PSYCHOPHARMACOLOGY OVERVIEW

I. Neurobiology

A. Neurotransmitters (For Each: Location in CNS, Precursors, Metabolic Products)

1. Dopamine
2. Norepinephrine
3. Serotonin
4. Acetylcholine
5. Gamma-amino-butyric acid

B. Type of Neurotransmitter Disorder Associated with

1. Schizophrenia
2. Mania
3. Depression
4. Anxiety
5. Dementia

C. Genetics and Transmission

1. Schizophrenia
2. Affective illness
3. Alcoholism
4. Dementia

D. Sleep

1. Stages and effect of drugs, disease, age on each stage
2. Disorders of sleep onset and sleep maintenance
   a. Types
   b. Mechanisms
   c. Diagnosis
   d. Treatments

3. REM
    a. Neurobiological mechanisms
    b. Effect of drugs, disease, age
    c. Association with dreams, affective illness

II. Neuroleptics
  A. Basic Pharmacology
    1. Structures of neuroleptics
      a. Phenothiazines
      b. Butyrophenones
      c. Thioxanthenes
      d. Indoles
    2. Parenteral preparations and long-acting preparations
    3. Relationship of dose to clinical response
    4. Relationship of blood levels to clinical response
    5. Relationship of receptor binding to clinical response
  B. Clinical Use of Neuroleptics
    1. High vs. low dose
      a. Differential efficacy
      b. Differential toxicity
    2. Rapid tranquilization
      a. Clinical indications
      b. Hazards

3. Percent of relapse on drug discontinuance
4. Comparative doses among different neuroleptic groups
    a. Therapeutic dose ranges
    b. Starting doses
    c. Maintenance doses

C. Side Effects
1. Sedation
    a. Mechanism
    b. Effect of age
    c. Differential toxicity production
2. Orthostatic hypotension
    a. Mechanism
    b. Effect of age
    c. Treatment
    d. Interactions with antihypertensives
3. Cardiac
    a. Cardiac rate
    b. Cardiac rhythm
4. Liver
    a. Obstructive jaundice
    b. Use in patients with liver disease
5. Bone marrow depression
    a. Time of occurrence
    b. Treatment
6. Anticholinergic effects, central and peripheral
    a. Symptoms and signs
    b. Time of onset

c. Differential production by neuroleptics

d. Diagnosis

e. Treatment

7. Extrapyramidal effects

a. Types

b. Time of onset

c. Gender difference

d. Age difference

e. Treatment of extra pyramidal reactions

i. Use of anticholinergics

ii. Use of amantadine

iii. Use of Benadryl (IM, IV)

f. Differential production by different neuroleptics

8. Tardive dyskinesia

a. Theoretical mechanism

b. Diagnosis

c. Treatment

9. Malignant neuroleptic syndrome

a. Diagnosis

b. Treatment

D. Special Uses of Neuroleptics

1. Gilles de la Tourette Syndrome

2. Dementia

E. Drug Interactions

III. Cyclic Antidepressants

A. Basic Pharmacology

1. Structural relationship of tertiary and secondary amines
2. Relationship of blood levels to clinical response
    a. Therapeutic window
3. Relationship of structure to neurotransmitter function
    a. Norepinephrine
    b. Serotonin
4. Theoretical mechanism of action
    a. Presynaptic re-uptake blockade
    b. Post-synaptic down regulation

B. Clinical Use of Cyclic Antidepressants

1. Starting dose
2. Therapeutic dose ranges
3. Maintenance dose
    a. Indications for maintenance theory
    b. Duration

C. Side Effects

1. Orthostatic hypotension
    a. Mechanism
    b. Effect of age, hypertension
    c. Differential toxicity
    d. Treatment
    e. Interaction with antihypertensives
2. Cardiac
    a. Cardiac rate
    b. Cardiac rhythm

c. Relationship of plasma levels to toxicity

d. Differential toxicity

3. Anticholinergic effects, central and peripheral

a. Symptoms and signs

b. Time of onset

c. Differential production

d. Diagnosis

e. Treatment

4. Sedation

a. Mechanism

b. Differential toxicity

5. Miscellaneous (signs and symptoms for each)

a. Weight gain

b. Sexual dysfunction

c. Skin rash

d. Seizures

e. Withdrawal reactions

D. Drug Interactions

IV. MAO Inhibitors

A. Basic Pharmacology

1. CNS production, location, function, metabolism

2. Types and substrates

3. Relationship of platelet MAO inhibition to clinical response

B. Clinical Use

1. Clinical indications

2. Clinical types, names, dose ranges

C. Side Effects

1. Hypotension

a. Mechanism

b. Effect of age

c. Treatment

d. Interactions and antihypertensives

2. Hypertension

a. Mechanism

b. Effect of age

c. Interactions with foods

d. Interactions with drugs

e. Treatment

3. Miscellaneous

a. Weight gain

b. Sexual dysfunction - types

c. Withdrawal reactions

D. Drug Interactions

V. Lithium

A. Basic Pharmacology

1. Pharmacokinetics

2. Hypothesized mechanisms of action

3. Relationship of plasma and cellular levels to clinical effect

B. Clinical Uses: Bipolar Illness, Unipolar, Impulsive, Labile Character Disorder, Violence

1. Acute treatment

a. Dose range

b. Therapeutic blood levels

2. Maintenance, prophylactic treatment

a. Dose range

b. Therapeutic blood levels

c. Duration (range) of treatment

C. Side Effects (Mechanisms, Symptoms, Diagnosis, Treatment)

a. Cardiovascular

b. Neurologic

c. Renal

d. Thyroid

e. Gastrointestinal

D. Drug Interactions

VI. ECT

A. Clinical Indications

B. Contraindications

C. Prognostic Factors

D. Technique

1. Pre-treatment workup

2. Anesthesia

3. Muscle relaxation

4. Technique of administration

E. Unilateral vs. Bilateral
   1. Efficacy
   2. Toxicity

F. Complications of Administration
   1. Acute
   2. Chronic, Cumulative

G. Physical Effects of Treatment
   1. CSF pressure
   2. Blood pressure
   3. Pulse rate
   4. Duration of seizure

H. Interaction with Drugs, Medical Illness

VII. Hypnotic Drugs

A. Types, Pharmacology, Dose Range, Drug Interactions
   1. Barbiturates
   2. Non-Barbiturate Hypnotics
   3. Benzodiazepines
   4. Neuroleptics
   5. Antidepressants
   6. Miscellaneous
      a. Antihistamines
      b. Chloral Hydrate

B. Clinical Use of Hypnotics
   1. Indications
   2. Contraindications

3. Duration of use
4. Choice of drug

C. Side Effects

1. Sedation
2. Disinhibition
3. Cognitive
4. Habituation
5. Disordered sleep
6. Withdrawal reactions

VIII. Miscellaneous

A. Medications Used in Medical Practice Associated with Psychiatric Syndromes (Types of Reactions, Toxic Drug Doses, Diagnosis, Treatment)

1. Diagnosis
2. Management
   a. Medical
   b. Emotional, psychiatric
   c. Pharmacological: acute illness

IX. Alcohol

A. Types of Disorders

1. Diagnosis
2. Symptoms, acute, chronic
3. Mechanism of production of symptoms

B. Treatment

1. Medical
2. Emotional, psychiatric
3. Pharmacological: acute, maintenance, prophylactic

X. Drug Abuse

A. Acute and Chronic Toxicity: Symptoms, Diagnosis, Treatment

1. Narcotics
2. Barbiturates
3. Amphetamines, stimulants
4. Hallucinogens
5. Marijuana, PCP, cocaine
6. Mixed toxicity

B. Synaptic Mechanisms of Drug Abuse

1. Intoxication
2. Drug agonists, antagonists

CLINICAL PHARMACOKINETICS

A. Factors affecting drug response

1. Bio availability of the drug - some generics may be poorly absorbed.
2. Absorption - concomitant meds e.g. Li decreases CPZ absorption.
3. Gut mucosal metabolizing enzymes - e.g. CPZ.
4. "First-pass" effect.
5. Route of administration.
6. Plasma protein binding - only "free" drug in equilibrium with tissue.
7. Blood-brain barrier (and other membrane transport).
8. Tissue sensitivity - includes paradoxical pharmacologic effects.
9. Drug metabolism - liver microsmal enzymes
   - -largely genetically determined - drug interactions
   - -age - ratio of parent compound to metabolites
10. Renal clearance - most important for lithium.
11. Assumption that the disorder under treatment is pharmacologically responsive to the drug.

B. Steady-state Blood Levels

when the rate of drug accumulation in plasma essentially equals the rate of elimination.

Time to steady-state depends on half-life (rate of elimination of a single dose).

Most psychotropics have relatively long half-lives and can be given once daily.

Exception - lithium. Variance in steady-state psychotropic blood levels at given doses in humans is high

Tricyclics - liver microsmal enzymes

CPZ - gut mucosal + liver enzymes

Lithium - renal clearance

Two basic complimentary methods are used to prescribe psychotropics (and the second is only available for a few drugs).

1. Titrate dose according to clinical response.
2. Get blood level into therapeutic range.

C. Clinical Use of Steady-state Blood Levels

1. Long lag to observable response
2. Suspected toxicity
3. Narrow therapeutic index
4. Evaluation of non-response, inadequate blood levels are common
5. Concept of "therapeutic window"
6. Blood-level/response relationship
7. Blood-level/side effect relationship
8. Draw blood levels before AM doses

CLINICAL PHARMACOKINETICS (cont'd)

D. Individual Drugs

1. CPZ - many metabolic pathways - 168 metabolites
   some active, some inactive
   radioreceptor assay
2. Nortriptyline - fairly good evidence for therapeutic window - 50-150 mg
3. Imipramine (+Desipramine) - direct relationship $\geq$ 180 mg
4. Amitriptyline - ?
5. Lithium - acute mania - direct
   maintenance - $\geq$ 0.6 meq/L

PSYCHOBIOLOGY OF SCHIZOPHRENIA

Genetic Studies Indicate Likely Inheritance

- increased concordance in monozygotic vs. dizygotic twins
- increased incidence in biologic vs. adoptive relatives of schizophrenic probands (Kety-Rosenthal-Wender Study)
- paternal 1/2 sibling vs. general population study underway

Dopamine Hypothesis

- all known antipsychotic drugs deplete (reserpine) or block dopamine
- drugs which facilitate dopamine may precipitate psychosis
- most studies show decreased platelet MAO in schizophrenics and relatives
- HVA studies (CSF) - no elevation
- post-mortem brains have elevated dopamine
- may be a selective hyperactivity in meso-limbic dopamine system

Transmethylation Hypothesis

- methylated amino acids (dimethyl-tryptophan) have potent hallucinogenic properties
- potent methyl acceptors (nicotinic a.) may be antipsychotic in some patients
- these ideas really have not been validated

Small Peptide Molecules as Psychotogens

- TRH can provoke exacerbation in schizophrenia

PSYCHOBIOLOGY OF SCHIZOPHRENIA (cont'd)

- des-tyr-γ-endorphin has been reported (inconsistently to be anti-psychotic)

- endorphin administration or measurement has not provided consistent effects
- opiate antagonists (naloxone) have been reported (inconsistently) antipsychotic
- abnormal endorphin in schizophrenic

CAT Scans, PET Scans + Smooth-Pursuit Eye Tracking

PSYCHOBIOLOGY OF DEPRESSION

Conclusions:

1) Pathophysiology of depression and mechanism of action of antidepressants are poorly understood.
2) Psychopharmacologic research has not resulted in major conceptual advances in antidepressant treatments.

Five Biologic Systems Which May Be Relevant To A Psychobiology Of Depression

1) Genetic inheritance

   Family, twin and linkage studies suggest that some forms of affective disorders may have an inherited component.

2) Biogenic amine nervous system

   Pharmacologic evidence of involvement in pathophysiology of affective disorders. Neuroanatomic and neurophysiologic evidence - deficiencies of simple NE or 5HT depletion hypotheses

   a) time to antidepressant effect
   b) amine precursors inconsistently antidepressant
   c) metabolite measures do not consistently reflect predicted deficits

   Complexity of interaction and regulation of these neurol systems requires more research into normal physiology. Recent emphasis on receptor studies: down-regulation of B-adrenergic receptors by several types of antidepressants in proper time may represent unifying mechanism.

   Methodologic problems of CNS amine studies in humans:

   a) no good animal model for affective disorders

b) problems of urine, CSF and neuro endocrine strategies

c) PET scans may offer better method

3) Neuroendrocrine function

Increased PAC function in depression is most robust lab abnormality

What does it mean?

Does it have diagnostic specificity?

Does it predict treatment response?

4) Electrolyte disturbances

Several observations suggest a role for altered electrolyte balance in affective disorders. Small shifts may be important.

Problem in lack of consistent reproducible findings to date

5) Endogenous opiates

May be involved in organism's normal mediation of pleasure or pain.

No consistent results so far from either measuring or administering them.

One problem is difficulty of assay.