Psychosis, Neuroleptics

Last updated: April 24, 2019

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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 – most often visual)
2) **DELUSIONS** (persecutory delusions are most common)
3) disorganized patterns of **thought** and **speech**.
4) bizarre and inappropriate **behavior**.

ETIOLOGY

Psychotic illnesses - **schizophrenic disorders** (schizophrenia, brief psychotic disorder, delusional disorder, schizoaffective disorder, schizophreniform 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 vasculitis, SLE, encephalitis (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, steroid / anabolic use)

- aggressively pursue medical / neurological 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 - modestly greater efficacy + reduced adverse effects.

MECHANISM OF ACTION

- competitive inhibitors at variety of receptors:

ANTIPSYCHOTIC EFFECTS depend on blocking of dopamine D_2 receptors*.

Affinity at D_2 receptors parallels clinical potency!

*N.B. neuroleptics also bind to other D receptors (i.e. not selective for D_2)!

- all neuroleptics block dopamine receptors in brain and in periphery:

  nigrostriatal tract (substantia nigra → caudate, putamen) – adverse extrapyramidal features;
  mesocortical tract (ventral tegmental area [VTA] in midbrain → frontal cortex), ***mesolimbic 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 D_2 blockade and blockade of serotonin 5-HT_2 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.

	Chl Eq (mg)*	Receptor Blocking Affinity					Sedation	Extra-pyramidal	BP↓
		D_2	5-HT_2	H_1	M	α_1			
PHENOTHIAZINES									
Alkylamines									
Chlorpromazine	100	+ + +	+ + +	+ + +	+ + +	+ + +	+ + +	+ +	+ + +
Prochlorperazine									
Piperidines									
Thioridazine	95-100	+	+ + +	+ + +	+ + +	+ + +	+ + +	+	+ + +
Mesoridazine	50						+ + +	+	+ +
Pimozide	1-2						+	+ + +	+
Piperazines									
Perphenazine	10	+ +	+ + +	+ +	+ +	+ +	+ +	+ +	+

Trifluoperazine	5	+ +	+ +	+ +	+ +	+ +	+	+ + +	+
Fluphenazine	2-4	+ + +	+	+	+	+	+	+ + +	+
THIOXANTHENES									
Thiothixene	3-5	+ + +	+	+	+	+	+ +	+ + +	+ +
CHLORPROTHIXENE									
BUTYROPHENONES									
Haloperidol**	1.6-2	+ + +	+	+	+	+	+	+ + +	+
Droperidol									
DIBENZOXAZEPINES									
Loxapine	10-15	+ +	+ + +	+ +	+ +	+ +	+	+ +	+
DIHYDROINDOLONES									
Molindone	10	+ +	+	+	+ +	+ +	+ +	+ +	+
ATYPICAL									
Clozapine***	50-60	+	+ + +	+ + +	+ + +	+ + +	+ + +	**0**	+ + +
Risperidone	1	+ + +	+ + +	+ + +	—	+ + +	+	+	+ + +
Olanzapine	2-3								
Quetiapine	100							**0**	
Ziprasidone		+ + +	+ + +	+ +	—	+ + +			
ARIPIPRAZOLE		+ + +	+ + +	+ +	—	+ +			
PALIPERIDONE****									
ILOPERIDONE									
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 D_1 and D_2 receptors, high affinity for D_4
****major active metabolite of RISPERIDONE and first oral agent allowing once-daily dosing; indicated for acute schizophrenia.

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 P-450 system in liver.
- **relatively long T½** allows once-daily dosing.
- DEPOT forms available (slow release - up to 2-4 weeks after IM injection):
  1) HALOPERIDOL decanoate
  2) FLUPHENAZINE decanoate and FLUPHENAZINE enanthate
  3) TRIFLUOPERAZINE
  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*.
   - LOXAPINE inhalation powder 10 mg is FDA approved for acute treatment of agitation associated with schizophrenia or bipolar I disorder in adults.

   N.B. ***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. **Antiemetic** – CHLORPROMAZINE, PROCHLORPERAZINE
   - all neuroleptics (except THIORIDAZINE) have antiemetic effects - by blocking D_2 receptors in chemoreceptor trigger zone of medulla.

3. **Other uses**:
   1) agitated 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! (H: use simple sedative, such as benzodiazepines).
   2) Tourette syndrome – PIMOZIDE (the only approved indication for this drug), HALOPERIDOL.
   3) chronic pain with severe anxiety (in combination with narcotic analgesics).
   4) intractable hiccups – CHLORPROMAZINE.
   5) neuroleptanesthesia – DROPERIDOL (in combination with FENTANYL).
   6) pruritus – PROMETHAZINE (antihistaminic effect).

SIDE EFFECTS

- occur in practically all patients (significant in ≈ 80%):

1. **Extrapyramidal side effects** - due to D_2 blockade in ***nigrostriatal pathway***. see p. Mov25 >>

   N.B. treatment with neuroleptics requires SIGNED INFORMED CONSENT because of risk of irreversible tardive dyskinesia; such consent is not required for antidepressants!

2. **Neuroleptic malignant syndrome** - believed to be blockade of D_2 receptors. see p. Mov25 >>

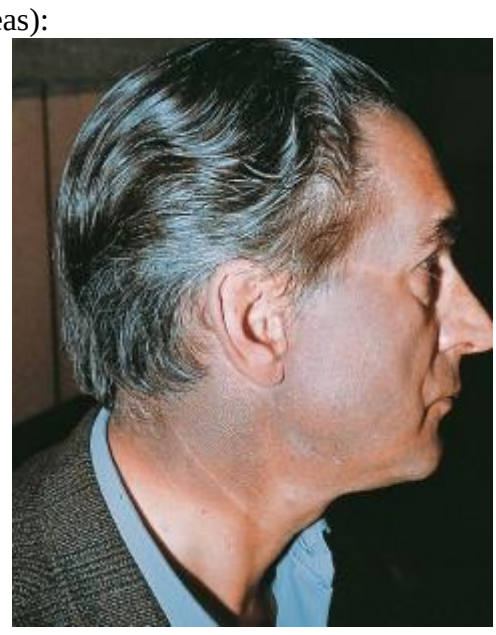
3. **Antimuscarinic effects** due to M blockade - all neuroleptics* (esp. THIORIDAZINE, CHLORPROMAZINE): loss of accommodation, dry mouth, sedation, confusion, GI & GU smooth muscle inhibition (constipation, urinary retention**).
   *except RISPERIDONE, ARIPIPRAZOLE, ZIPRASIDONE
   **H: BETHANECHOL

4. **Orthostatic hypotension** due to α-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_1 blockade.

6. Neuroleptics lower seizure threshold - can aggravate / provoke epilepsy!!!

7. Neuroleptics depress hypothalamus → amenorrhea, galactorrhea*, infertility, impotence, increased appetite (weight gain), poikilothermia (body temperature varies with environment).
   *due to D_2 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).
10. Jaundice and elevation of liver enzymes.
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 >>