Psychosis, Neuroleptics

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Psychosis

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Neuroleptics (s. Antipsychotics, Major Tranquilizers)

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Psychosis

- grossly impaired cognitive or perceptual ability → inability to test reality → loss of contact with reality (deficits in ability to think, remember, communicate, respond emotionally, behave appropriately, perceive sensory stimuli correctly, and interpret reality).

• psychosis does not describe specific diagnosis.

Primary symptoms:

1) Hallucinations (may be auditory, vs. delirium – mostly very usual)

2) Delusions (persecutory delusions are most common)

3) disorganized patterns of thought and speech.

4) bizarre and inappropriate behavior.

Psychiatric illnesses - schizophrenic disorders (schizophrenia, brief psychotic disorder, delusional disorder, schizoaffective disorder, schizophriniform disorder).

Psychotic features may also be present in:

1) major affective disorders (depression, bipolar disorder)

2) autism

3) obsessive-compulsive disorder

4) delirium

5) dementia (often mimics negative symptoms of schizophrenia, esp. dementia with Lewy bodies)

6) medical / neurologic disorders - temporal lobe tumors / epilepsy!; tumors of limbic system, normal pressure hydrocephalus, variant Creutzfeldt-Jakob disease, Wilson's disease, porphyria, thyroid dysfunction, Wernicke-Korsakoff syndrome, cerebral vasculatitis, SLE, encaphalitis (esp. herpetic, HIV and opportunistic infections, variant Creutzfeldt-Jakob disease, neurosyphilis (general paresis), Huntington disease (> 75% patients initially present with psychiatric symptoms).

7) substance-related disorders (e.g. amphetamines, cocaine, anticholinergics, dopaminergics, alcohol, barbiturate withdrawal, phencyclidine, thyroid / anabolic use)

• progressively pursue medical / neurologic cause of psychosis in patients with no diagnosed psychiatric disease, particularly if there are unusual symptoms, altered consciousness, or concomitant medical or neurological signs.

– typically, patients with organic causes of psychosis have higher amount of insight into illness and are distressed by their symptoms.

– concomitant medical / neurological condition may cause exacerbation of present psychosis.

Childhood Psychoses can be differentiated into four major categories:

1. Autism

2. Childhood-onset pervasive developmental disorder

3. Childhood disintegrative disorder

4. Childhood schizophrenia.

Neuroleptics (s. Antipsychotics, Major Tranquilizers)

Atypical (2nd generation) neuroleptics - modesty greater efficacy + reduced adverse effects.

Mechanism of Action

- competitive inhibitors at variety of receptors.

Antipsychotic Effects depend on blocking of dopamine D3 receptors*.

Affinity at D3 receptors parallels clinical potency! *N.B. neuroleptics also bind to other D receptors (i.e. not selective for D3!)

– all neuroleptics block dopamine receptors in brain and in periphery.

α2-receptor (substance nagra = caudate, putamen) – adverse extrapyramidal features,

mesocortical tract (ventral tegmental area [VTA] in midbrain → ventral frontal cortex; mesolinic tract [VTA → limbic structures] – therapeutic antipsychotic features.

– actions of neuroleptics are antagonized by dopaminergic agents (e.g. amphetamines, L-dopa) – these agents exacerbate psychotic symptoms!

• newer “atypical” drugs exert their unique action through more selective D3 blockade and blockade of serotonergic 5-HT receptors.

• drugs vary in their potency, but no one drug is clinically more effective than another.

Chlorpromazine is prototypic low potency drug, but used infrequently because of high incidence of serious side effects.

• classification by chemical structure is of modest importance – because within each chemical group, different side chains have profound effects on potencies of drugs.

<table>
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<th>ChEq</th>
<th>Receptor Blocking Affinity</th>
<th>Solution</th>
<th>Extra-pyramidal</th>
<th>BP</th>
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<td>Piperazines</td>
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Psychos, Neuroleptics

Psy9 (1)
HALOPERIDOL
FLUPHENAZINE
LOXAPINE
RISPERIDONE
ZIPRASIDONE

4. Other uses
(a) ingested and disruptive behavior in nonpsychotic individuals (neuroleptics improve mood and behavior without producing excessive sedation).
(b) Tourette syndrome – Pimozide (the only approved indication for this drug).
Haloperidol
(c) chronic pain with severe anxiety (in combination with narcotic analgesics).
(d) intracerebral bocpaks – Chlorpromazine.
(e) neuroleptanesthesia – Droperidol (in combination with tentanyl).
(f) pruritus – Promethazine (antihistaminic action).

SIDE EFFECTS
- occur in practically all patients (significant in ≈ 80%):
1. Extrapyramidal side effects – due to D2 blockade in nigrostriatal pathway, see p. 205
2. Neuroleptic malignant syndrome – believed to be blockade of D2 receptors, see p. 205
3. Antinomocasine effects – due to M blockade – all neuroleptics (esp. Thiothixene, Chlorpromazine): loss of accommodation, dry mouth, sedation, confusion, GI & GU smooth muscle inhibition (constipation, urinary retention)**
*except risperidone, aripiprazole, ziprasidone
**E: butane. 
4. Orthostatic hypotension due to adrenergic blockade (esp. risperidone, clozapine)
5. Drowsiness, confusion (esp. in elderly, usually during first 2 weeks with low-potency, high-anticholinergic activity subclass) – due to H blockade.
6. Neuroleptics lower seizure threshold – can aggravate/ provoke epilepsy!!!

PHARMACOKINETICS
- almost all neuroleptics are available in oral forms.
- IM / IV forms of most typical neuroleptics are available.
- variable absorption after oral administration.
- readily pass into brain.
- metabolized by P450 system in liver.
- relatively long T1/2 allows once-daily dosing.
- depot forms available (slow release – up to 2-4 weeks by IM injection):
  1) HALOPERIDOL laconate
  2) FLUPHENAZINE decanoate and FLUPHENAZINE enanthate
  3) TRILUPIRANONOL
  4) RISPERIDONE (as long-acting injection that uses biodegradable polymers).

INDICATIONS
1. Antipsychotic (primarily schizophrenia; also mania, paranoid states, alcoholic hallucinosis, irritability in autism) – reduced hallucinations and agitation; calming effect and reduced spontaneous physical movement; improvement in insight, judgment, and logic is slower and more variable.
- neuroleptics do not depress intellectual function (!!!), and motor incoordination is minimal (vs. CNS depressants).
- antipsychotic effects take several weeks to occur.
- neuroleptics produce some tolerance but little physical dependence.
- ziprasidone has antidepressant properties.
- clozapine: inhalation powder 10 mg is FDA approved for acute treatment of agitation associated with schizophrenia or bipolar I disorder in adults.
- N: atypical neuroleptics increase mortality* of elderly patients with dementia-related psychosis
*most deaths are cardiovascular (e.g. heart failure, sudden death), or infectious (e.g. pneumonia)
2. Antiepileptic – CHLORPROMAZINE, PROCHLORAZINE
- all neuroleptics (except thioridazine) have antiepileptic effects – by blocking D2 receptors in chemonocceptor trigger zone of medulla.
3. Other uses:
(a) agitation and disruptive behavior in nonpsychotic individuals (neuroleptics improve mood and behavior without producing excessive sedation).
- Acute agitation of alcohol withdrawal may be aggravated by neuroleptics.
(b) use simple sedative, such as benzodiazepines.
(c) Haloperidol
(d) thiothixene
(e) chlorpromazine
(f) thioridazine
(g) ziprasidone
(h) quetiapine
(i) aripiprazole
(j) paliperidone
(k) lurasidone

*Chlorpromazine Equivalent – given patient responds similarly to 100 mg of chlorpromazine or 2 mg of haloperidol.
**Haloperidol (prototypic high potency drug) – drug of choice for acute psychosis!
***Clozapine (perhaps most effective antipsychotic agent) has similar and low affinity for D2 and D3 receptors, high affinity for D4.
****major active metabolite of risperidone and first oral agent allowing once-daily dosing; indicated for acute schizophrenia.
7. Neuroleptics depress hypothalamus → amenorrhea, galactorrhea*, infertility, impotence, increased appetite (weight gain), poikilothermia (body temperature varies with environment). *due to D₂ Blockade in pituitary (very rare for OLanzAPINE, QuetiAPINE).

8. Long QT syndrome (THiorIDAZINE, HaloperIDOL, MesorIDAZINE, OLANzapINE, RisperIDone, ZIprasIDone).

9. Hyperglycemia and dyslipidemia (major concern for all atypical antipsychotics).


11. Pigmentary retinopathy (THiorIDAZINE in doses > 800 mg, THioTHIXene).

12. Metabolites of phenothiazines can cause striking abnormal skin coloration (particularly in exposed areas).

13. Both classes (classic and atypical) have increased risk of death when used in elderly patients for dementia-related psychosis!

CHLorPROMAZINE - high side effect profile.

TRIFLUOPERAZINE - high side effect profile.

CLOzapINE - bone marrow suppression (potentially fatal agranulocytosis in 1-2% patients; H: mandatory weekly WBC monitoring!!), cardiovascular side effects, venous thromboembolism, weight gain; do not use with CARBAMAZEPINE!

RISPERIDone - cytochrome P450 effects.

OLanzAPINE - relatively high rate of sedation, weight gain.

QUetiAPINE - sleepiness, palpitations, cataracts (with prolonged use).

PIMOZIDE - do not use with stimulants.

ACUTE INTOXICATION

High therapeutic index - overdose is relatively safe!

1. Somnolence → coma
2. Cardiac arrhythmia, hypotension, hypothermia
3. SEizures (H: diazepam IV)
4. Extrapyramidal (dystonic) reactions (H: DiphENHyDRamine or BenZTROPINE).

BIBLIOGRAPHY for ch. “Psychiatry” → follow this LINK >>

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