The purpose of this activity is to enable the nurse practitioner to appropriately prescribe and treat the patient with diseases of the Neurological System.

By the end of the presentation, the audience should be able to:

- Be familiar with the neurotransmitters involved in psychiatric illnesses, as well as the effects these neurotransmitters have on the body.
- Identify typical presentations and signs/symptoms of common psychiatric illnesses.
- Understand and differentiate drug therapies for the treatment of these conditions.

Objectives

Overview

Neurotransmitters

Beneficial

Receptors & Locations

Adverse Effects

Medications

Treatment Guidelines
Neurotransmitters

Excitatory
- norepinephrine
- glutamate

Inhibitory
- serotonin
- GABA

Both
- dopamine
- acetylcholine

• Sympathetic nervous system
• “Fight or Flight” response

Norepinephrine

Leads to increased BP, HR, blood glucose. Causes vasoconstriction and increased blood flow to muscles.

Glutamate

- Most abundant excitatory NT

Involved with cognitive functions, including learning and memory.
Serotonin

- Inhibitory neurotransmitter
- Located in both the brain and the GI system

Regulates appetite, sleep, memory, learning, temperature, mood, behavior, muscle contraction, cardiovascular function and hormone balance.

Picture courtesy of: http://binged.it/1UZkw1J

GABA

- Inhibitory neurotransmitter
- Involved in the neural circuitry of the PFC

Reduces anxiety, promotes calming of the mind, and helps to relieve tension. Also involved in the temporal and spatial organization needed for higher order cognitive functions.

Picture courtesy of: http://binged.it/1qbfoeB

Dopamine

- Can be both inhibitory or excitatory, depending on the location of the receptors

Involved in voluntary movement, reward pathways and hormonal regulation

Picture courtesy of: http://binged.it/1RRK2CN
• Involved in the parasympathetic nervous system
• “Rest and Digest” or “Feed and Breed”

Acetylcholine

Leads to vasodilation and increased gastric secretions. Promotes REM sleep and helps with decision making, attention and learning.

Neurotransmitters

Receptors

Locations

• Norepinephrine: alpha and beta receptors
• Glutamate: NMDA, AMPA and kainate receptors
• Serotonin: 5-HT₁-7
• GABA: GABA<sub>A</sub> and GABA<sub>B</sub> receptors
• Dopamine (DA): D1-D5 (maybe D6 and D7)
• Acetylcholine (ACh): nicotinic (N1 and N2) and muscarinic (M1-5)
Receptors’ Locations

**alpha 1**
- vascular smooth muscle
- GI/urinary sphincters
- eye
- hair follicles

**alpha 2**
- involved in negative feedback loop

**beta 1**
- cardiac pacemaker
- myocardium
- salivary gland ducts
- sweat glands

**beta 2**
- GI tract
- bladder
- skeletal muscle arteries
- bronchioles
- coronary vessels

Receptors’ Locations

**NMDA**
- located primarily in the brain and CNS
- specifically hippocampus, temporal cortex, frontal cortex regions

**AMPA**
- located primarily in the brain and CNS
- specifically hippocampus and temporal cortex

**Kainate**
- located primarily in the brain and CNS
- specifically hippocampus, temporal cortex, cortex, cerebellum

Receptors’ Locations

**5-HT Receptors**
- 90% located in the GI system
- 10% located in the brain and CNS

**GABA and DA Receptors**
- located primarily in the brain and CNS

**ACh**
- Nicotinic-nervousmuscular junction, CNS, adrenal medulla
- Muscarinic-CNS, heart, bronchioles, eyes, smooth muscle, stomach
Antipsychotics

- **Desired effect**: reduce dopamine hyperactivity in the mesolimbic area in order to decrease positive symptoms
- **Desired effect**: increase dopamine hypoactivity in the prefrontal cortex in order to decrease negative symptoms
- **Desired effect**: antagonize 5-HT<sub>2A</sub> in order to increase dopamine release in prefrontal cortex
- **Other**: it is thought that there is a deficit of glutamate and GABA, and an abundance of ACh in schizophrenia, however, it is unknown at this time what role (if any) these play in therapy

**Undesired effect**: certain antipsychotics bind to alpha 1 and 2 receptors, which can lead to orthostatic hypotension

- Undesired effect: certain antipsychotics bind to H1, which can lead to drowsiness, sedation, headache
- Undesired effect: certain antipsychotics bind to M1, which can lead to anticholinergic effects, such as sedation, constipation, urinary retention, confusion, irritation, etc.
- **Undesired effect**: Drugs that affect the nigrostriatal pathway in the brain have a higher incidence of extrapyramidal side effects
- **Undesired effect**: Drugs that affect the tuberoinfundibular pathway in the brain have a higher incidence of increased prolactin
Antidepressants

- Desired effect: increase serotonin, norepinephrine, and dopamine in order to improve mood symptoms
- Undesired effect: by increasing serotonin, it also can lead to GI upset and serotonin syndrome
- Undesired effect: by increasing norepinephrine, it also can lead to anxiety, jitteriness, and insomnia
- Undesired effect: by increasing dopamine, it also can lead to nausea, vomiting, headaches, drowsiness, dizziness

Medications for Dementia

- Desired effect: increase acetylcholine by inhibiting cholinesterase, which improves memory and cognition
- Desired effect: reduce glutamate’s overstimulation of the NMDA receptor, which can lead to impaired memory and cognition
- Undesired effect: by increasing acetylcholine, it also can lead to GI upset, bradycardia, and hypotension
- Undesired effect: by decreasing glutamate, it also can lead to confusion

Neurotransmitters

- Neurotransmitters
- Receptors
- Locations
- Beneficial Effects
- Adverse Effects
- Medications
Antipsychotics

In General:
- Most psychotropic drugs are lipophilic polycyclic amines
- Most act by binding to catecholamine- or indolamine- uptake binding sites, or release of other monoamines
- Lot of overlap, leads to beneficial effects, but also adverse effects

Antipsychotics

In General:
- Most are highly protein bound
- **ALL psychotropics (except lithium) are metabolized, at least partially, by CYP450 enzymes (DDIs)
- IM administration = faster onset, usually reserved for acute agitation (except LAIs)

Antidepressants

In General:
- Most psychotropic drugs are lipophilic polycyclic amines
- Most act by binding to catecholamine- or indolamine- uptake binding sites, or release of other monoamines
- Lot of overlap, leads to beneficial effects, but also adverse effects
Antipsychotics

In General:
- Two mainstays of treatment:
  - First generation antipsychotics (FGA, typical antipsychotics)
  - Second generation antipsychotics (SGA, atypical antipsychotics)
- FGA adverse effect: Extrapyramidal Symptoms
- SGA adverse effect: Metabolic Effects
- Initial selection is often based on adverse effect profile

Dopamine Related Pathway

<table>
<thead>
<tr>
<th>Tract</th>
<th>Effect When Blocking Specific Tract</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mesocortical (prefrontal cortex)</td>
<td>Worsening negative symptoms</td>
</tr>
<tr>
<td>Mesolimbic (basal ganglia)</td>
<td>Relief of positive symptoms</td>
</tr>
<tr>
<td>Nigrostriatal (substantia nigra)</td>
<td>Extrapyramidal Symptoms (EPS)</td>
</tr>
<tr>
<td>Tuberoinfundibular (hypothalamus)</td>
<td>Increased prolactin release</td>
</tr>
</tbody>
</table>

EPS
- Parkinsonism
- Akathisia
- Tardive Dyskinesias
- Rigidity
- Inability to sit or stand still
- Slowed movement
- Tremor at rest
- May be minor symptoms
Antipsychotics

FGA Adverse Effect Risk:
- Sedative effects: haloperidol and molindone lowest; chlorpromazine and thioridazine highest
- Anticholinergic effects: haloperidol lowest; chlorpromazine and thioridazine highest
- EPS: chlorpromazine and thioridazine lowest; haloperidol and fluphenazine highest
- Hypotension: haloperidol and pimozide lowest; chlorpromazine and thioridazine highest

Antipsychotics

Other FGA Adverse Effects to monitor:
- NMS (0.5-2.4% incidence rate)
- Cardiac effects (ECG changes including flattened T waves and QTc prolongation)
- Dermatologic (allergic rash, photosensitivity, skin color changes)

Antipsychotics

Other FGA Adverse Effects to monitor:
- Ophthalmologic (whitish-brown granular deposits; rare)
- Seizure risk (most agents lower seizure risk)
- Weight gain (may be less likely with haloperidol and loxapine)
- Hypothalamic Actions: impaired temperature regulation, amenorrhea, galactorrhea, gynecomastia
**Antipsychotics**

**SGA Adverse Effect Risk:**
- Dose Related EPS: quetiapine and clozapine lowest; risperidone and paliperidone highest
- Increased Prolactin: lurasidone and aripiprazole lowest; paliperidone and risperidone highest
- Weight gain: lurasidone, asenapine, ziprasidone and aripiprazole lowest; olanzapine and quetiapine highest
- Glucose Intolerance: aripiprazole, iloperidone, asenapine, lurasidone, ziprasidone lowest; clozapine and olanzapine highest

**Other SGA Adverse Effects to monitor:**
- EPS (0.5-1.5% for SGA vs 4-5% with FGA)
- Anticholinergic and sedative effects: clozapine, olanzapine, quetiapine highest risk
- Dose-dependent lowering of seizure threshold: clozapine highest risk

**Antipsychotics**

**Other SGA Adverse Effects to monitor:**
- Increased LFTs: olanzapine and quetiapine highest risk
- Lipid abnormalities: clozapine, olanzapine highest risk
- QTc prolongation (class effect; ziprasidone may be highest risk)
- Orthostatic hypotension: clozapine and quetiapine highest risk
Antipsychotics

Clozapine monitoring:
- Weekly for the first 6 months
- Every 2 weeks for the following 6 months
- Every 4 weeks for the following 12 months
- WBC ≥ 3500 mm$^3$ and ANC ≥ 2000 mm$^3$

Antidepressants

In General
- Keep in mind antidepressants may take a long time to work for some patients (up to 12 weeks in some)
- Typically will see somatic symptoms improve before mood symptoms
- BBW for increased suicide in pts ≤ 24 yo
Antidepressants

In General
- Two mainstays of treatment:
  - Selective serotonin reuptake inhibitors (SSRIs)
  - Serotonin-norepinephrine reuptake inhibitors (SNRIs)
- Some SSRIs carry other FDA-approved indications: Bulimia, GAD, MDD, OCD, Panic Disorder, PTSD, PMDD, SAD
- Some SNRIs carry other FDA-approved indications: Fibromyalgia, GAD, MDD, chronic musculoskeletal pain, diabetic neuropathy, Panic Disorder, SAD

Antidepressants

In General
- Other treatments used:
  - Adjunctive- Bupropion (inhibits NE and DA transporters)
  - Adjunctive- Mirtazapine (increases serotonin and NE; serotonin RA)
  - Tricyclic antidepressants- increases serotonin and NE by preventing their reuptake
  - Monoamine oxidase inhibitors (MAOIs)- inhibits the enzyme that breaks down monoamines (such as serotonin and NE)

Antidepressants

SSRI/SNRI Adverse Effects to monitor:
- Anxiety
- Insomnia or sedation (can cause both depending on the pt)
- GI (up to 30%; nausea, diarrhea, anorexia)
- Sexual dysfunction (up to 28%; bupropion may help)
- Serotonin Syndrome- higher risk with other drugs that ↑ serotonin
- QTc prolongation- Most common with citalopram
Antidepressants

TCA Adverse Effects to monitor:
- Common: sedation/anticholinergic effects, cardiac effects
- Weight gain (can cause both depending on the pt)
- Sexual dysfunction (up to 28%; bupropion may help)
- Overdose/toxicity: can be lethal, other (common) drugs increase plasma concentrations

Antidepressants

MAOI key points:
- More contraindications/warnings
- LOTS of DDIs
- Dietary and medication restrictions
- Adverse effects similar to SSRI/SNRIs (added risk of hypertensive crisis)

Medications for Dementia
Medications for Dementia

In General:
- Two mainstays of therapy:
  - Cholinesterase inhibitors: inhibit the enzyme that breaks down acetylcholine.
  - NMDA Antagonist: slows the stimulation of NMDA receptor by glutamate.
- Not a cure, only slows the progression.
- May or may not be effective, depending on the patient.
- Titrations required for all.

Medications for Dementia

Key points for Cholinesterase inhibitors:
- N/V/D are a big adverse effect. May administer with food to help tolerability.
- Greater functional improvement seen with higher doses, but it increases the risk of AE.
- Also monitor for increased risk of GI bleed, bradycardia, insomnia and weight loss.
- If no efficacy seen at 3 months of max dose, attempt a switch.

Medications for Dementia

Key points for NMDA Antagonist:
- Main AE: dizziness, headache, hallucinations, insomnia, confusion, constipation.
- Only approved for moderate to severe Alzheimer’s Disease.
- Available in IR and XR forms.
- Must renally adjust for CrCl <30 ml/min.
Guidelines

- Schizophrenia: Four practice guidelines
- Depression: Three practice guidelines
- Dementia: Five practice guidelines
Guidelines

International Psychopharmacology Algorithm Project

SGA → SGA → Clozapine → Clozapine Augmentation, SGA

Guidelines

Depression Treatment Guidelines

American Psychiatric Association

Texas Medication Algorithm Project

National Institute for Health and Clinical Excellence

Guidelines

American Psychiatric Association

SSRI, SNRI, mirtazapine, bupropion

Switch or augment (antidepressant or atypical antipsychotic)

Switch or augment (TCA, lithium, or T3)

Treatment resistance: MOAI or ECT
Guidelines

Texas Medication Algorithm Project

SSRI, SNRI, bupropion, mirtazapine
Switch or augment (antidepressant, buspirone or T3)
Augment: TCA (+/- lithium) or MAOI

Treatment resistance: Augment with lamotrigine, dopamine agonist, risperidone, or olanzapine

Guidelines

National Institute for Health and Clinical Excellence

SSRI
SNRI, TCA
Augment: lithium, aripiprazole, olanzapine, quetiapine, risperidone, or mirtazapine

Treatment resistance: MAOI

Guidelines

Dementia Treatment Guidelines

American Psychiatric Association
National Institute for Health and Clinical Excellence
American College of Physicians
American Academy of Family Physicians
World Federation of Societies of Biological Psychiatry
British Association for Psychopharmacology
Guidelines

American Psychiatric Association

“Cholinesterase inhibitors for mild to moderate Alzheimer’s Disease, and may be helpful in severe Alzheimer’s Disease.
Memantine monotherapy or combination can be used in moderate to severe Alzheimer’s Disease.”

Guidelines

National Institute for Health and Clinical Excellence

• First line: cholinesterase inhibitors for mild to moderate Alzheimer’s Disease
• Second Line: Memantine is a possible treatment for patients who cannot tolerate the cholinesterase inhibitors

Guidelines

American College of Physicians/ American Academy of Family Physicians

“Clinicians should base the decision to initiate a trial of a cholinesterase inhibitor or memantine on individualized assessment.”
Guidelines

World Federation of Societies of Biological Psychiatry

"Combination therapy with a cholinesterase inhibitor and memantine has been shown to be beneficial."

Guidelines

British Association for Psychopharmacology

"Cholinesterase inhibitors for mild to moderate Alzheimer’s Disease. Memantine is effective in moderate to severe dementia (monotherapy and in combination)."

Guidelines

Neurotransmitters

Receptors

Locations

Beneficial

Adverse

Effects

Medications

Treatment Guidelines
Conclusion

References


Questions?