ANTIPSYCHOTICS: A CLINICAL UPDATE

A. A Review and Update of Traditional Issues and New Approaches in Antipsychotic Use.

1. The major classes of antipsychotics including new agents such as propranolol and old ones such as reserpine.
2. The major therapeutic indications and actions of the antipsychotics. Are these drugs antischizophrenic or antipsychotic? Is the term major tranquilizer misleading?
3. Review of kinetic data and possible mechanisms of action as they relate to clinical usage.
4. Are some schizophrenic signs and symptoms selectively responsive to antipsychotics?
5. Some liabilities of treatment including akinesis and tardive dyskinesia. What are reasonable rules of thumb for antipsychotic usage given the risks?
6. The relationship of plasma levels to clinical response. Assessing the immediate future of plasma levels in antipsychotic treatment.
7. Predicting antipsychotic outcome from the initial subjective response. The importance of listening to the patient's complanits.
8. Some practical issues for the practitioner that keep arising:
   a. Maintenance treatment: A rational approach.
   b. IM Fluphenazine: Indications and risks. Conversion from p.o. dosage.
   c. Low versus high dose antipsychotic treatment.

B. The use of antipsychotics in the DSM III psychotic spectrum of illnesses will be discussed. This discussion will focus on guidelines for antipsychotic usage and the relationship to the DSM III.

ANTIPSYCHOTIC AGENTS

1) Diagnostic types in which antipsychotic agents are useful:

   a) Schizophrenia

      (1) altered affect, ambivalent feelings, autism, loose associations, concrete thinking

      (2) delusions, hallucinations, inability to perceive reality correctly, bizarre responses

      (3) intact sensorum in terms of memory, calculation, orientation

      (4) motor signs - posturing, stereotyped movements

      (5) previous episodes

      (6) no organic cause

   b) Mania - flight of ideas, euphoria, pressure of speech, logorrhea, irritability

   c) Organic brain syndrome with psychosis (confusion, etc.)

   d) Gilles de la Tourette's syndrome

   e) ? useful in depression

   f) Severe panic or agitation

   g) Incipient schizophrenia

   h) Paranoid states

2) Rationale:

   a) NE - DA Hypothesis

      (1) role of reserpine (depletes catecholamines)

      (2) role of antipsychotics (blocks catecholamines)

      (3) role of MAOI, tricyclics, L-Dopa, amphetamines (increases catecholamines)

b) Cholinergic-anticholinergic balance

c) Cholinergic-dopaminergic balance

d) Feedback mechanisms - increased HVA & DA with DA blockade

e) Denervation hypersensitivity (cause of tardive dyskinesias?)

3) Responsive Symptoms: (3/4 of patients respond)

a) Thought disorder

b) Affect blunting

c) Withdrawal

d) Autistic thinking

e) Delusions

f) Hostility

g) Resistiveness

4) Drugs Used:

a) Neuroleptics (antipsychotic drugs)

(1) Phenothiazines -

chlorpromazine (Thorazine) butapenazine (Repoise)

trifluoperazine (Stelazine)

thioridazine (Mellaril)

perphenazine (Trilafon)

fluphenazine (Prolixen)

(2) Thioxanthenes

thiothixene (Navane)

chlorprothixene (Taractan)

(3) Butyrophenones -

haloperidol (Haldol)

b) Reserpine (Serpasil)

c) Non-effective antipsychotics -

(1) promazine (Promazine)

(2) prochlorperazine (Compazine ?)

d) Ineffective drugs -

sedative hypnotics, antianxiety drugs, antidepressants, too low a dose of antipsychotic medication, non-compliance

5) Administration Issues:

a) Time course (1-2 months for maximum effectiveness) - Need to use high doses when acutely psychotic

b) Relapses occur when medications stop (early or late)

d) Different dosage forms -

(1) IM - use in resistant or agitated patients

(2) IM - Enanthate, Decanoate - used in patients who are non-comliers (Prolixen evanthate)

(3) p.o.

(4) IV - perphenazine, chlorpromazine

e) "Merry-go-Round" phenomena

f) Deterioration may occur on drug

g) No need to give more than one antipsychotic agent

h) Megadoses

i) Low doses in elderly

j) Stopping drug may lead to improvement

6) Choice of an antipsychotic agent:

a) Base selection on side effects

(1) anticholinergic (Thioridazine, Chlorpromazine)

(2) antidopaminergic-cholinergic (Haloperidol, Trifluroperazine)

(3) All drugs about the same effectiveness - except for dosages needed to obtain effects

(4) dosage needs to be adequate

(5) some individuals do better on one drug than another

7) Relative equivalent dosages:

Chlorpromazine 100 mg. - Perphenazine 10 mg. Chlorprothixine 10 mg.

Thioridazine 100 mg. - Fluphenazine 2 mg. Thiothixine 5 mg.

Trifluroperazine 5 mg. - Haloperidol 2 mg.

8) Administration of antipsychotic drugs:

a) Build up dose over 2 days to 2 weeks

b) Frequency of administration - can give q day

c) Monitoring of side effects (BP, pulse, EKG, etc.)

d) Dosage - adequate = 400-800 mg. or more chlorpromazine or equivalent of another drug

e) Side effect determines choice of drug

(1) hypotension, sedation and anticholinergic

(2) extrapyramidal

ANTICHOLINERGIC	IN-BETWEEN	CHOLINERGIC
Thioridazine	Thiothixine	Trifluorperazine
Chlorpromazine	Chlorprothixine	Butaperazine
	Perphenazine	Fluphenazine
		Haloperidol

9) Side effects: Common

a) Extrapyramidal - based on adrenergic-cholinergic balance

(1) dystonias - muscle spasms

(2) akathesias (restlessness may present as deterioration on drug)

(3) parkinsonian symptoms - akinesia, pill rolling tremor, mask-like facies, stiffness

(4) tardive dyskinesias - to be described

b) Cardiovascular

(1) hypotension (postural)

(2) tachycardia

c) Lethargy and drowsiness

d) Anticholinergic effects - dry mouth, loss of accomodation, constipation

e) Skin changes - pigmentary

f) Eye changes - lenticular opacities

g) Weight gain

10) Side effects: Rare

a) Hematologic - leucopenia, agranulocytosis

b) Hepatic - cholestatic jaundice (Mostly with chlorpromazine)

c) Endocrine - galactorrhea, amenorrhea, etc.

d) Seizures (greatest occurrence with chlorpromazine)

e) Impotence (with Thioridazine)

f) Allergic reaction (rashes, etc.)

g) Cardiac arrhythmias (with Thioridazine)

h) Retinitis pigmentosa (with Thioridazine)

11) Tardive dyskinesias:

a) Buccal -Facial-Lingual; extremities, trunk

b) Occurs in elderly, brain damaged, female

c) Often irreversible

d) Caused and suppressed by antipsychotics

e) Drug holiday reveals presence

f) Usually caused by chronic antipsychotic drug ingestion

g) Incidence up to 60-70% of geriatric patients on psychiatric units

h) Increase with dose and time or drug (3 months to 10 years)

12) Treatment of extrapyramidal side effects:

a) Parkinsonian Symptoms

(1) trihexyphenidyl (Artane) 2-8 mg/day

(2) benztropine (Cogentin) 1-6 mg/day

(3) diphenhydramine (Benadryl) 25-50 mg/day

b) Dystonias

(1) as above

(2) benztropine 1-2 mg IM

(3) diphenhydramine 25-50 mg IM or IV

c) Akathesias

(1) as per parkinsonian symptoms

d) Tardive dyskinesias

(1) no good treatment

(2) reserpine, deanol, increased antipsychotic drug dose

(3) DC antipsychotics when possible; give lowest dose possible

13) Administration of anticholinergics:

a) anticholinergics can be given prophylachtically

b) anticholinergics are best given after onset of symptoms

c) stop anticholinergics after 6 weeks due to 97% of patients developing tolerance to parkinsonian side effects

14) Treatment of:

a) Sedation

(1) decrease dose or change drug

(2) methylphenidate may alleviate sedation

(3) don't drive when drowsy

(4) usually passes in 1 week to 2 weeks

b) Hypotension

(1) have get up slowly (and move legs)

(2) decrease dose or change drug

(3) Ritalin decreases hypotension

(4) Mellaril and Thorazine most likely to cause hypotension

c) Skin changes

(1) Benadryl for allergic reaction

(2) sunscreen to prevent photosensitivity

(3) switch to another compound

15) Other considerations:

a) Danger of abuse

(1) not addicting

(2) safe in overdose (relatively)

b) Support of patient on antipsychotic medications

(1) in acute schizophrenia, see patient frequently (2-3 times/week or more) to offer support, monitor drug intake and side effects, evaluate whether the patient is improving, getting suicidal, etc. Utilize family to make sure patient takes medicine, etc. Hospitalize when patient cannot be controlled out of hospital

(2) as patient stabilizes, can be seen each month for 10 minutes

(3) use compassionate, reality-oriented approach with schizophrenics. Treat drugs as "psychic insulin".

(4) References:

Klein, D.F. and Davis, J.M. Diagnosis and drug treatment of psychiatric disorders. Williams & Wilkins Co., Baltimore, 1969.

Davis, J.M. Archives of General Psychiatry 13:552, 1965.

16) Contraindications:

a) Coma

b) History of hypersensitivity or agranulocytosis

c) Seizures

d) Pulmonary decompensation

17) Drug interactions:

a) Anesthetics - augments side effects of these drugs

b) Barbiturates and sedative hypnotics (augments effects of these drugs)--barbiturates lower antipsychotic drug levels

c) Guanethidine (blocks guanethidines)

d) Ehtanol - see anesthetics

e) Amphetamines, L-Dopa (antagonizes effects of these drugs and vice versa)

f) Increases antidepressant blood levels

18) Use of Reserpine:

a) Effective antipsychotic

b) 0.5 -2.0 mg/day = dose

c) Side effects serious - generally cholinergic and anti-adrenergic such as hypotension, nausea, vomiting, depression, lethargy

d) Doesn't cause tardive dyskinesias, may help tardive dyskinesias

TREATMENT OF THE SCHIZOPHRENIC PATIENT: PRACTICAL ISSUES

I. Need for Neuroleptics

A) Many studies have shown high incidence of relapse when neuroleptic drugs are withdrawn.

B) When comparing prevention of relapse between fluphenazine hydrochloride and fluphenazine decanoate over a one year period, there was no difference between the two forms.

C) Summarizing all the relapse data:

1) At least 40% of patients taken off neuroleptics relapse within 6 months.

2) Relapse less likely in patients hospitalized for more than 15 years.

3) Relapse less likely in patients continuing to take low doses of neuroleptics.

4) Relapse may inversely correlate with neuroleptic blood level.

II. Side Effects of Neuroleptics

A) All neuroleptics have essentially equivalent therapeutic efficacy; differ only in side effects.

B) Some neuroleptics may have unique features for some patients

III. Comparison of Neuroleptic Side Effects

A) Overview:

1) Low potency neuroleptics are high in sedation, hypo-

tension and anticholinergic symptoms, low in extra-pyramidal symptoms.

2) High potency neuroleptics are low in sedation, low in hypotension, low in anticholinergic symptoms, high in extra-pyramidal symptoms.

B) Sedation:

1) Can be used clinically for the most agitated patient.

2) Is worse in the elderly.

3) May persist the following day due to long half-life.

4) Tolerance develops after about 2 weeks.

C) Hypotension:

1) Due to blockade peripheral alpha adrenergic receptors.

2) Occurs in about 20% of patients receiving neuroleptics.

3) Incidence increases with age.

4) Particularly dangerous in the elderly at night.

5) Is made worse by the use of epinephrine.

6) Decreases in patients who are heavy cigarette smokers due to increase in hepatic metabolism.

D) Extra-pyramidal symptoms:

1) Occur in about 10% of all neuroleptic recipients.

2) Dose related.

3) More likely in patients with brain damage.

4) More likely with advancing age.

5) Acute dystonia; maximum risk 1-5 days.

6) Akathisia; maximum risk 5-60 days.

7) Parkinsonism; maximum risk 5-30 days.

E) Anticholinergic side effects:

1) Inverse correlation with potency.

2) Thioridazine > chlorpromazine > acetophenazine > perphenazine > fluphenazine > trifluperazine > haloperidol.

3) Equivalent doses of antiparkinson agents: amantadine 1-300 mg; benztropine 1-6 mg; biperiden 2-6 mg; trihexyphenidyl 5-15 mg; diphenhydramine 5-100 mg.

IV. Pharmacokinetics of Neuroleptics

A) Absorption

B) Distribution

C) Protein binding

D) Metabolism

V. Pharmacokinetics of Neuroleptics and Their Clinical Implications

A) Absorption:

1) 30-45 minute delay of oral dose effect.

2) Further delayed by anticholinergics and antacids.

B) Distribution:

1) Sequestered in lipidoidal tissue.

2) Long biological half-life.

3) Increase sequestering with age.

C) Protein binding:

1) Decrease of starvation, illness and age.

2) Competition with tricyclics for binding sites.

D) Pre-hepatic metabolism:

1) Chlorpromazine metabolism impaired with age.

2) Impaired with intestinal disease.

E) First pass effect:

1) IM doses at least twice as strong as oral.

2) Reduced by age, cardiovascular and hepatic disease.

3) Decreased by propanolol, cimetidine.

F) Hepatic metabolism:

1) Impaired by age, disease.

2) Neuroleptics without active metabolites are therefore clinically preferred.

3) Altered by other drugs.

G) Long elimination of half-life:

1) At least 5 days to eliminate 90% of neuroleptics.

2) At least 5 days to reach steady-state blood level.

3) At steady-state, drugs need to be given only once a day.

VI. Plasma levels of Neuroleptics in Chronic Schizophrenic Patients

A) 17-fold range in ratios of serum neuroleptic concentration.

B) Thioridazine and mesoridazine produce the highest serum neuroleptic concentration per unit dose.

C) Haloperidol and thiothixene produce lowest neuroleptic concentration.

D) Thus, the concept of "chlorpromazine equivalent doses" may be erroneous.

VII. Drug Interactions with Neuroleptics

A) Anticholinergics:

1) Delay absorption.

2) Alter metabolism and blood levels.

3) Increase anticholinergic toxicity.

B) Anticonvulsants:

1) Accelerate metabolism, decrease plasma levels, decrease clinical effect.

2) Neuroleptics decrease anticonvulsant effect.

C) Narcotic analgesics:

1) Increase sedation

2) Increase anticholinergic effect.

3) Increase respiratory depression.

D) Lithium:

1) Neurotoxicity.

2) Decrease neuroleptic levels (?).

E) Antidepressants:

1) Decrease metabolism, increase blood levels.

2) Increase sedation.

3) Increase hypotension.

4) Increase anticholinergic effects.

5) Decrease E.P.S.

6) Neuroleptic may displace tricyclic from protein binding site and increase effect.

F) Antacids, kaopectate, milk of magnesia:

1) Decrease absorption, delay onset, decrease clinical and toxic effect.

G) Propranolol, cimetidine:

1) Decrease first pass effect, increase clinical and toxic effect.

H) Coffee and tea:

1) Precipitates chlorpromazine, decreases absorption.

2) May increase metabolism.

I) Levodopa:

1) Exacerbation of psychosis.

2) Decrease effect of levodopa.

J) Antihypertensives:

1) Decrease antihypertensive effect of guanethidine, bethanidine, clonidine.

2) Increase haloperidol toxicity with methyldopa.

3) Increase orthostatic hypotension with thiazide diuretics.

K) Tobacco:

1) Decreases neuroleptic blood levels.

L) Alcohol:

1) Same as tobacco.

M) Benzodiazepines:

1) Increased sedation.

2) Decreased EPS.

3) Decreased TD.

4) Increased confusion in elderly.

N) Barbiturates, hypnotics:

1) Increase metabolism, decreases effect.

O) Insulin, orinase, etc.:

1) Chlorpromazine increases blood glucose; compromises insulin effect.

P) Coumadin:

1) Chlorpromazine and haloperidol decrease prothrombin time. Increase bleeding.

Q) Epinephrine, phenylephrine:

1) Hypotension.

2) Sedation, depression.

R) Monoamine oxidase inhibitors:

1) Increase sedation.

2) Increase hypotension.

S) Allopurinol:

1) Increased sedation.

T) Antihistamines:

1) Increased sedation.

2) Increased anticholinergic toxicity.

VIII. Summary of Guidelines for Prescribing Neuroleptics in Chronic Patients

A) Use only one drug.

B) Use low doses, reduce high doses.

C) Administer only once a day.

D) Administer on empty stomach, small amount of food, juice.

E) Attempt drug holiday at least once.

F) Maintenance anticholinergic usually unnecessary.

G) Avoid polypharmacy.

H) Discourage caffeine, tobacco.

CLINICAL USE OF ANTIPSYCHOTICS

Despite widespread clinical use for nearly thirty years, there is a striking dearth of quantitative pharmacological information about these compounds based on human studies.

A. Dose-Response Relationships

1. Dose response and blood level response relationships are poorly worked out.
2. Particularly for high potency antipsychotic drugs, the therapeutic index is very large.
3. Available data suggest that, "statistically speaking", the equivalient of 900 mgm of CPZ is optimal for "schizophrenia" (Davis et al, 1980).
4. Some patients require higher doses, but clinical indications for this are not clear. Pharmacokinetic factors may be important.
5. High doses produce somewhat more side effects - particularly extrapyramidal.
6. Virtually nothing is known about dose-response relationships for antipsychotic drug use in other disorders. Mania, delusional depression and schizo typal personalities generally require lower doses.
7. Recent studies by Snyder's group (Tune et al, 1980) suggest that antipsychotic blood levels as measured by radioreceptor assay (a measure of parent compound plus active metabolities) correlate with antipsychotic efficacy.

B. Efficacy

1. Many studies have established efficacy of antipsychotic drugs for acute (schizophreniform) psychoses.
2. All drugs are equally efficacious.
3. Course of improvement is variable and up to six weeks may be required.
4. Generally speaking "good-premorbid" "schizophrenics" benefit from both acute and maintenance drug treatment. Effects in chronic, process schizophrenics are more variable and should be evaluated on a case by case basis.
5. These medications are not selectively antischizophrenic - they are antipsychotic.

C. Selecting an Antipsychotic Drug

1. More potent drugs cause more acute extrapyramidal symptoms (dystonia, akathisia, parkinsonism) and? more tardive dyskinesia.
2. Less potent drugs cause more sedation and orthostatic hypotension.
3. Maximum daily dose of thioridizine is 800 mgm.
4. The patient's history of antipsychotic drug response should be taken into account.
5. Non-compliant patients may benefit from depot fluphenazine.

D. Initiating Therapy

1. Test dose
2. Drug history

3. Monitoring - target symptoms, side effects, vital signs
4. Prophylactic antiparkinson drugs
5. Selecting a final dose

E. Side Effects and Toxicity

1. Dystonia
2. Akathesia
3. Parkinsonism - catatonia
4. Neuroleptic malignant syndrome
5. Tardive dyskinesia