Depression Pharmacology

UNIVERSITY OF HAWAI‘I HILO PRE-NURSING PROGRAM
NURS 203 – GENERAL PHARMACOLOGY
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Learning Objectives

- Know what medications belong in the individual drug classes
- Understand the pharmacology of each medication class
- Know the characteristics of medications that separate individual agents from their general drug class
- Understand the place in therapy for each medication class
- Know the alternate uses for these medications
Overview

- Introduction to depression
- SSRIs
- SNRIs
- TCAs
- Others
  - Trazodone/nefazodone
  - Dopamine/NE reuptake inhibitors
  - MAOI
Depression – General Information

8 million visits to the ambulatory care setting (2009-2010)

Can be an acute or long term problem
- Acute (6-14 months)
- Long term (2 years or longer)

30-40% of patients remit with drug therapy

Drug therapy should be continued for 6-12 months

Most patients (85%) will relapse at least once

Maintenance therapy should be considered for:
- ≥ 2 MDD episodes in 5 years
- ≥ 3 MDD episodes a lifetime
Depression – Signs & Symptoms

Sleep – Changes in sleep habits (increase or decrease)
Interest – Loss of interest in things that previously brought pleasure
Guilt – Feelings of worthlessness, decreased self value
Energy – Fatigue/loss of energy
Concentration – Difficulty concentration or decreased cognition
Appetite – Decreased or increased weight
Psychomotor – Agitation or lethargy
Suicide - Thoughts
Depression - Under normal circumstances

Strong signal – transmission to next nerve

SERT

NE
5HT
Da
Ach...
Depression - Pathophysiology

Weak signal - no transmission

SERT

NE
5HT
Da
Ach...
Antidepressant Medications

Other indications
- General anxiety disorder
- Post traumatic stress disorder
- Obsessive compulsive disorder
- Panic disorder
- Premenstrual dysphoric disorder
- Weight gain/weight loss
- Pain
- Enuresis in children
- Vasomotor symptoms
- Some sexual disorders
- Sleep disorder
- ADHD

Consider alternate therapy
- Bipolar depression

Include in depression treatment plan
- Cognitive behavioral therapy

Neurotransmitter receptors in areas of the brain that modulate:
- Mood
- Memory processing
- Sleep
- Cognition

Taper off these medications
Selective Serotonin Reuptake Inhibitors (SSRIs)

MOA – Inhibition of the serotonin transporter (SERT) resulting in increased concentrations of serotonin in the synaptic cleft

- Drug in the class
  - Fluoxetine
  - Sertraline
  - Citalopram/escitalopram
  - Paroxetine
  - Fluvoxamine
Depression - Pathophysiology

Weak signal - no transmission

SERT
SSRI

Strong signal – transmission to next nerve
SSRIs

Kinetics
- Lipophilic
- Highly protein bound
- Metabolized by the liver
- Cleared by the kidneys
- Half life – varies (20-180 hours – parent drug & metabolites)

ADRs
- Nausea, GI upset, diarrhea
- Loss of libido, delayed orgasm, diminished arousal
- Headache, insomnia, wakefulness
- Weight gain

Interactions
- Other serotonergic medications, MAOIs (serotonin syndrome), CYP2D6 medications (TCAs)
- CI with MAOIs
- Pregnancy category C
  - Except paroxetine - D
SSRI – Individual drug class exceptions

Potent CYP2D6 inhibitors
- Paroxetine
- Fluoxetine

CYP3A4 inhibitor
- Fluvoxamine

Very long half life
- Fluoxetine (parent & metabolite - taper)
- Sertraline (metabolite)

How do you choose between SSRIs
- Pretty equal in effects
- Cost
- Insurance/availability
- Adverse effect profile
- Patient preference/history

At least 2 SSRIs should be tried before trying another class
Serotonin syndrome

Results from excess serotonin in the body

Symptoms
- Agitation or restlessness
- Confusion
- Rapid heart rate and high blood pressure
- Dilated pupils
- Loss of muscle coordination or twitching muscles
- Muscle rigidity
- Heavy sweating
- Diarrhea
- Headache
- Shivering
- Goose bumps

Severe symptoms
- High fever
- Seizures
- Irregular heartbeat
- Unconsciousness
Selective Serotonin-Norepinephrine Inhibitors

**MOA** – Inhibit the SERT and NET reuptake transporter to increase concentrations of serotonin and norepinephrine

**Drugs in the class**
- Venlafaxine/desvenlafaxine
- Duloxetine
- Levomilnacipran

Greater affinity for the SERT protein
SNRI

NE
5HT
Da
Ach...

NET
SERT
SNRI

NET

SERT

NE
5HT
Da
Ach...

B₁, K, Cu, Zn, Fe, Se, D, Na, A, E, B₆, Ca
SNRI

Strong signal – transmission to next nerve

NET

SERT

NE
5HT
Da
Ach...
SNRI

Kinetics
- Venlafaxine – metabolized by CYP2D6 to desvenlafaxine (not heavily metabolized)
  - Half life (both) 8-11 hours
  - Protein binding 27-30%
  - Excretion (unchanged in the urine)
    - Desvenlafaxine (45%)
    - Venlafaxine (4-8%)
- Duloxetine
  - Well absorbed
  - Half life 12-15 hrs..
  - Protein bound (97%)
  - Metabolized heavily by CYP2D6 & 1A2 (altered by hepatic impairment)

***All dosed daily

ADRs
- Similar to SSRI
- Increased blood pressure & heart rate, insomnia, anxiety, & agitation (NE effects)

Interactions
- CYP2D6 medications, other psychologic medications (MAOIs & TCAs), CYP3A4 inhibitors (levomilnacipran)
- CI with MAOIs

Notes
- Taper

Used in
- Neuropathic pain
- Menopausal symptoms
Tricyclic Antidepressants (TCAs)

Former first line agents

MOA – Inhibition of SERT, NET, ACh, and Histamine receptor proteins. Antidepressant actions from the binding of SERT & NET – affinity varies

Drugs in the class
- Imipramine/desimipramine
- Amitriptyline
- Nortriptyline
- Doxepin
- Protriptyline
- Clomipramine
- Trimipramine
TCAs

Kinetics
- Well absorbed
- Long half lives (9-92 hrs., daily dosing)
- Metabolized – CYP2D6
- Excretion – only 5% unchanged in urine

Used in
- Pain
- Migraine prophylaxis
- Sleep
- Depression

ADRs
- Similar to SSRIs & SNRIs
- Sedating (dosed at night), dry mouth, constipation, urinary retention, blurred vision, confusion, weight gain
- Orthostatic hypotension

Blocks H1 & alpha receptors

Interactions
- CYP2D6 inhibitors, anticholinergic agents, blood pressure medications

Overdose can be fatal
Trazodone & nefazodone

MOA – Antagonist of the 5HT-2 receptor on the presynaptic neuron – blocks the attenuation of the release of neurotransmitter in the synaptic cleft. Antagonist at the post synaptic 5HT-2 receptor to help mediate behavioral effects, anxiety, and other functions.
Trazodone & nefazodone
Trazodone

Kinetics
- Onset
  - Antidepressant – up to 6 weeks
  - Sedation – 1-3 hrs.
- Absorption – well absorbed (increases after high fat meal)
- Protein binding – 85-95%
- Metabolism – Extensive CYP3A4 metabolism w/active metabolite
- Half life – 7-10 hours
- Excretion – primarily in urine (~1% unchanged) but some feces

Dosing – at bedtime
- Sedation 25-50 mg
- Antidepressant up to 200 mg

ADRs –
- Sedation, HA (headache), dizziness, fatigue
- Constipation, decreased libido, blurry vision, back pain

Interactions
- CYP3A4 inducers/inhibitors, alcohol, other serotonergic drugs, MAOI, St. John’s Wort
- Pregnancy – C
  - In breast milk
Dopamine/norepinephrine reuptake inhibitors

MOA – Not clearly understood but therapeutic effects are related to the reuptake inhibitor actions of dopamine and norepinephrine
## Bupropion (Wellbutrin & Zyban)

### Kinetics
- Absorption – rapid
- Protein binding – 84%
- Metabolism – Extensive CYP2B6
- Half life
  - Distribution – 3-4 hours
  - Elimination – 21 hours (including metabolites at steady state/chronic dosing)
- Excreted – 87% in the urine as metabolites, 10% in feces also as metabolites

### Used for:
- Depression 300-450 mg daily
- **Smoking cessation 300 mg daily**
- ADHD 1.4-6 mg/kg/day (off label)

### ADRs – (>10%)
- Tachycardia, HA, agitation, dizziness, insomnia, sweating, **weight loss**, dry mouth, nausea, blurred vision, pharyngitis, seizures
- **No sexual dysfunction**

### Contraindicated
- Seizures
- Eating disorders

### Interactions
- Alcohol, agents effecting dopamine (antipsychotics/Parkinson’s) & NE, MAOI, CYP 2D6 & 2B6
Alpha 2 antagonist - mirtazapine

MOA – Central (and some peripheral) alpha2 antagonist on the presynaptic nerve, leads to an increase in the release of serotonin and norepinephrine. Also antagonist of 5HT\textsubscript{2&3}. Antagonist of histamine receptors.
Mirtazapine

Kinetics
- Absorption – rapid and complete
- Protein binding – 85%
- Metabolism – Extensive CYP 1A2, 2D6, 3A4
- Half life – 20-40 hours (increased in liver impairment)
- Excretion – urine 75% & feces 15% - both as metabolites

Used for
- Depression
- Weight gain
- Sedation (low doses 7.5 mg increased to 15 mg)

ADRs
- Drowsiness, weight gain, increased cholesterol, dry mouth, increased appetite, constipation, muscle pain & weakness, dizziness
- ***LESS sexual dysfunction than SSRI

Interactions
- CYP 2D6, 1A2, & 3A4 inhibitors/inducers, alcohol, clonidine, MAOI, CNS depressants
- Pregnancy C
  - Found in breast milk
Monoamine Oxidase Inhibitors

MOA – Inhibits the enzyme monoamine oxidase responsible for clearing the synaptic cleft of monoamines, catecholamines, and other transmission molecules (neurotransmitters) leading to an increased concentrations of transmission molecule availability.

Drugs in class:
- Phenelzine
- Tranylcypromine
- Selegeline
MAOI

Strong signal – transmission to next nerve

SERT
MAOI
MAOI & SSRI
MAOI & SSRI

HYPERTENSIVE CRISIS!!!
MAOI

Kinetics
- Absorbed – well
- Metabolized – liver (1st pass effect)

Phenelzine
- Onset 2-4 weeks
- Duration – 2 weeks after d/c
- Half life – 12 hours
- Metabolism – monoamine oxidase pathways
- Excretion – urine (75% as metabolites)

ADRs
- Weight gain, orthostatic hypotension, high incidence of sexual side effects, activation, insomnia, restlessness, somnolence (phenelzine), confusion
- **Do not stop abruptly
  - Serious CNS side effects – delirium, psychosis, confusion

Interactions
- Many!!! – See page 404 in your book (test question on the section “MAOI Interaction”)
- Tyramine containing foods
- Serotonin syndrome
- Pregnancy
  - Adverse effects in animal studies no other info available on risk score or breast milk secretion
Serotonin syndrome

Results from excess serotonin in the body

Symptoms
- Agitation or restlessness
- Confusion
- Rapid heart rate and high blood pressure
- Dilated pupils
- Loss of muscle coordination or twitching muscles
- Muscle rigidity
- Heavy sweating
- Diarrhea
- Headache
- Shivering
- Goose bumps

Severe symptoms
- High fever
- Seizures
- Irregular heartbeat
- Unconsciousness
Tyramine foods interaction

Tyramine rich foods
- Aged cheeses
- Herring
- Broad beans
- Yeast
- Beer
- Snails
- Processed meat
- Liver
- Raisins
- Ripe avocado
- Coffee
- Sardines
- Soy sauce
- Etc......
Tyramine foods interaction

Tyramine rich foods
- Aged cheeses
- Herring
- Broad beans
- Yeast
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- Processed meat
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- Coffee
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- Etc......
Questions