Antipsychotic Drugs

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March, 2018

Antipsychotic Drugs

These are the drugs used in the treatment of psychotic diseases(e.g. schizophrenia).

Major Tranquilizers (المهدئات الكبرى)

Neuroleptics (مضادات الذهان)

ANTIPSYCHOTIC DRUGS

Chlorpromazine is the prototype ANTIPSYCHOTIC. Its actions are:

A Antipsychotic effect in psychotic patients (therapeutic effect)

N Neuroleptic syndrome in normal persons (unpleasant effect)

T Temperature control is disturbed

I Increased chances of epileptic fits due to decreased seizure threshold

P Prolactin release increases – galactorrhoea & gynaecomastia

S Side effects – Extrapyramidal
e.g. Parkinsonism, dystonias, akathisia, dyskinesia

Y Yellowness i.e. cholestatic jaundice

C Cholinergic antagonism leading to dry mouth,etc

H Hypotension

O Obesity

T Tolerance to some effects like sedation

I Inhibition of gonadotropin secretion

C Certain spasticity conditions are relieved

Psychosis

- A variety of mental disorders of abnormal perceptions (hallucinations), thoughts (delusions), behaviors, and aggressiveness.

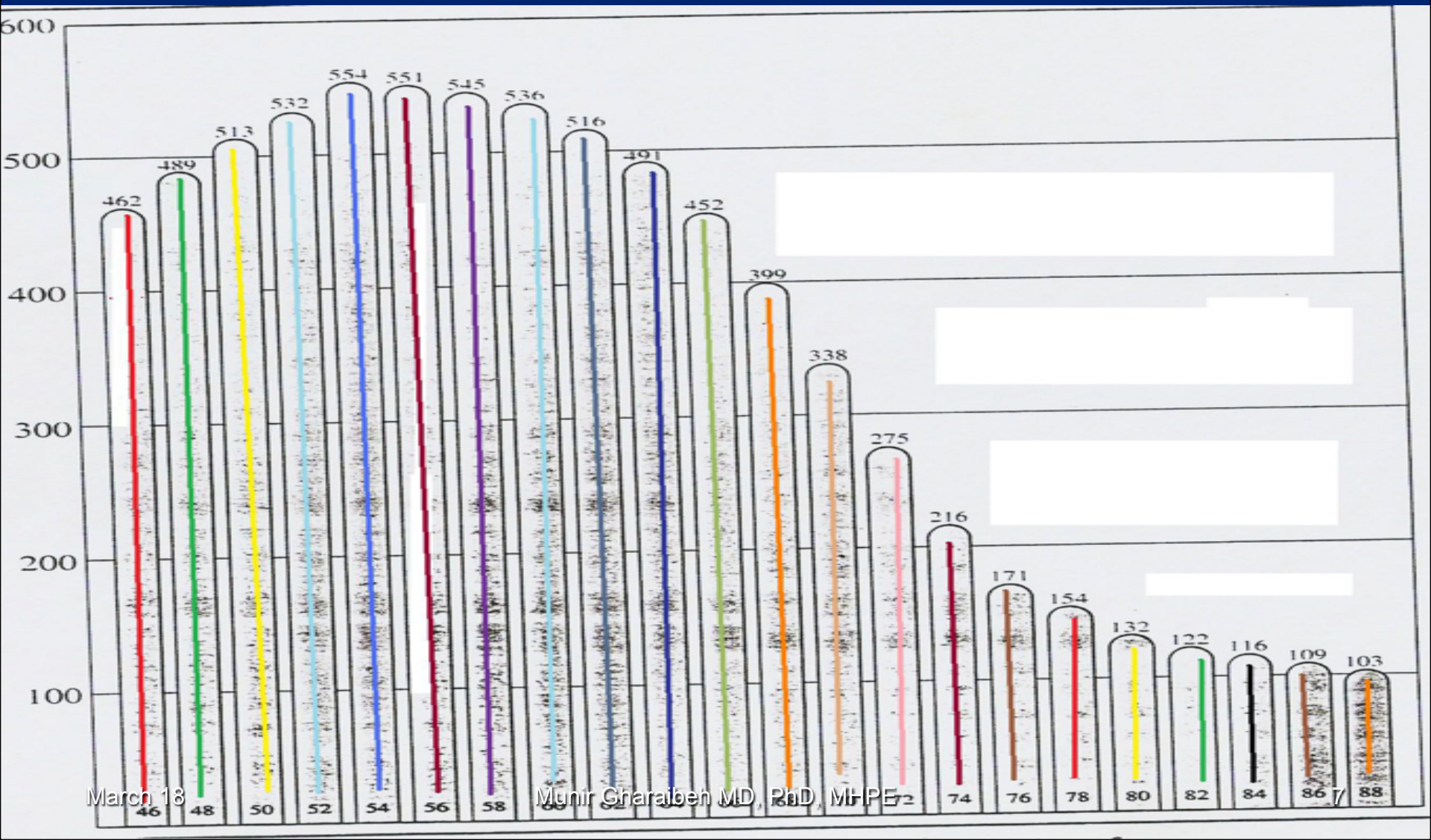
Schizophrenia

- Genetic predisposition.
- A gene encoding neuregulin 1 is associated with schizophrenia in Icelandic and northern European populations.
- Abnormalities of amine neurotransmitter functions, especially dopamine.
- Glutamate, GABA and Acetylcholine receptors, also proposed to participate.

History of Antipsychotic Treatment

- Incarcination.
- Herbal.
- Psychosurgery.
- Electroconvulsive Therapy (ECT).
- Electrode Implantation.
- Antipsychotic Drugs(1952).

Effect of Chlorpromazine on the Number of Psychiatric Inpatients




WESTON STATE HOSPITAL
Authorized as a western asylum by the state of Virginia in 1858. Construction was started in 1860. completed by the new State. and opened in 1864 as a hospital for mentally ill. This is the largest hand-cut stone building in America.
RANS-ALLEGHENY LUNATIC ASYLUM
OFFICE OPEN 9-4 M-F
VOLUNTEER SATURDAYS 10-4
THURSDAY MEETINGS 7:30 PM
OPEN TO THE PUBLIC

Weston State Hospital

- The hospital; 307-acre complex; is the second of the world's largest hand-cut sandstone structures, a National Historic Landmark, that once housed more than 2,500 patients but has stood largely silent since 1994.

Weston State Hospital

- After struggling to find a suitable, sustainable use, the state sold it at auction for $1.5 million to an asbestos demolition contractor.
- The daily tours — which cost $10 to $30, depending on duration — focus on issues such as the evolution of mental health care, the Civil War, the Great Depression, even architecture.

Mechanism of Action

- A common mechanism to all antipsychotic drugs is dopamine receptor antagonism (D1, D2, D3, D4, D5). The therapeutic effects are mainly due to D2 antagonism(70-80%).
- Many of them also, work to antagonize other receptors like $5HT_{2A}$, α, H_1, and M receptors. Most importantly $5HT_{2A}$.

Dopamine Pathways

- **NIGROSTRIATAL:**

  Coordination of posture and voluntary movement.
- **MESOLIMBIC-MESOCORTICAL:**

  Behavioral, mental and emotional.
- **TUBEROINFUNDIBULAR:**

  Inhibits prolactin secretion.

. **MEDULLARY-PERIVENTRICULAR:**

  Eating behavior.
- **Incertohypothalamic:**

  Anticipatory motivational phase of copulatory behavior in rats.

Dopamine1-Like Receptors

- **D1 Receptor:**

  Coded by a gene on chromosome 5.

  Increases cAMP.

  Located mainly in the putamen, nucleus accumbens, and olfactory tubercle.

- **D5 Receptor:**

  Coded by a gene on chromosome 4

  Increases cAMP.

  Located mainly in the hippocampus and hypothalamus.

- ***Binding affinity of drugs to these receptors does not correlate with therapeutic potency.***

Dopamine2-Like Receptors

- **D2 Receptor:**

  Coded on chromosome 11.

  Decreases cAMP.

  Opens K+ channels.

  Inhibits Ca++ channels.

  Found in the caudate- putamen, nucleus accumbens and olfactory tubercle.

. ***Binding affinity of drugs to D2-like receptors strongly correlates with antipsychotic and extrapyramidal potency.***

Dopamine2-Like Receptors

D3 Receptor:

Also coded on chromosome 11.

Decreases cAMP.

Located in the frontal cortex, medulla and midbrain.

D4 Receptor:

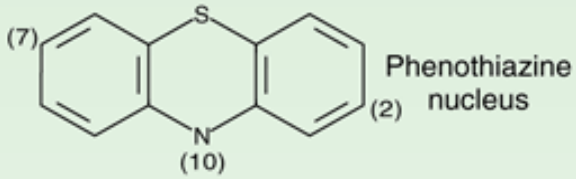
Also decreases cAMP.

Antipsychotic Drugs

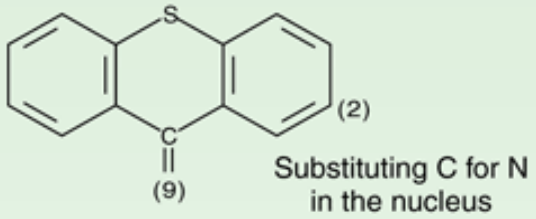
- * Different Affinities for the receptors.
- Different Potencies.
- * Different Activities & Toxicities.
- * Different Responses of Patients.
- * Each may have special benefits for selected patients.
- * Older drugs have lower cost and can be given by depot IM injections.

Typical or Older Antipsychotic Drugs

Phenothiazine derivatives



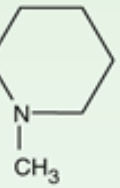
Thioxanthene derivative



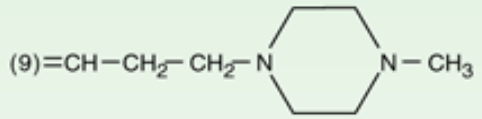
Aliphatic side chain

Chlorpromazine (2)—Cl (10)—CH_2—CH_2—CH_2—N—$(CH_3)_2$

Thioridazine (2)—SCH_3 (10)—CH_2—CH_2—



Thiothixene (2)—$SO_2N(CH_3)_2$



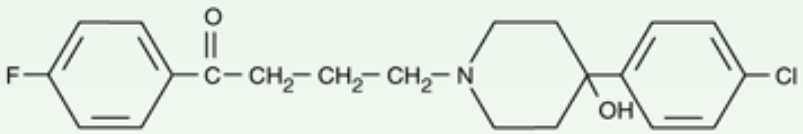
Piperazine side chain

Trifluoperazine (2)—CF_3 (10)—CH_2—CH_2—CH_2—N N—CH_3

Perphenazine (2)—Cl (10)—CH_2—CH_2—CH_2—N N—CH_2—CH_2—OH

Fluphenazine (2)—CF_3 (10)—CH_2—CH_2—CH_2—N N—CH_2—CH_2—OH

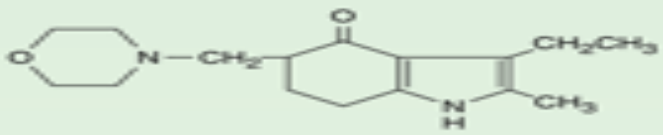
Butyrophenone



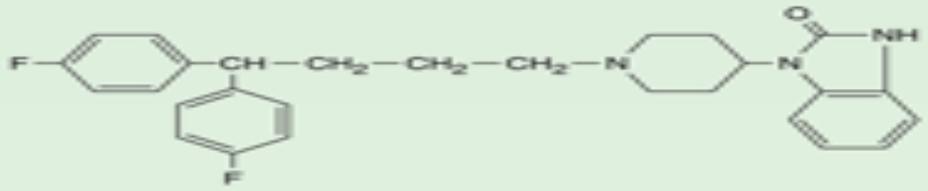
Haloperidol

Source: Katzung BG, Masters SB, Trevor AJ: *Basic & Clinical Pharmacology, 12th edition*: www.accessmedicine.com

Atypical or New Antipsychotic Drugs

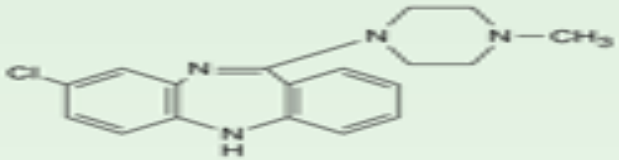


Molindone

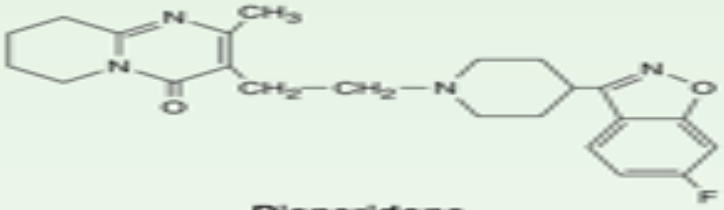


Pimozide

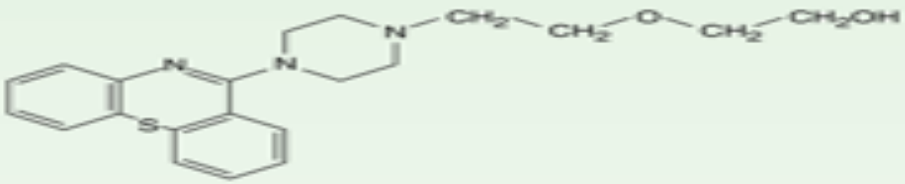
Loxapine



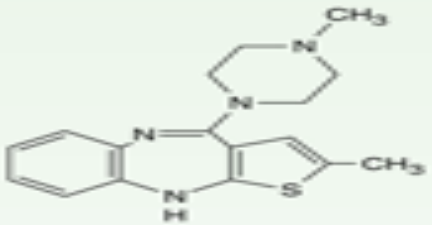
Clozapine



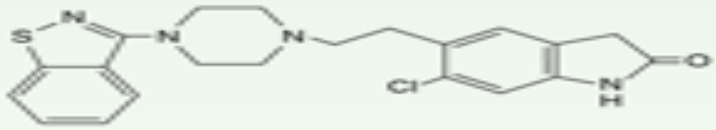
Risperidone



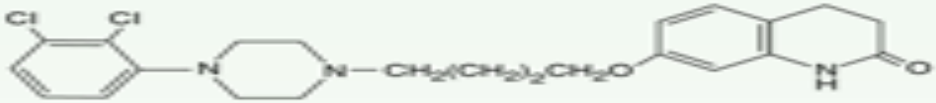
Quetiapine



Olanzapine



Ziprasidone



Aripiprazole

TYPICAL	ATYPICAL	
Pure DA_2 Antagonists	Pure DA_2 – $5HT_2$ Antagonists	Multireceptor Antagonists DA_2 – DA_4 – $5HT_2$
Low Potency: Chlorpromazine	Risperidone	Clozapine Quetiapine Ziprasidone Olanzapine Aripiprazole
High Potency: Haloperidol		

Typical or Old Antipsychotic Drugs

- **Chlorpromazine.**
- **Phlephenazine.**
- **Thiothixine.**
- **Haloperidol.**
  - **These have high occupancy of D2 receptors, but inhibit $5HT_{2A}$ receptors to a much lesser extent.**
  - **They also can inhibit α, muscarinic, and histamine receptors. This will contribute to their wide spread of side effects.**
  - ***This means increased antipsychotic activity and high toxicity.***

Atypical or New Antipsychotic Drugs

- **Clozapine.**
- **Olanzapine.**
- **Risperidone.**
  - Have lower occupancy of D2 receptors.
  - Inhibit both D2 and $5HT_{2A}$
  - 5HT(serotonin), differentially inhibits dopamine release at various sites.
  - So, these drugs will increase dopamine release in the nigrostriatal, mesocortical, and hypothalamic pathways, but not in the mesolimbic pathway.
  - ***This means increased antipsychotic activity and reduced extrapyramidal toxicity***

Table 29–4 Dose Relationships of Antipsychotics.

	Minimum Effective Therapeutic Dose (mg)	Usual Range of Daily Doses (mg)
Chlorpromazine	100	100–1000
Thioridazine	100	100–800
Trifluoperazine	5	5–60
Perphenazine	10	8–64
Fluphenazine	2	2–60
Thiothixene	2	2–120
Haloperidol	2	2–60
Loxapine	10	20–160
Molindone	10	20–200
Clozapine	50	300–600
Olanzapine	5	10–30
Quetiapine	150	150–800
Risperidone	4	4–16
Ziprasidone	40	80–160
Aripiprazole	10	10–30

Table 29 –1 Antipsychotic Drugs: Relation of Chemical Structure to Potency and Toxicities.

Chemical Class	Drug	D_2/5-HT_{2A} Ratio[1]	Clinical Potency	Extrapyramidal Toxicity	Sedative Action	Hypotensive Actions
Phenothiazines						
Aliphatic	Chlorpromazine	High	Low	Medium	High	High
Piperazine	Fluphenazine	High	High	High	Low	Very low
Thioxanthene	Thiothixene	Very high	High	Medium	Medium	Medium
Butyrophenone	Haloperidol	Medium	High	Very high	Low	Very low
Dibenzodiazepine	Clozapine	Very low	Medium	Very low	Low	Medium
Benzisoxazole	Risperidone	Very low	High	Low[2]	Low	Low
Thienobenzodiazepine	Olanzapine	Low	High	Very low	Medium	Low
Dibenzothiazepine	Quetiapine	Low	Low	Very low	Medium	Low to medium
Dihydroindolone	Ziprasidone	Low	Medium	Very low	Low	Very low
Dihydrocarbostyril	Aripiprazole	Medium	High	Very low	Very low	Low

[1] Ratio of affinity for D_2 receptors to affinity for 5-HT_{2A} receptors.

Pharmacokinetics

- Incompletely absorbed.
- First - pass metabolism.
- High lipid solubility.
- Highly bound to proteins.
- Oxidative microsomal metabolism & Conjugation.
- T½ 10 - 24h. But, have much longer clinical duration than would be estimated from their plasma half- lives .

Psychological Effects

In Psychotic Patients:

- Profound sedation, sleepiness and alleviation of psychosis, together with improvement in performance.

In Normal People:

Unpleasant subjective effects, sedation, restlessness, and autonomic effects create bad experiences, unlike those of sedatives and hypnotics.

EEG shows slowing pattern of frequencies and increased synchronization, some drugs lower seizure threshold(2-5%of patients taking clozapine).

Clinical Uses

- **Schizophrenia:**

  All are the same.

  Clozapine.

  Haloperidol.

  Use smallest doses.

  Mainstay of treatment, however, many patients show little response and none show complete response.

- **Schizoaffective Disorders:**

  Together with antidepressants, lithium or valproic acid, or, olanzapine.

  Alone for acute mania.

Clinical Uses

- **Tourette's Syndrome:**

  Motor & Vocal Tics

- **Alzheimer's Disease:**

  For disturbed behavior.

- **Antiemetic:**

  Prochlorperazine.

. **Preoperative sedatives**, ***promethazine***

. **Neuroleptanesthesia, *droperidol***

. **Pruritus**

Table 29–2 Adverse Pharmacologic Effects of Antipsychotic Drugs.

Type	Manifestations	Mechanism
Autonomic nervous system	Loss of accommodation, dry mouth, difficulty urinating, constipation	Muscarinic cholinoceptor blockade
	Orthostatic hypotension, impotence, failure to ejaculate	α-Adrenoceptor blockade
Central nervous system	Parkinson's syndrome, akathisia, dystonias	Dopamine-receptor blockade
	Tardivedyskinesia	Supersensitivity of dopamine receptors
	Toxic-confusional state	Muscarinic blockade
Endocrine system	Amenorrhea-galactorrhea, infertility, impotence	Dopamine-receptor blockade resulting in hyperprolactinemia
Other	Weight gain	Possibly combined H_1 and 5-HT_2 blockade

Table 16–4 Neurological Side Effects of Antipsychotic Drugs

REACTION	FEATURES	TIME OF ONSET AND RISK INFO	PROPOSED MECHANISM	TREATMENT
Acute dystonia	Spasm of muscles of tongue, face, neck, back	Time: 1-5 days. Young, antipsychotic naïve patients at highest risk	Acute DA antagonism	Anti-parkinsonian agents are diagnostic and curative[a]
Akathisia	Subjective and objective restlessness; *not* anxiety or "agitation"	Time: 5-60 days	Unknown	Reduce dose or change drug; clonazepam, propranolol more effective than anti-parkinsonian agents[b]
Parkinsonism	Bradykinesia, rigidity, variable tremor, mask facies, shuffling gait	Time: 5-30 days. Elderly at greatest risk	DA antagonism	Dose reduction; change medication; anti-parkinsonian agents[c]
Neuroleptic malignant syndrome	Extreme rigidity, fever, unstable BP, myoglobinemia; can be fatal	Time: weeks–months. Can persist for days after stopping antipsychotic	DA antagonism	Stop antipsychotic immediately; supportive care; dantrolene and bromocriptine[d]
Perioral tremor ("rabbit syndrome")	Perioral tremor (may be a late variant of parkinsonism)	Time: months or years of treatment	Unknown	Anti-parkinsonian agents often help[c]
Tardive dyskinesia	Orofacial dyskinesia; rarely widespread choreoathetosis or dystonia	Time: months, years of treatment. Elderly at 5-fold greater risk. Risk ∝ potency of D_2 blockade	Postsynaptic DA receptor supersensitivity, up-regulation	Prevention crucial; treatment unsatisfactory. May be reversible with early recognition and drug discontinuation

Adverse Effects

. **Extrapyramidal Reactions:**

Parkinson's disease: Can be treated with antiparkinson drugs of the antimuscarinic type or with amantadine, but not with levodopa.

Akathisia: uncontrolled restlessness.

Acute dystonic reactions: spastic retrocollis or torticollis.

Both respond to anticholinergic, antiparkinsonism drugs or sedative antihistamines with anticholinergic properties.

- **Tardive Dyskinesia:**

  Late occurring, most serious.

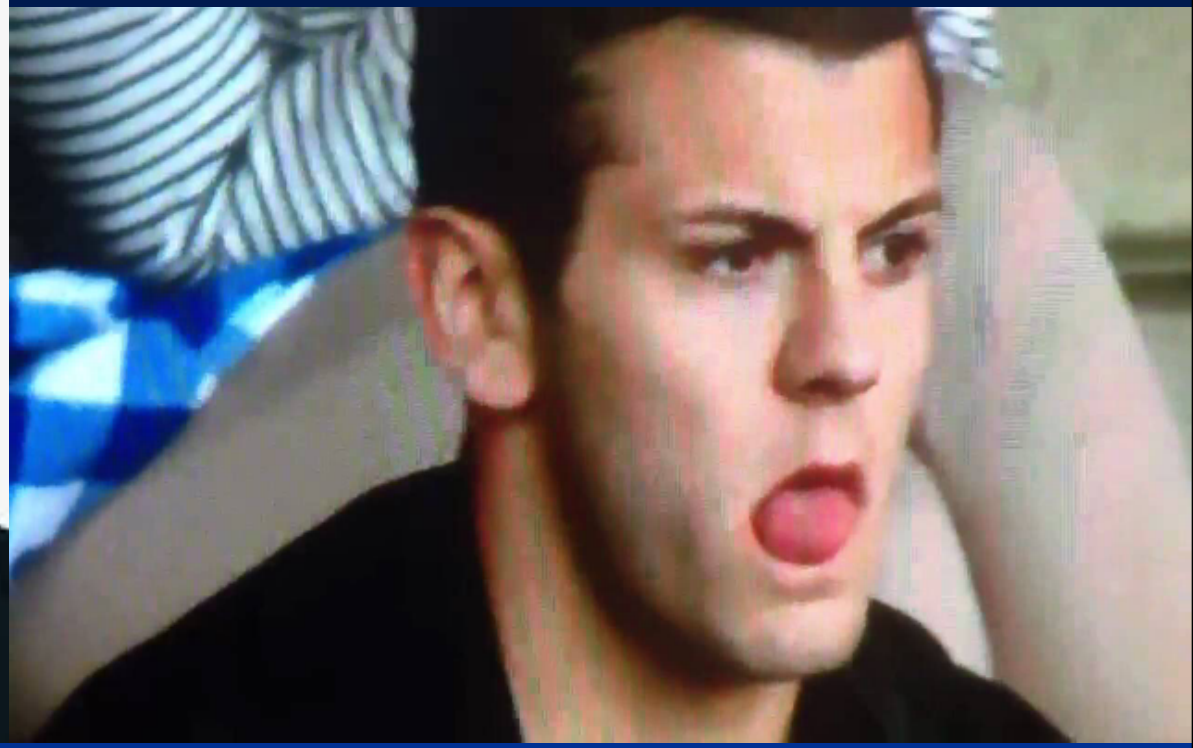
  Prevalence was 20-40% with the old drugs.

  Abnormal choreoathetoid movements (chewing, tongue protrusion, facial gramacing, jerky movements).

  Caused by a relative cholinergic deficiency due to supersensitivity of dopamine receptors in the caudate-putamen.

  Should be treated early, otherwise, irreversible.

Reduce the dose, discontinue or replace with a newer agent, or add diazepam(30-40mg).



- **Sedation**
- **Autonomic Effects:**

  Postural hypotension

  Tachycardia.

  Urinary retention.

  Constipation.

  Prolongation of QT interval.

- **Behavioral Effects:**

  Peusodepression, due to akinesia, responds to antiparkinsonism drugs.

  Toxic confusional states, with high doses due to antimuscarinic activity.

- **Jaundice**
- **Blood Dyscrasias:**

  Eosinophilia

  Agranulocytosis (1-2% with Clozapine, immune reaction, fatal)
- **Skin Reactions.**
- **Eye Reactions:** Photophobia.

  Blurring.

  Corneal & Lens Opacities.

  Retinal Pigmentation.

- **Reproductive and Endocrine Reactions:**

  ***Due to blockade of dopamine's tonic inhibition of prolactin secretion*.**

  Women: Amenorrhea,
  Infertility,
  Galactorrhea,
  Increased Libido

  Men: Gynecomastia,
  Impotence.

  Weight gain and hyperglycemia.

Neuroleptic Malignant Syndrome:

- Life-threatening.
- Marked muscle rigidity, impaired sweating, fever, leukocytosis, autonomic instability, high creatine kinase isozymes.
- Results from rapid blockade of postsynaptic dopamine receptors, resulting in a severe form of extrapyramidal syndrome.
- Treatment is by cooling, antiparkinson's drugs, muscle relaxants like diazepam or dantrolene and dopamine agonists like bromocriptine.

TABLE 29–3 Some representative antipsychotic drugs.

Drug Class	Drug	Advantages	Disadvantages
Phenothiazines			
Aliphatic	Chlorpromazine[1]	Generic, inexpensive	Many adverse effects, especially autonomic
Piperidine	Thioridazine[2]	Slight extrapyramidal syndrome; generic	800 mg/d limit; no parenteral form; cardiotoxicity
Piperazine	Fluphenazine[3]	Depot form also available (enanthate, decanoate)	(?) Increased tardive dyskinesia
Thioxanthene	Thiothixene	Parenteral form also available; (?) decreased tardive dyskinesia	Uncertain
Butyrophenone	Haloperidol	Parenteral form also available; generic	Severe extrapyramidal syndrome
Dibenzoxazepine	Loxapine	(?) No weight gain	Uncertain
Dibenzodiazepine	Clozapine	May benefit treatment-resistant patients; little extrapyramidal toxicity	May cause agranulocytosis in up to 2% of patients; dose-related lowering of seizure threshold
Benzisoxazole	Risperidone	Broad efficacy; little or no extrapyramidal system dysfunction at low doses	Extrapyramidal system dysfunction and hypotension with higher doses
Thienobenzodiazepine	Olanzapine	Effective against negative as well as positive symptoms; little or no extrapyramidal system dysfunction	Weight gain; dose-related lowering of seizure threshold
Dibenzothiazepine	Quetiapine	Similar to olanzapine; perhaps less weight gain	May require high doses if there is associated hypotension; short $t_{1/2}$ and twice-daily dosing
Dihydroindolone	Ziprasidone	Perhaps less weight gain than clozapine, parenteral form available	QT_c prolongation
Dihydrocarbostyril	Aripiprazole	Lower weight gain liability, long half-life, novel mechanism potential	Uncertain, novel toxicities possible

[1]Other aliphatic phenothiazines: promazine, trifluprom[illegible]

[2]Other piperidine phenothiazines: piperacetazine, mesoridazine.

[3]Other piperazine phenothiazines: acetophenazine, perphenazine, carphenazine, prochlorperazine, trifluoperazine.