Orientation for New Child and Adolescent Psychiatry Residents: Module Four – Pediatric Psychopharmacology

Objective:
To discuss basic principles of psychopharmacology in children and adolescents.
Pharmacokinetics: handling and disposition of drugs within the body
(what the body does to a drug)

Pharmacodynamics: biochemical and physiologic effects of drugs at their active site
(what a drug does to the body)
Review of Pharmacokinetic Principles
Pharmacokinetics includes:

- Absorption AND Distribution
  …determine speed of onset of drug effect
- Metabolism AND Excretion
  …terminate the drug action by removing it from the body
A Drug is a “Foreigner”

Once in the bloodstream the drug is…
- Diluted in the plasma
- Protein bound

Then…
- Excreted by kidneys  \text{OR}
- Transformed by liver to more water soluble form excreted in urine, bile, or feces

The object is to eliminate the “foreigner” from the body but a sufficiently large dose can persist and produce a drug effect
First Order Kinetics are Linear

- Amount of drug in blood is proportional to amount of drug eliminated
- 1:1 relationship between changes in dosage and plasma concentration
- Most psychotropic drugs follow first order kinetics
- Fluoxetine, nefazodone, EtOH and others follow zero order kinetics: cannot predict plasma levels from dose changes
More Review

Plasma half life ($t_{\frac{1}{2}}$) = time required for plasma drug concentration to decrease by one-half

Steady state concentration ($C_{ss}$) = equilibrium between amount of drug ingested and amount of drug eliminated = no net change in plasma concentration

Steady state is reached in 5 half lives
Children and Adolescents
General Principles

- Genetics influence pharmacokinetics more than age.
- Lack of information on age related pharmacokinetic differences.
- Increased rates of metabolism and elimination in children and adolescents result in shorter half-lives and thus ...
- Larger, weight adjusted doses are needed to achieve blood levels comparable to adults.
Absorption
General Principles

- Oral drugs absorbed in stomach or small intestine
- pH and gastric emptying time affect absorption
- Once absorbed, the drug then enters the portal circulation (liver)
- This first pass effect results in hepatic metabolism so only a fraction of the absorbed drug enters the systemic circulation
Effects of Young Age

- Not much data

- Theoretically…
  - Less acidic stomachs may cause slower absorption of weakly acidic drugs eg. anticonvulsants, amphetamines, antidepressants
  - Shorter intestinal transit time may decrease uptake of slow release preparations

- Absorption may be more rapid for some drugs
Distribution

\[ Cp = \frac{D}{Vd} \]

- \( Cp \): plasma concentration
- \( D \): absorbed drug
- \( Vd \): Volume of distribution
Total Body Water/ Extracellular Water

- Extracellular water decreases with age (relative to body weight)
- More extracellular water – more volume in which to distribute water soluble drugs (eg. lithium)…
- What would you expect to be the effect on plasma concentration in younger children?
- Lower plasma concentrations
Amount of Adipose Tissue

- Children have less adipose tissue than adults (in general)
- Less body fat – less volume of distribution for **lipophilic drugs** (eg. neuroleptics, antidepressants)...

What would you expect to be the effect on plasma concentration in younger children?
- Higher plasma concentration in children

**BUT**

- Lower plasma concentration has been observed!!! (increased metabolism??)
Metabolism
General Principles

- Most drugs lipophilic – must be metabolized to hydrophilic for excretion
- Biotransformation in liver via cytochrome P450 system
- Metabolized via Phase I metabolic reactions
  - Hydroxylation
  - Reduction
  - Hydrolysis
- Metabolites usually less toxic and active EXCEPT desipramine (from imipramine)
- Phase II reactions – conjugation usually via glucuronic acid
- Occurs in organs other than liver - 3-hydroxybenzodiazepines rapidly cleared through kidney despite age
Cytochrome P450 System

- Cytochromes more efficient in childhood so drugs metabolized more quickly to less active forms than in adults
- Genetic factors – trump age?
  - 7-10% whites are slow metabolizers for 2D6
  - 1-3% whites slow metabolizers for 2C9
  - 18-23% Japanese slow metabolizers for 2C19
  - <0.5% whites slow metabolizers for 2D6 and 2C19
Inhibitors and Inducers

- **Inhibition of CYPs** – more unmetabolized drug enters circulation – increased plasma concentration
  - Quick process – requires blocking pathway

- **Induction of CYPs** – more drug is metabolized – decreased plasma concentration
  - Takes 3-10 days to start or 5-12 days to stop due to need to synthesize, or stop synthesizing, more protein

- Consult database to predict interactions
Excretion

- Via kidney
- No significant age related differences
Review of Pharmacodynamics of Psychotropic Medications
Synaptic Neurotransmission

**Presynaptic**
- Membrane bound receptors
  - 2nd messenger response
- Membrane bound transporters
  - Pump NT back into cell

**Postsynaptic**
- Fast acting, class I (inotropic) receptors
  - Opens ion channels (Ca, Na, Cl, K)
- Slow acting, class II (G-Protein coupled) receptors
  - G-Protein regulation of ion channels and 2nd messengers
Major Neurotransmitters

- Serotonin
- Dopamine
- Norepinephrine
- Acetylcholine
- GABA
- Glutamate

Figure 76.3. Serotonergic neurotransmission.
Figure 76.4. Dopaminergic neurotransmission.
Figure 76.5. Noradrenergic neurotransmission.
Figure 76.6. Cholinergic neurotransmission.
Cell bodies:
- Cortex
- Thalamus
- Striatum
- Septum
- Hippocampus
- Cerebellum
- Substantia nigra
- Spinal chord

Glutamate → GAD → GABA

(2) = GABA<sub>δ</sub> receptor
Agonist:
- Baclofen

(3) = GABA transporter

(1) = GABA<sub>α</sub> receptor
Modulators:
- Benzodiazepines
- Channel: Barbiturates
- Ethanol

Nucleus

Figure 76.7. GABAergic neurotransmission.
Figure 76.8. Glutamatergic neurotransmission.
Seven Principles of Clinical Psychopharmacology in the Pediatric Population
One: Consider the Role of Development on Pharmacodynamics

- CNS undergoes change during childhood
- Changes in NT (neurotransmitter) systems influence therapeutic response and side effects
- Limited information on these changes
Age related effects on NT systems

- Dopamine: Adolescents have higher risk of dystonic reactions with neuroleptics compared to adults
- Serotonin: Prepubertal children are at higher risk for activation with SSRIs
- Norepinephrine: TCAs less effective in children than adults due to later maturation of adrenergic system

Age effects on these major NT systems are apparent but what are they? What other ways do they affect pharmacodynamics?
Promotion of Product Study in Pediatric Populations to Increase Knowledge

- Food and Drug Modernization Act passed in 1997
- 6 additional months of market exclusivity for products evaluated in children
- 1999: FDA requires Pharma to evaluate products in children likely to be used in children
- NIH funds committed to research networks established to conduct multi-site studies in children (eg. CAPTN, RUPP)
Two: Limits of the DSMIV in Children

- Psychiatric disorders in children are heterogeneous
- Comorbidity is the norm
- Differences in clinical response
Three: Importance of Thorough Assessment

- Multiple informants
- Identify target symptoms
Four: Assess for Adverse Effects

- Open ended inquiry
- PAIRED WITH
- Drug specific side effect questions
- AND
- Monitoring parameters specific to drug
Five: Involve the Family

- Involve family and child (as developmentally appropriate) in decision making process
- Address the meaning to the family and child of taking a medication
Six: Integrate Other Modalities

Eg. Psychotherapy, speech therapy, etc.
Seven: Ground Treatment Plans on Evidence

Class A: good empiric support based on consistently positive results in Randomly Controlled Trials (RCTs)

Class B: fair empiric support showing positive but inconsistent results in RCTs or positive results from small sample trials

Class C: minimal empiric support based on accumulated clinical experience from case reports and open-label studies
Evidence Examples

A level
- Stimulants for ADHD
- Fluvoxamine for OCD, anxiety
- Sertraline for OCD
- Fluoxetine for depression
- Haloperidol, pimozide for tics

B level
- Sertraline for depression
- Clonidine for tics
- Guanfacine for ADHD
- Fluoxetine for OCD
End of Module Four

Quiz Instructions:
Print the quiz
Complete the quiz
Turn the quiz in to Dorothy Winkler

Quiz Question One

For most psychotropic medications, steady state is reached in _____ half lives.

a. 3
b. 5
c. 7
d. 9
e. Cannot be determined
Quiz Question Two

In general, which of the following is NOT true about age effects on pharmacokinetics?

a. Shorter intestinal transit time in children may decrease uptake of slow release preparations.

b. More extracellular water in children results in lower plasma concentrations of lithium than in adults at the same weight adjusted dose.

c. Less adipose tissue in children should result in higher plasma concentrations of most psychotropic medications compared to adults but the opposite has been observed.

d. More efficient cytochrome action results in more rapid metabolism of drugs in children compared to adults except perhaps in genetic slow metabolizers.

e. Even in adults with adequate kidney function, excretion of drugs is significantly slower than in children.
Quiz Question Three

Larger, weight adjusted doses of medications are needed in children to achieve blood levels comparable to adults.

a. True
b. False
Quiz Question Four

According to Lewis, which methods of synaptic transmission are affected by venlafaxine?

a. Presynaptic 5HT receptors; presynaptic 5HT transporters
b. Postsynaptic inotropic 5HT receptors; postsynaptic G-protein coupled DA receptors
c. Presynaptic 5HT receptors; Postsynaptic G-protein coupled NE receptors
d. Presynaptic 5HT transporters; presynaptic NE transporters
e. Postsynaptic inotropic NE receptors; Postsynaptic G-protein coupled NE receptors
Quiz Question Five

Which of the following statements is NOT true about NT systems in the pediatric population?

a. Adolescents have a higher risk of dystonic reactions with neuroleptics compared to adults.
b. Prepubertal children are at higher risk than adults for activation with SSRIs.
c. TCAs are less effective in children than in adults due to later maturation of adrenergic system.
d. The effects of development on NT systems are well characterized after many years of study.
Quiz Question Six

Which of the following are TRUE regarding psychopharmacologic principles in the pediatric population?

a. Clinical response to medications in children differs because of diagnostic heterogeneity.
b. Thorough assessment using multiple informants is essential in establishing appropriate target symptoms in children.
c. Assessment for side effects in children should include both open ended inquiry and drug specific questions for thoroughness.
d. Both the family and the child (as developmentally appropriate) should be involved in decisions regarding medications.
e. All of the above
Quiz Question Seven

Which of the following medications DO NOT have good empiric support based on consistently positive results in RCTs for the accompanying diagnoses in the pediatric population?

a. Fluvoxamine for OCD
b. Fluoxetine for depression
c. Fluoxetine for OCD
d. Stimulants for ADHD
e. Sertraline for OCD