Psychosis, Neuroleptics

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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 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-HT2receptors.
* drugs vary in their potency, but no one drug is clinically more effective than another.
* chlorpromazineis 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↓** |
| **D2** | **5-HT2** | **H1** | **M** | **α1** |
| 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 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 T½** allows once-daily dosing.
* depot forms available (slow release - up to 2-4 weeks after IM injection):
	1. haloperidoldecanoate
	2. fluphenazinedecanoate 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)

1. **Antiemetic** – chlorpromazine, prochlorperazine
* all neuroleptics (except thioridazine) have antiemetic effects - by blocking D2 receptors in chemoreceptor trigger zone of medulla.
1. **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).

* 1. Tourette syndrome – pimozide (the only approved indication for this drug),haloperidol.
	2. chronic pain with severe anxiety (in combination with narcotic analgesics).
	3. intractable hiccups – chlorpromazine.
	4. neuroleptanesthesia – droperidol (in combination with fentanyl).
	5. 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 >>](http://www.neurosurgeryresident.net/Mov.%20Movement%20disorders%2C%20Ataxias%5CMov25.%20Drug-Induced%20Movement%20Disorders.pdf)

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

1. **Neuroleptic malignant syndrome** - believed to be blockade of D2 receptors. [see p. Mov25 >>](http://www.neurosurgeryresident.net/Mov.%20Movement%20disorders%2C%20Ataxias%5CMov25.%20Drug-Induced%20Movement%20Disorders.pdf)
2. **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

1. **Orthostatic hypotension** due to α-adrenergic blockade (esp. risperidone, clozapine)
2. Drowsiness, confusion (esp. in elderly, usually during first 2 weeks with low-potency, high-anticholinergic activity subclass) - due to H1 blockade.
3. Neuroleptics lower seizure threshold - can aggravate / provoke epilepsy!!!
4. 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)

1. Long QT syndrome (thioridazine, haloperidol, mesoridazine, olanzapine, risperidone, ziprasidone).
2. **Hyperglycemia and dyslipidemia** (major concern for all atypical antipsychotics).
3. Jaundiceand elevation of liver enzymes.
4. Pigmentary retinopathy (thioridazine in doses > 800 mg, thiothixene).
5. Metabolites of phenothiazines can cause striking abnormal skin coloration (particularly in exposed areas):



1. 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 >>](http://www.neurosurgeryresident.net/Psy.%20Psychiatry%5CPsy.%20Bibliography.pdf)

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