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Pediatric Psychopharmacology: Understanding Receptor Targets to Identify Medications That May Work Best for Children and Teens

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Speaker Disclosure

- We have no conflicts of interest to disclose.
- We will be discussing off label uses of psychiatric medications in the pediatric population.

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Learning Objectives:

- Describe monoamines and how these neurotransmitters are implicated in the development of psychopathology and are therefore often regulated by psychiatric medication.
- Identify receptors that are bound by different psychiatric medications at different serum concentrations.

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Learning Objectives:

- Recognize the interaction between neurotransmitters, receptors, and psychiatric medications to create therapeutic and other effects in the brain and body.
- Recognize that first-line treatments for mental health concerns may bind different receptors than secondary treatments, making some first-line treatments ineffective or poorly tolerated by certain individuals and these poor responders may experience better outcomes with second-line or adjunctive therapies.

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Neurotransmitter (NRTs) Brief Review:

- NRTs are chemical messengers transmitted
  - From neuron to neuron
  - From neuron to muscle cell
  - From neuron to gland cell
- Hence, NRTs are involved in many physiological functions throughout the body

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Types of NRTs: Monoamines

- Derived from aromatic amino acids (tyrosine, tryptophan, phenylalanine)
- Serotonin (5HT), dopamine (DA), norepinephrine (NE), melatonin and histamine
- Possess reuptake transporters
- HIGHLIGHTED NRTs WILL BE OUR PRIMARY FOCUS TODAY

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Types of NRTs: Other

- Cholinergic
  - Acetylcholine
- Amino Acids
  - GABA, glycine, glutamate, aspartate
- Primary peptides
  - ACTH, GH, Oxytocin, Vasopressin, TSH, Prolactin

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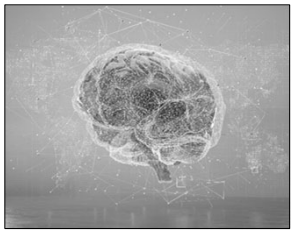
Monoamine Receptor Hypothesis



- Decades of research implicate monoamine neurotransmitter pathway involvement in psychiatric disorders
- Targeting receptor pathways for 5HT, DA, and NE has led to many of the psychopharmacologic treatments used today

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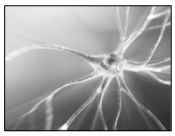
Monoamine Receptors: Serotonin (5HT)

- Tryptamine-derived NRTs
- Neurons project widely throughout the CNS from the raphe nucleus
  - Frontal cortex: Mood
  - Basal ganglia: Movement
  - Limbic area: Anxiety and panic
  - Hypothalamus: Appetite and eating behavior



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Monoamine Receptors: Serotonergic Receptors

- $5HT_1$ Family:
  - Present in high concentrations across many areas of the brain
  - Presynaptic and postsynaptic activity
  - Involved in mood/emotion, anxiety, cognition/integrative functions
- $5HT_2$ Family:
  - Prominently expressed in the brain (emotion, regulation of motor behavior)
  - Creates multiple peripheral effects (vascular and non-vascular smooth muscle, platelets)

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Monoamine Receptors: Serotonergic Receptors

- $5HT_3$ Family:
  - CNS (anxiety, cognition)
  - Brainstem (emetic center)
  - Spinal cord (pain)
  - Periphery (gut function)
- $5HT_4$ Family:
  - CNS (slow excitatory, learning and memory)
  - Periphery (gut motility)
- $5HT_5$ Family:
  - CNS (cerebellar function)

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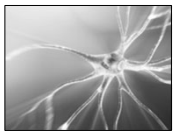
Monoamine Receptors: Dopamine (DA)

- Catecholamine-derived NRTs
- Mesolimbic Projections
  - Associated with reward behaviors & addiction
  - Excess DA = (+) symptoms of schizophrenia, aggression
- Mesocortical Projections
  - Associated with cognition & motivation
  - DA deficiency = (-) symptoms and cognitive changes of schizophrenia



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Monoamine Receptors: Dopamine (DA)

- Catecholamine-derived NRTs continued
- Nigrostriatal Projections
  - DA deficiency = Parkinsonian symptoms, akathisia, dystonia
  - DA excess = Chorea, dyskinesia, tics
- Tuberoinfundibular Pathway
  - Originates in the hypothalamus and regulates pituitary function
  - DA blockade = elevated prolactin ---> galactorrhea, amenorrhea, sexual dysfunction

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Monoamine Receptors: Dopaminergic Receptors

- D1: Locomotion, learning, attention, impulse control, sleep
- D2: Locomotion, learning, attention, sleep
- D3: Locomotion, cognition, attention, impulse control, sleep, regulation of food intake
- D4: Cognition, impulse control, attention, sleep
- D5: Cognition, attention, decision making, motor learning

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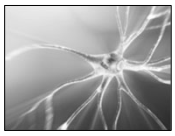
Monoamine Receptors: Norepinephrine (NE)

- Catecholamine-derived NRTs
- Locus Ceruleus Projections
  - Reach far and wide
  - Frontal cortex: Mood
  - Prefrontal cortex: Attention
  - Limbic effects: Emotions, energy/fatigue
  - Cerebellum: Balance, motor movements, tremor
  - Peripheral nervous system: CV and sympathetic effects



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Monoamine Receptors: Noradrenergic Receptors

- NE Receptors
- Alpha-1
  - Primarily postsynaptic
- Alpha-2
  - Only presynaptic NE receptor
  - Postsynaptic receptors in frontal cortex associated with cognition and focus

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Monoamine Receptors: Noradrenergic Receptors

- NE Receptors
- Beta-1
  - Frontal cortex (mood modulation)
  - Most antidepressants down-regulate these receptors
  - Agonists used in PTSD (help regulate emotional memory)
- Beta-2
  - Predominantly in airway and smooth muscle
- Beta-3
  - Located in brown fat (lipolysis and thermoregulation)

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Psychotropic Medications: Choosing a Therapy

- Receptors inhabit brain and body
- Creating potential therapeutic effects
- Creating potential side effects/adverse effects
- Using case examples, we will look at:
  - SSRIs (Sertraline, Fluoxetine, Escitalopram)
  - Stimulants (Amphetamine and Methylphenidate Classes)
  - NRIs (Viloxazine, Atomoxetine)
  - NDRI (Bupropion)
  - 2nd Generation Antipsychotics (Risperidone, Aripiprazole)
  - Alpha-2 Agonists (Clonidine, Guanfacine)

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Receptor Binding: Medications and Their Affinities

- Selective = has affinity for the intended receptor target that is many times greater than for the next target
- Binding affinity for a target ≠ drug's intrinsic action on the target
- Relative receptor binding affinity and whether there is full or partial agonism/antagonism helps us to understand the pharmacology of different drugs in a therapeutic class
- For example, atypical antipsychotic medication aripiprazole is a partial agonist at D_2 greatly reducing risk for EPS

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Dose Dependent Receptor Binding:

- Depression Medications and Sleep
- Somnolence: trazodone > mirtazapine > escitalopram > sertraline > placebo > bupropion
- Mirtazapine
  - Prescribed off label at low doses for sleep
  - Sleep effects attenuated at higher doses due to increased 5HT and NE release
- Trazodone
  - Dose dependent effects on sleep architecture

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Patient Management:

Case 1: Bree
Case 2: Miguel
Case 3: Carl

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Case #1: Bree

- 16 y.o. non-binary adolescent with two-year history of depression and anxiety
- Seeing DBT therapist weekly
- Grandmother brings them in for follow up concerned B is expressing "I want to end it all"
- Endorses: Poor focus, low energy, anhedonia, being more isolative, sleeping all the time, weight gain due to quitting swim team
- Stressors: Behind in school, conflict with family

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Case #1: Bree, Psychotropic Trials

- Failed fluoxetine early 2022
  - Somnolence
  - Persistent daily headaches
- Current regimen sertraline 150 mg daily
  - Managing mood dysphoria well previous 6 months
  - No longer having daily panic episodes
  - Over time can get decreased response or emotional flattening, cognitive slowing, apathy

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Case #1: Bree, Where do we go from here?

- Complete safety planning
- Option 1: Increase SSRI dose
  - Max daily dose 200 mg
- Option 2: Change to another SSRI
  - Has not tried escitalopram
- Option 3: Try a different medication class
  - SNRI
  - SGA
  - NDRI

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Case #1: Bree, Where do we go from here?

- After discussion of options, risk vs. benefit, etc.
- Add on bupropion XL
  - Norepinephrine and Dopamine Reuptake Inhibitor (NDRI)
  - Well tolerated
  - Quick response
  - Behavioral activation/mild stimulant like effect for amotivation
  - Appetite suppression, contraindicated in eating disorders
  - Can reduce SSRI induced sexual dysfunction
  - Mitigates nicotine cravings

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Case #1: Bree, Where do we go from here?

- Bupropion dosing:
  - MDD 12 y.o. + (off label)
  - Formulations XL tab 150 mg and 300 mg
  - Start 150 mg PO qam
  - Increase to 300mg PO qam after 2 wks
  - Inpatient we titrate much faster
  - Seizure risk is 0.1% at 300 mg dose; 2% with 600 mg dose

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Case #1: Bree

- Sertraline is targeting. . .
- Inhibition of 5HT reuptake in the pre-synapse of the synaptic cleft
- High affinity for 5HT uptake transporters = blocks them
- Desensitizes 5HT receptors (especially 5HT-1A)
- Some ability to block DA reuptake
- Low affinity for NE uptake transporters

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Case #1: Bree

- Bupropion is targeting. . .
- Boosts DA and NE availability in the synapse
- Blocks DA and NE reuptake transporters
- Lacks therapeutic activity for anxiety/panic symptoms
- Can exacerbate psychosis and delirium related to dopaminergic activity

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Case #1: Bree

- Synergistic effect of sertraline & bupropion
- Combo targets all 3 monoamines
- "Well-Loft"

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Case #1: Bree

- Outcome at 4 weeks
- Motivation and focus are much improved, Bree is attending school daily and has caught up on academics
- Going out with friends again
- Continues with DBT therapist weekly
- Grandma is looking into family therapy to improve communication with Bree

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Case #2: Miguel

- Miguel is a 10 y. o. male
- Diagnosed with ADHD at age 6 years
- Parents have been in behavioral management classes and Miguel completed social skills counseling in the past
- Last month at follow up visit parents shared he was having difficulty focusing and getting more fidgety at school
- Recently had a growth spurt (current weight = 45 kg)
- Methylphenidate ER was increased from 27 mg to 36 mg daily at that time

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Case #2: Miguel

- At one month follow up visit after stimulant dose increase family reports the following
  - Teachers indicate focus is better in the classroom
  - Reduced appetite with 1.5 kg weight loss
  - Difficulty with sleep initiation

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Case #2: Miguel, Where do we go from here?

- Option 1: Change stimulant
  - Well-managed on methylphenidate and tolerating up until now
  - Amphetamine-based stimulant = greater risk of appetite suppression
  - Family reluctant to switch for these reasons
- Option 2: Decrease stimulant dose and add an adjunct therapy
  - Decrease methylphenidate ER back to 27 mg daily dose
  - Add guanfacine ER
  - Alpha-2 agonist FDA approved as 2nd line ADHD treatment for children 6 y. o. and older

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Case #2: Miguel, Where do we go from here?

- Add guanfacine ER
  - Weight-based dosing
  - There is short-acting guanfacine, needs to be dosed BID
  - For 6-17 y. o. (41.5-49.5 kg), start 1 mg PO daily; increase by 1 mg/day every week until therapeutic effect achieved
  - Dosing parameters for our patient state target of 3-5 mg/day; in practice no increased benefit above 4 mg/day, only increased risk for side effects

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Case #2: Miguel, Where do we go from here?

- Methylphenidate is targeting . . .
  - Presynaptic neurons DA and NE reuptake blockade
  - Primarily effecting vigilance functions
  - Less impact on response inhibition, interference control, or other executive functions
- Guanfacine is targeting . . .
  - Selective Alpha-2 adrenergic agonist
  - Improves working memory, response inhibition, and other cognitive control functions (attention/learning)

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Case #2: Miguel, Where do we go from here?

- Option 3: Trial a non-stimulant viloxazine (Qelbree), an FDA approved 2nd line agent for ADHD in children 6 y. o. and older
- Targets . . .
  - Selectively inhibits NE reuptake
  - Also 5HT potentiation; originally marketed as an anti-depressant
  - Good tolerability/safety profile
  - Early onset effects
  - Compared with atomoxetine, another NRI, which takes several weeks to see effects, has BBW for SI, and risk for liver injury

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Case #2: Miguel, Where do we go from here?

- Viloxazine: ER caps 100 mg, 150 mg, and 200 mg
  - Dosing is age and weight dependent
  - For our patient, 6-11 y. o., dose 100-400 mg daily; start 100 mg PO daily, may increase by 100 mg/day every week
  - 12 y. o. and older, dose 200-400 mg daily

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Clonidine vs Guanfacine

- Similarities
  - Both are FDA approved in extended-release forms as 2nd line treatments or adjunctive therapies for ADHD management
  - Similar mechanism = postsynaptic agonism in the prefrontal cortex
  - Enhanced NE transmission and regulation of attention, thought, and working memory

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Clonidine vs Guanfacine: Differences

- Clonidine
  - Metabolized via CYP2D6
  - Excreted renally and hepatically
  - Used frequently by our team in inpatient setting due to higher calming effects
- Guanfacine
  - Metabolized via CYP3A4
  - Excreted renally
  - 10x less potent than clonidine, reduced CV side effects
  - Higher specificity for alpha-2A receptors, less risk for sedation/anti-cholinergic effects

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Case #3: Carl

- Carl is a 12 y. o. male, diagnosed with ASD at age 3 years
- Limited verbal communication and moderate cognitive impairment
- Had 2 years of ABA training in the past (from age 3-5)
- Continues to engage in self-injury (headbanging) when frustrated and can become aggressive with caretakers

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Case #3: Carl

- Previous psychotropic trial: Risperidone
  - Discontinued due to weight gain, increased LFTs, and gynecomastia
- Current regimen: Aripiprazole 15 mg at bedtime
  - Effective for target behaviors
  - Concern for side effects:
    - Weight gain (+10% body wt.)
    - Elevated HbA1c (6.0%)
    - Hypertriglyceridemia (150 mg/dL)

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FDA Approved SGAs for Use in Pediatric Patients with ASD

- Risperidone
  - Approved for treatment of irritability in children with ASD from age 5-16 years. Max dose: children 3 mg/day, adolescents 6 mg/day
- Aripiprazole
  - Approved for the same symptoms in children with ASD from age 6-17 years. Max dose: 30 mg/day
- Both work by binding D2 receptors and serotonin receptors
  - 5HT binds to 5HT-receptors on DA neurons, inhibits DA release
  - Blocking 5HT-receptors, DA release NOT inhibited

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FDA Approved SGAs for Use in Pediatric Patients with ASD

- Monitoring patients for safe dosing and side effects
  - Due to activity at multiple receptors (H1, 5HT-2A, 5HT-2C, 5HT-6, D2, alpha-1, M3)
  - Metabolic side effects (risperidone > aripiprazole)
  - Increased appetite and weight gain
  - Elevated blood glucose/dyslipidemia
  - Extrapyramidal symptoms
  - Cardiovascular effects (tachycardia, hypotension, QT interval alterations)
  - Hyperprolactinemia/gynecomastia

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Case #3: Carl, Where do we go from here?

- Option 1: Change to yet another anti-psychotic
  - So far this med class has been effective for Carl
  - Compared to other SGAs, aripiprazole = lower risk for metabolic side effects
- Option 2: Decrease aripiprazole dose and add an Alpha-2 agonist
  - Aripiprazole target = D2 receptor partial agonist
  - Competes with endogenous DA (modulation of DA receptor, not blockade)
  - Strong 5HT-7 antagonist = improves mood, used for augmentation in depression
  - Strong 5HT2C agonist = less wt gain compared to other atypicals

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Case #3: Carl, Where do we go from here?

- Option 2 (cont): Add alpha 2-agonist = clonidine
  - Target Review . . .
    - Postsynaptic alpha-2 agonist stimulation
    - Modulates subcortical activity in the prefrontal cortex
    - Regulating emotions, attentions, and behaviors
    - Reducing hyperactivity, impulsiveness, and distractibility

  - Dosing
    - Weight dependent
    - Comes in a patch for around the clock coverage
    - Start dose: 0.025-0.05 mg
    - Max dose: 0.2-0.4 mg/day

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