
  - Concerta and Strattera have not been well studied in TBI population and should be avoided unless necessary
  - Antidepressants
    - Wellbutrin 50-150mg BID

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### Neuropharmacology Cheat Sheet

- What medicine do I choose?
  - Attention deficits
    - Neurostimulant (Dopaminergic, Noradrenergic)
  - Spasticity
    - Dantrium, Baclofen, Zanaflex
  - Depression
    - SSRI, SNRI, Novel type
  - Anxiety
    - Alprazolam, Clonazepam, Vistaril
    - SSRI, Buspirone, Inderal
  - Anger/Aggression
    - Depakote, Tegretol
    - Seroquel, Risperdal, Geodon
  - Poor sleep
    - Melatonin, Trazadone
    - Restoril, Ambien

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Thank You!!



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