PSYCHIATRY
SCHIZOPHRENIA

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Genetic abnormalities

- hSKCa3 located on 11q22, leads to an increased risk to schizophrenia.
- hSKCa3 codes for a K^+ channel and acts to dampen the electrical activity and as an "off switch" to signals that are triggered by the NMDA receptors.
- hSKCa3 also contains a characteristic CAG repeat.
- This poly tri-nucleotide repeat may also lead to anticipation, in which subsequent generations accumulate CAG repeats
- This increased poly-glutamine stretch is correlated to earlier onset and worsened states of the disease.

Genetic abnormalities

- 2-6% of schizophrenia associated with deletion of COMT gene at 22q11
- Dopamine depletion results.
- SNP mutations in the ZNF804A (at 2q32) affect neural network coordination in the dorsolateral prefrontal cortex.
- Copy number variations in the Ca^{2+} channel gene (CACNA1C, L-type, at 12p13) affects neurotransmitter release.
- May account for mood changes

Genetic abnormalities

- GRIN1 and GRIN2 NMDA receptors (at 9q43, affecting glutamate release)
- GRIN3 alters NMDA receptor to prevent activation by
- PLXNA2 (plexin or semaphorin, at 1q32) affects axon signals
- Dysbindin (at 6p22)

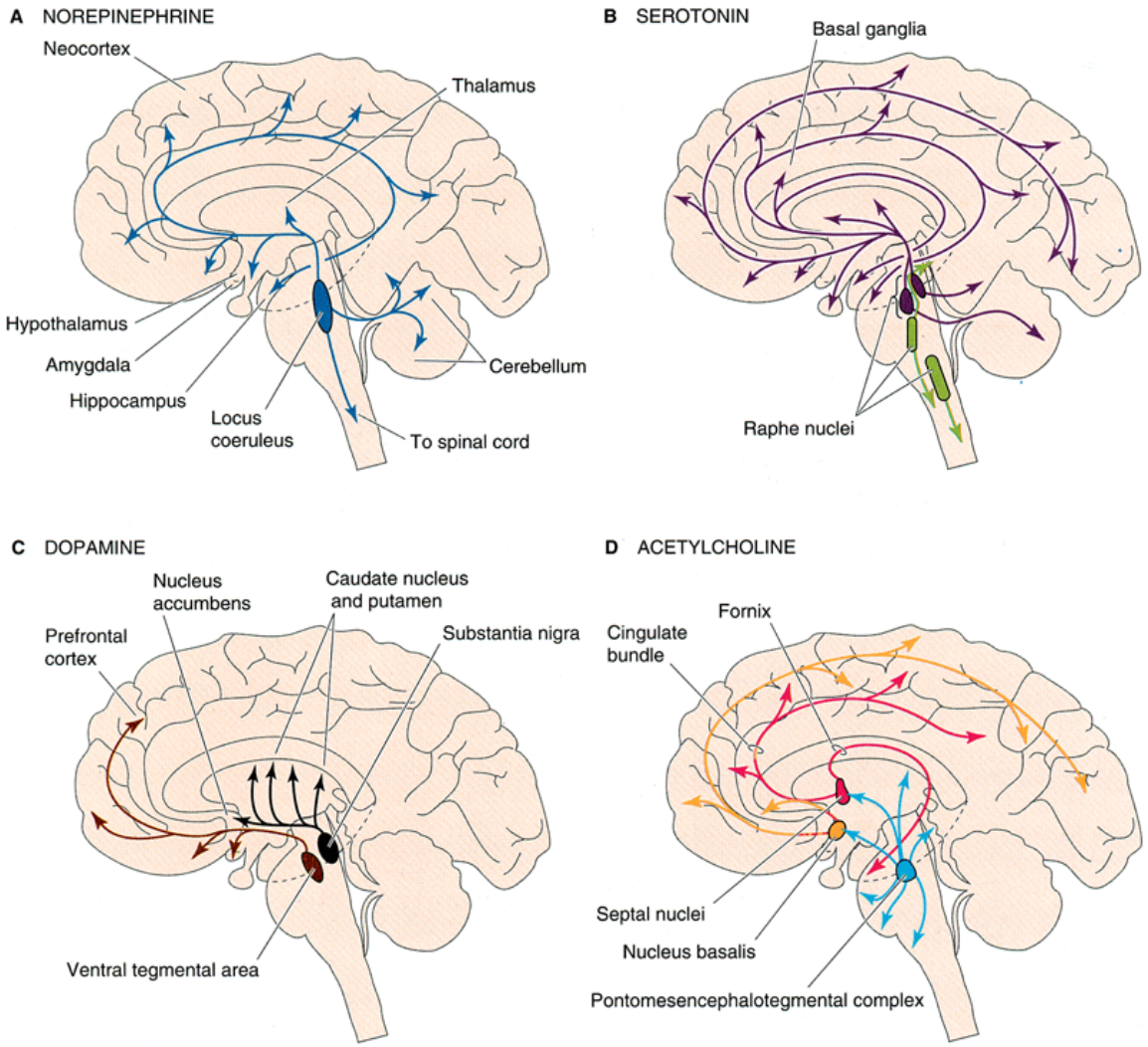
Genetic abnormalities

- DISC-1 (disrupted in schizophrenia gene-1, at 1q42)
- Neuroregulin (at 8p23)
- Dopamine receptor (at 5q35)
- DOC2A (at 16p11) affects Ca2+ release and brain neurotransmitter function.
- Not an SNP; rather, variation in copy numbers
- GABA receptor (at 6p21)

Behavior

- Dopamine regulates movement, reward, cognition.
- Norepinephrine regulates mood, arousal, cognition.
- Serotonin regulates mood, anxiety, sleep, pain, and cognition.
- Acetylcholine regulates memory, arousal, cognition.

Neurotransmitters and pathways



Source: Barrett KE, Barman SM, Boitano S, Brooks H: *Ganong's Review of Medical Physiology, 23rd Edition*: http://www.accessmedicine.com

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Neurotransmitters

Neurotransmitter	Areas of Concentration
Acetylcholine (ACh)	Neuromuscular junction, autonomic ganglia, parasympathetic neurons, motor nuclei of cranial nerves, caudate nucleus and putamen, basal nucleus of Meynert, portions of the limbic system
Norepinephrine (NE)	Sympathetic nervous system, locus ceruleus, lateral tegmentum
Dopamine (DA)	Hypothalamus, midbrain nigrostriatal system
Serotonin (5-HT)	Parasympathetic neurons in gut, pineal gland, nucleus raphe magnus of pons
Gamma-aminobutyric acid (GABA)	Cerebellum, hippocampus, cerebral cortex, striatonigral system
Glycine	Spinal cord
Glutamic acid	Spinal cord, brain stem, cerebellum, hippocampus, cerebral cortex

Integrated dopamine hypothesis of schizophrenia

- Symptomatology in schizophrenia is explainable by dysregulation of dopamine pathways:
- Hyperactivity of the mesolimbic system is associated with positive symptoms
- Hypoactivity of the mesocortical pathway
- (a) To the dorsolateral prefrontal cortex
- Associated with cognitive difficulties (and negative symptoms that suggest lack of interest)
- (b) To the ventromedial prefrontal cortex
- Associated with symptoms of affect (and negative symptoms that suggest lack of interest).

Dopamine

- Neurotransmitter pathways in the brain may explain symptomatology (as well as adverse effects of medication use).
- The nigrostriatal pathway that runs from the substantia nigra to the basal ganglia (striatum)
- Modulates motor movement.
- The mesolimbic pathway that runs from the ventral tegmentum to the nucleus accumbens.
- Associated with pleasure and reward, delusions.

Dopamine

- The mesocortical pathway projects from the ventral tegmentum to the prefrontal cortex
- Modulates cognitive function (dorsolateral prefrontal cortex)
- Modulates affective symptoms (ventromedial prefrontal cortex).
- The tuberoinfundibular pathway projects from the hypothalamus to the pituitary
- Controls prolactin secretion.

Dopamine

- Projections from the peri-aqueductal gray, the ventral meso-encephalon, hypothalamus, and lateral parabrachial nucleus project to the thalamus.
- Associated with arousal and sleep.

Norepinephrine

- Ascending adrenergic projections originate principally in the locus ceruleus
- Project to the cerebellum, hypothalamus, amygdala, hippocampus, basal forebrain, and the pre-frontal cortex.
- Descending projections in the spinal cord regulate pain pathways.
- Norepinephrine regulates mood, arousal, and cognition, among other functions.

Serotonin

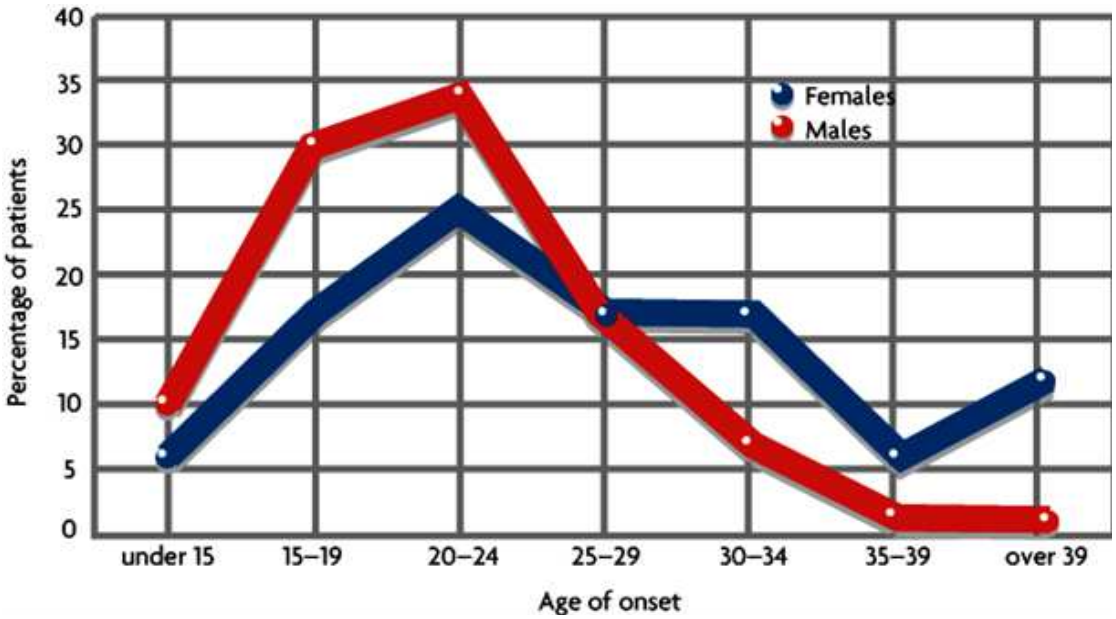
- Ascending serotonin projections originate in the ventral tegmentum
- Project to the cerebellum, hypothalamus, amygdala, hippocampus, striatum, nucleus accumbens, basal forebrain, and the pre-frontal cortex.
- Descending projections in the spinal cord regulate pain pathways.
- Serotonin regulates mood, anxiety, and arousal, among other functions.

Acetylcholine

- Acetylcholine projections originate principally in the ventral tegmentum
- Project to the hypothalamus, thalamus, amygdala, hippocampus, basal forebrain, and the pre-frontal cortex.
- Regulate arousal, cognition, and memory, among other functions.

Diagnosis of schizophrenia

- Symptoms must occupy a significant portion of time during the day.
- For a significant portion of the time due to the disturbance, marked impairment is noticed in academics, interpersonal relationships, self-care, work or any other major area of functioning.
- The symptoms are not due to a medical condition or drug use.


40
35
30
25
20
15
10
5
0
Percentage of patients
Females
Males
under 15
15–19
20–24
25–29
30–34
35–39
over 39
Age of onset

Diagnosis of schizophrenia

- Characterized by two or more of the following present for a significant portion of time over one month:
- Hallucinations
- Often auditory (“voices”)
- Two or more persons conversing with each other
- A voice that affects one’s thoughts or behavior
- Delusions
- Incorrect inferences about external reality
- Persecution
- Grandeur
- Thought control

Diagnosis of schizophrenia

- Disordered speech
- Word salad
- Flight of ideas
- May also have
- Grossly disorganized behavior or catatonia
- Lack of communication, flat affect, ambivalence, lack of interest
- Impaired cognitive ability

Differential diagnosis

- Schizophreniform behaviors are of at least one month duration and last for less than 6 months.
- One-third will progress to schizophrenia.
- If the symptoms are continuous and persist for more than 6 months, the diagnosis is schizophrenia.
- >50% will attempt suicide.
- If both parents are schizophrenic, there is a 40% increased risk of schizophrenia in a child
- If a sibling is schizophrenic, there is a 10% increased risk of schizophrenia in a sibling.

Differential diagnosis

- Schizoaffective patients meet the criteria for schizophrenia, have mood symptoms, and show psychotic symptoms in the absence of a mood episode.
- Delusional patients do not manifest the bizarre delusions of a schizophrenic.
- May show egomaniacal, grandiose, jealous, persecutory, somatic delusions.
- Onset is in middle age.
- Respond to anxiolytics.

Differential diagnosis

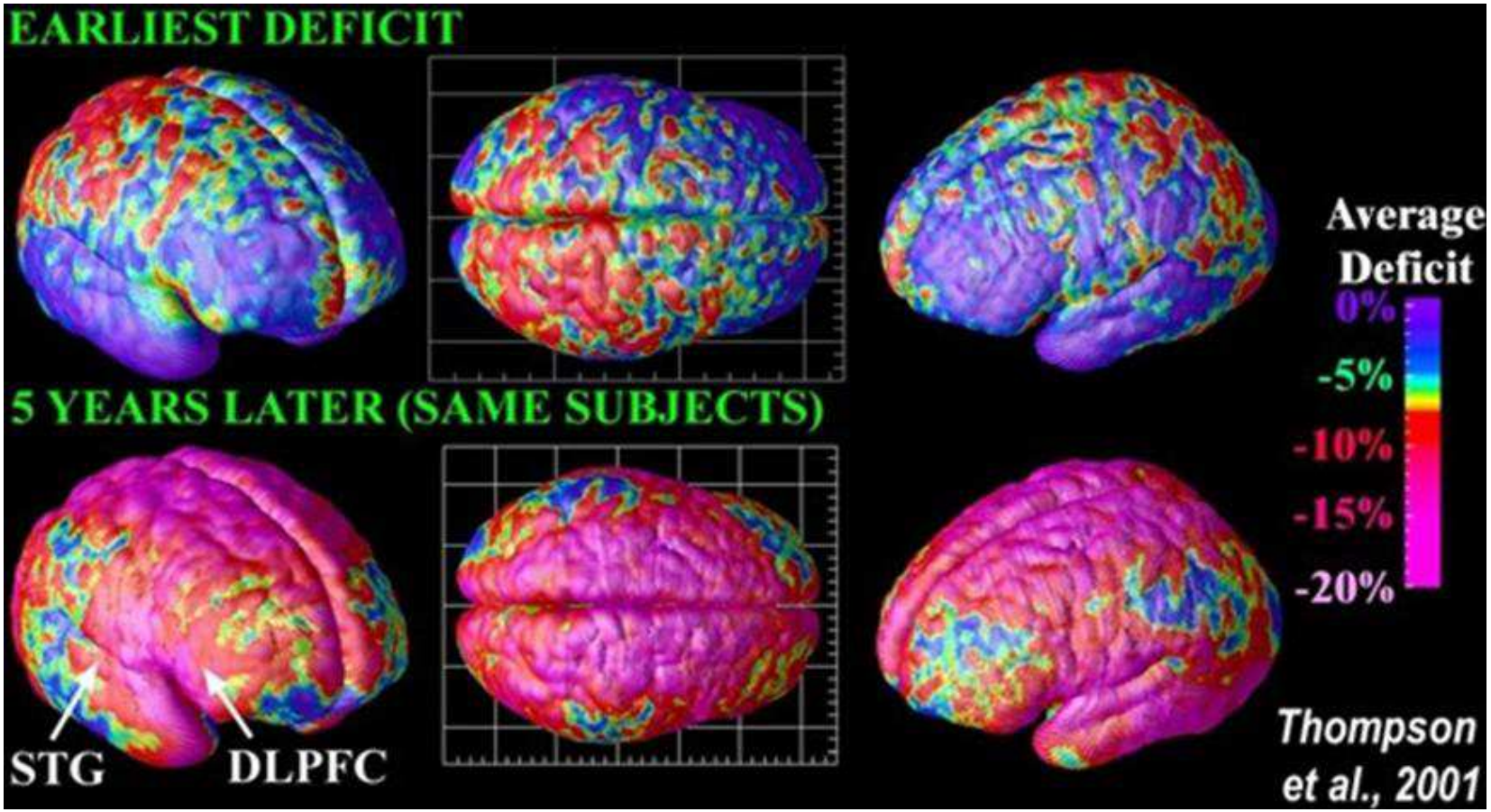
- Brief psychotic disorder
- More than a day but less than a month
- Follows major stressor
- Onset in the 30's
- 9% of first onset psychoses
- Patients who manifest psychosis only during mood episodes are not schizophrenic.
- Type A personality disorders may show weird behavior, but are not schizophrenic.

Subtypes of schizophrenia

- Paranoid, catatonic, disorganized, undifferentiated, and residual are no longer described in DSM5
- Paranoid patients are delusional, hallucinate.
- Good self-care.
- Best prognosis.
- Catatonic patients are in a stupor, show waxy flexibility (catalepsy).
- May respond to benzodiazepines
- Electroconvulsive therapy if unresponsive
- Disorganized patients are disinhibited, have poor grooming habits, inappropriate emotional responses.
- Worst prognosis of all subtypes.

Schizophrenia

- There is a hypofunctioning frontal lobe and abnormalities in the hippocampus and pulvinar, yet dopamine receptor density is increased.
- MAO is diminished (as measured in platelets).
- Dopamine activity is associated with positive symptoms
- Serotonin levels correlate with positive and negative symptoms
- Glutamate antagonist associated with schizophrenia-like symptoms (Phencyclidine or PCP)


EARLIEST DEFICIT
5 YEARS LATER (SAME SUBJECTS)
Average Deficit
0%
-5%
-10%
-15%
-20%
STG
DLPFC
Thompson et al., 2001

Anti-psychotics

- D_1 potency does not predict anti-psychotic effectiveness.
- Phenothiazines are lipid soluble.
- If there are 3 or more Carbon atoms between the Nitrogen at the 10^{th} position and the Nitrogen on the side chain, there are fewer secondary effects noted.
- Chlorpromazine (first generation): $\alpha_1 = 5\text{-}HT_2 > D_2 > D_1$
- Haloperidol (second generation): $D_2 > D_1 = D_4 > \alpha_1 > 5\text{-}HT_2$
- Clozapine (atypical): $D_4 = \alpha_1 > 5\text{-}HT_2 > D_2 = D_1$

Anti-psychotics

- First generation
- Post-synaptic D_2 receptor antagonism
- Antagonism of muscarinic, H_1 (histamine), and α_1-adrenergic receptors.
- Risk of tardive dyskinesia increased.
- Second generation
- Post-synaptic D_2 receptor antagonism as well as serotonin ($5HT_2$) receptor antagonism.
- Atypical anti-psychotics may also show D_2 receptor antagonism with rapid dissociation
- OR D_2 and $5HT_2$ partial agonism.

Anti-psychotic action

- Antagonism of mesolimbic dopamine pathway.
- Reduces positive psychotic symptoms.
- May block reward mechanisms.
- Apathy, anhedonia, lack of motivation, reduced interest and joy from social interactions (secondary negative symptoms).

Anti-psychotic action

- Antagonism of the tuberoinfundibular dopamine pathway
- Leads to increased prolactin release.
- Galactorrhea and amenorrhea are noted.
- May see sexual dysfunction (particularly in men).
- Antagonism of nigrostriatal dopamine pathway
- Can cause Parkinson-like movement disorders
- Chronic antagonism may cause tardive dyskinesia
- D_2 receptors upregulated

Tardive dyskinesia

- Brought on by the use of antipsychotic drugs or metoclopropamide and persists after the drugs are discontinued.
- First generation (“typical”) antipsychotics more likely to cause problems than are the second generation (“atypical”) antipsychotics.
- Clozapine only antipsychotic proven to have low probability of tardive dyskinesia adverse reaction.
- Pretreatment with dopamine depleting agents, benzodiazepines, anti-Parkinsonian agents increases risk.

Tardive dyskinesia

- Usually head and neck muscles (mainly mouth and tongue), back muscles.
- Drug treatment results in hypersensitivity at the D2 dopamine receptor.
- Results in an imbalance in nigrostriatal influence.
- Sydenham chorea associated with rheumatic disease.

Morbidity

- Cardiovascular disease is the leading cause of premature mortality in schizophrenia.
- Antipsychotic therapy is associated with:
- Moderate risk of weight gain
- High risk of sexual side effects
- Low risk of metabolic effects.

First generation anti-psychotics

- Adverse effects include sedation, orthostatic hypotension, tachycardia, weight gain, and anticholinergic side effects.
- Extrapyramidal effects
- 10% have leukopenia
- 1% have liver damage.
- At high doses associated with pigmented retinal lesions, corneal opacities.
- Seizures are related to dose.

First generation anti-psychotics

- Chlorpromazine likelier to be associated with adverse effects.
- Thioridazine is associated with moderate risk of cardiac conduction abnormalities (prolong QT_c).

Second generation anti-psychotics

- Many atypical antipsychotics are antagonists at the $5HT_{2A}$ receptor as well as the D_2 receptor.
- $5HT_{2A}$ antagonism disinhibits the D_2 receptor and leads to dopamine release and competition with the drug at the D_2 receptor.
- This limits extrapyramidal symptoms in the nigrostriatal system and throughout the mesocortical system
- Improves cognition, affect, and diminishes anhedonia.

Second generation anti-psychotics

- $5HT_{2A}$ antagonism may increase dopamine release in hypoactive mesolimbic pleasure centers and reduce negative, affective, and cognitive symptoms.
- $5HT_{2A}$ antagonism blocks the serotonergic excitation of cortical pyramidal cells, reducing their glutamate release, and lowering the hyperactive drive on the mesolimbic dopamine pathway, which reduces positive symptoms.

Second generation anti-psychotics

- Less likely to cause extrapyramidal symptoms or neuromuscular symptoms than are first generation (high-potency) agents.
- Photosensitizers
- Diabetes mellitus and hyperglycemia may occur.

Second generation anti-psychotics

- Haloperidol, fluphenazine, trifluoperazine are associated with extrapyramidal symptoms because of their dopamine blockade.
- Little orthostatic hypotension or anticholinergic effect.
- Haloperidol used to treat delerium (with lorazepam), aggression, tics and vocal utterances in patients with Tourette's syndrome.

Therapy

- Atypical antipsychotics preferred initial therapy
- Both D2 and 5HT antagonists
- First employ weight-neutral agents:
- Ziprasidone
- Lurasidone
- Aripiprazole
- Other atypical antipsychotics include respiradone, clozapine

Classes of antipsychotic drugs

	High potency	Low potency	Atypical
Prototype	**Haloperidol**	**Chlorpromazine**	**Risperadone, clozapine**
Extrapyramidal effects (dystonia, akathisia, tardive dyskinesia, Parkinsonism)	**High incidence**	**Low incidence**	**Low incidence**
Autonomic effects (anticholinergic, antihistaminic, orthostatic hypotension)	**Low incidence**	**High incidence**	**Medium incidence**
Positive symptoms	**Works well**	**Works well**	**Works well**
Negative symptoms	**Works poorly**	**Works poorly**	**Works**

Major drug side-effects

- Thioridazine: retinal pigment deposits
- Clozapine: agranulocytosis
- Chlorpormazine: photosensitivity, cholestasis