

Psychosis, Neuroleptics

Last updated: September 5, 2017

PSYCHOSIS 1
 ETIOLOGY 1
NEUROLEPTICS (S. ANTIPSYCHOTICS, MAJOR TRANQUILIZERS) 1
 MECHANISM OF ACTION 1
 PHARMACOKINETICS 2
 INDICATIONS 2
 SIDE EFFECTS 2
 ACUTE INTOXICATION 3

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 D₂ receptors***.

Affinity at D₂ receptors parallels clinical potency!

*N.B. neuroleptics also bind to other D receptors (i.e. not selective for D₂)!

- 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 D₂ blockade** and blockade of **serotonin 5-HT₂ 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		+++	+++	++	—	+++			
ARIPIRAZOLE		+++	+++	++	—	++			
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 D₁ and D₂ receptors, high affinity for D₄

****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 T_{1/2}** 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 D₂ 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 **D₂ 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 D₂ 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, ARIPIRAZOLE, 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 **H₁ 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 **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**).
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 >>](#)