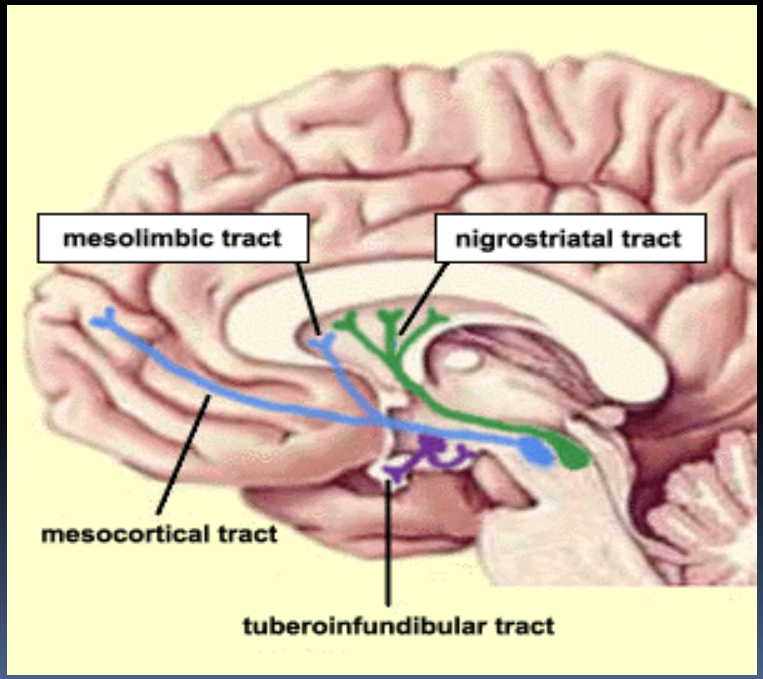
ANTIPSYCHOTIC DRUGS

Old group names: major tranquilizers, ataractics, neuroleptics

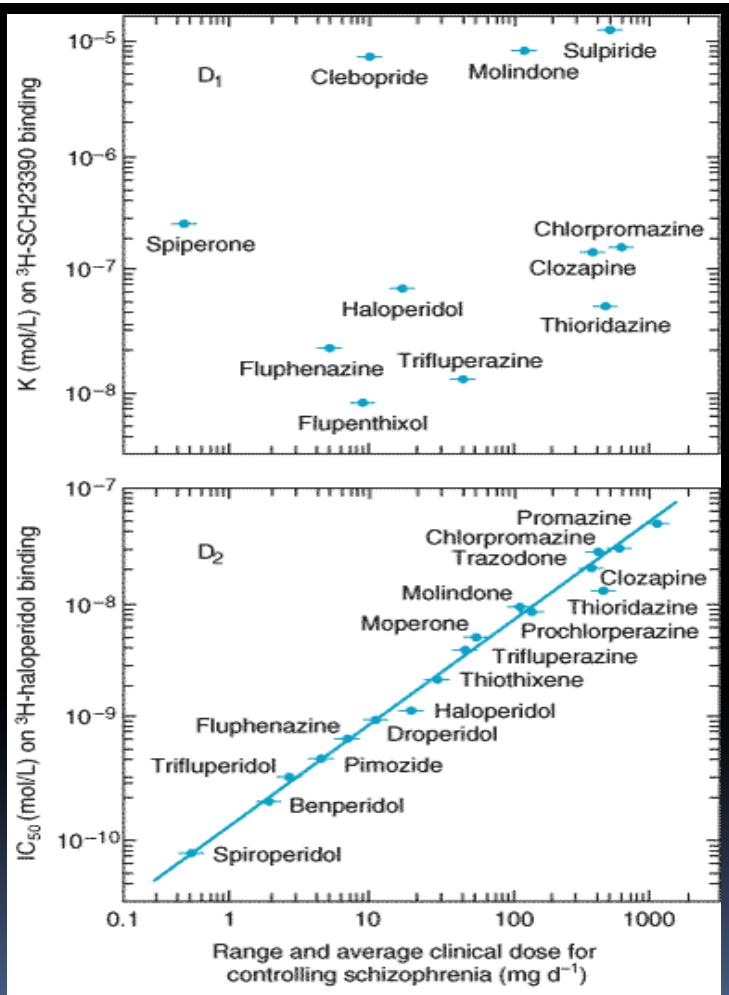
Dopaminergic pathways



System	Nucleus of origin	Site(s) of termination
Meso-telencephalic[a]		
Nigrostriatal	Substantia nigra, pars compacta; ventral tegmental area	Neostriatum (caudate-putamen), globus pallidus
Mesocortical	Ventral tegmental area; substantia nigra, pars compacta	Isocortex (mesial frontal, anterior cingulate, entorhinal, perirhinal) Allocortex (olfactory bulb, anterior olfactory nucleus, olfactory tubercle, piriform cortex, septal area, nucleus accumbens, amygdaloid complex)
Tubero-hypophysial	Arcuate and periventricular hypothalamic nuclei	Neuro-intermediate lobe of pituitary, median eminence
Retinal	Interplexiform cells, of retina	Inner and outer plexiform layers of retina
Incerto-hypothalamic	Zona incerta, posterior hypothalamus	Dorsal hypothalamic area, septum
Periventricular	Medulla in area of dorsal motor vagus, nucleus tractus solitarius, periaqueductal and periventricular gray	Periventricular and peri-aqueductal gray, tegmentum, tectum, thalamus, hypothalamus
Olfactory bulb	Periglomerular cells	Glomeruli (mitral cells)

Dopamine

- Important neurotransmitter
- Present mainly in the nigrostriatal, mesolimbic and tubero-infundibular pathways
- Originally there were only thought to be two main groups of dopamine receptor: D_1 and D_2 . These stimulate and inhibit adenylate cyclase respectively
- Subsequently D_3 (related to D_1) and D_4 (related to D_2) receptors were discovered
- D_2 receptors are mainly responsible for the actions of anti-psychotic drugs



Dopamine functions

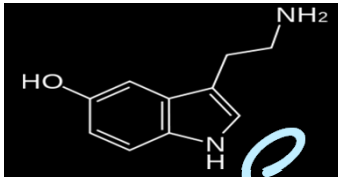
- Motor control - nigrostriatal system
  - *Deficiency results in rigidity, tremor and difficulty initiating movement*
- Behavioural effects - mesolimbic system
  - *Overactivity in rats leads to abnormal behavior*
- Endocrine control - tubero-infundibular system
  - *Dopamine and dopamine agonists suppress prolactin release, dopamine antagonists may stimulate it*

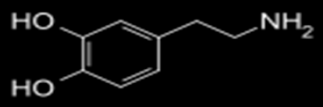
Schizophrenia - dopamine

- Amphetamine (which releases dopamine) can produce a syndrome similar to the 'positive' features of schizophrenia
- Levodopa may aggravate the condition
- Apomorphine and bromocriptine (D_2 agonists) produce behavioral abnormalities in animals
- D_2 receptor antagonists are effective in controlling the positive features of the disorder
- ? Increased D_2 receptor binding in the brains of schizophrenic subjects. Evidence of genetic variation in the D_4 receptor to which some anti-psychotic drugs have high affinity
- For antipsychotic effect require 80% D2 receptorial blockade

Schizophrenia - serotonin

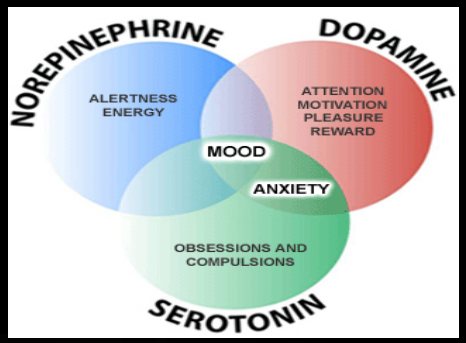
- LSD which has mixed agonist/antagonist serotonergic actions produces hallucinations and behavioral disturbance
- Some antipsychotic drugs also act at 5-HT receptors (antagonists of $5HT_2$)
- 5-HT has a modulatory effect on dopaminergic neurones
- Primavanserin (5-HT2A inverse agonist)
- Quetiapine (5-HT1A partial ag

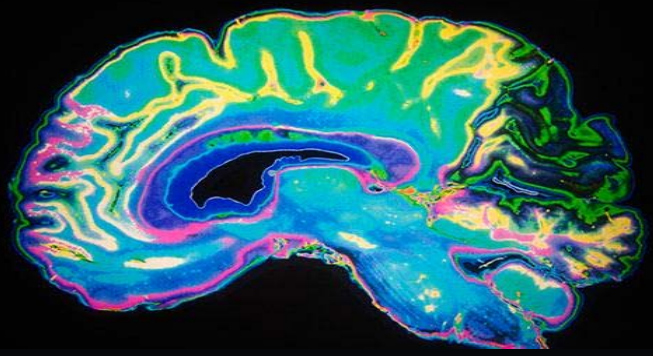




Serotonin and Dopamine

14 5





Dopamine is love. Dopamine is lust. Dopamine is adultery. Dopamine is motivation. Dopamine is attention. Dopamine is feminism. Dopamine is addiction.

Technically the only two things you enjoy!

Modes of action

- All anti-psychotic drugs have inhibitory effects on the D_2 receptor
- Some have actions against the D_4 receptor
- All have other effects - to varying degrees
  - Serotonin $5HT_2$ blockade (may improve negative symptoms)
  - Histamine H_1 blockade (drowsiness)
  - Alpha adrenoceptor blockade (postural hypotension)

How do we know they work?

- Mostly " by accident" for early drugs
  - designing drugs to reduce anxiety in surgical patients
- Clinical experience
- Clinical trials
  - especially more recent drugs
- PET scanning showing blockade of central D_2 receptors

Delayed effectiveness

- Therapeutic effects require several weeks to fully develop, because of three time dependent changes in dopamine transmission:
  - 1. Blockade of postsynaptic receptors will cause dopamine synthesis, release and metabolism.
  - 2. Continued blockade causes depolarizational block.
  - 3. Dopamine release reduced in mesolimbic and nigrostriatal dopaminergic systems (effect plus EPS side effects development)

Symptom assessment

- Brief Psychiatric Rating Scale (BPRS)
- Positive and Negative Symptoms Scale (PANSS)

PANSS

Positive scale

Delusions, Conceptual disorganization,
Hallucinations
Hyperactivity
Grandiosity
Suspiciousness/persecution
Hostility

Negative scale

Blunted affect
Emotional withdrawal. Poor rapport
Passive/apathetic social withdrawal
Difficulty in abstract thinking
Lack of spontaneity and flow of conversation
Stereotyped thinking

General Psychopathology scale

Somatic concern
Anxiety
Guilt feelings
Tension
Mannerisms and posturing
Depression
Motor retardation
Uncooperativeness
Unusual thought content
Disorientation
Poor attention
Lack of judgment and insight
Disturbance of volition
Poor impulse control
Preoccupation, Active social avoidance

BPRS

1 Somatic concern
2 Anxiety
3 Depression
4 Suicidality
5 Guilt
6 Hostility
7 Elated Mood
8 Grandiosity
9 Suspiciousness
10 Hallucinations
11 Unusual thought content
12 Bizarre behaviour
13 Self-neglect
14 Disorientation
15 Conceptual disorganisation
16 Blunted affect
17 Emotional withdrawal
18 Motor retardation
19 Tension
20 Uncooperativeness
21 Excitement
22 Distractibility
23 Motor hyperactivity
24 Mannerisms and posturing

Clinical effects

- Control the 'positive' features of the disease, but little effect on the 'negative' features
  - clozapine may be superior in this regard
- The main side-effects are on the extrapyramidal motor system (EPS)
  - Acute dystonias (reversible)
    - Akathisia (hours)
    - Dystonias (hours to days)
    - Parkinsonism (weeks to months)
      - rigidity, tremor, and loss of mobility
  - Tardive dyskinesia (months to years) (irreversible)
    - Repetitive abnormal movements of face and upper limbs
    - Thought to be due to proliferation of D_2 receptors in the striatum

Akathisia

- Subjective feeling of restlesness
- Unable to sit still, pacing
- Incidence 20-30%, lower with low dose
- Dif Dx.: psychosis, agitation, anxiety
- Tx: Propranolol 30-90 mg/d (not in asthma or diabetes)
- SSRI Antidepressants can cause akathisia too

Tardive Dyskinesia (TD)

- Slow choreo-athetotic movements
- Oro-facial muscles
- Risk 4% per year of exposure
  - Risk factors elderly women, mood DO, diab.
- Risk management
  - document informed consent, AIMS Tests
- Tx?: Vit E 1600 U/d, Clozapine low risk

Neuroleptic Malignant Syndrome (NMS)

- Medical Emerg, mort. 20% (now 4%)
- 1. Fever >100.4F / 37.5C
- 2. Severe EPS: lead-pipe/cogwheel rigidity, sialorrhea, oculogyric crisis
- 3. Autonomic DysFx: BP fluctuations, tachycardia, tachypnea, diaphoresis
- Also: Alt. conciousness, delirium, leukocytosis (>15.000 WBC), CPK > 300, seizures, arrithmias, mioglobinuria

NMS

- Incidence 0.1-1%, (60% of it in 1st 2 wks)
- Risk factors: multiple IM injections, high dose, rapid increase of dose agitation, dehydration, heat, lithium use
- Tx: STOP ALL antipsychotics, Metoclopramide, antidepressants

NMS Treatment

- Stop ALL Antipsychotics
- Dif. Dx: fever & delirium
- Dantrolene (muscle relax) 1-3 mg/kg/day NTE 10 mg/kg/d
- Bromocriptine (DA Agonist) 5 mg tid-qid
- Supportive Tx:
  - IV fluids, antipyretics, cooling blankets, close cardiac & renal monitoring

Clinical effects

- Newer 'atypical' anti-psychotic drugs are less inclined to produce these effects - possible due to their greater affinity for the mesolimbic over the striatal areas of the brain

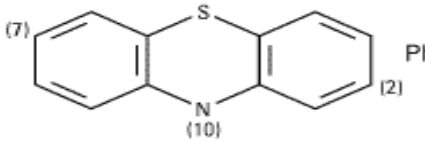
Other effects

- Some are effective anti-emetics
- Anti-muscarinic effects lead to dry mouth, blurred vision, difficulty with micturition
- α antagonist effects lead to postural hypotension
- Antihistamine effects (H_1 receptor) lead to drowsiness
- Prolactin stimulation may lead to breast development
- Agranulocytosis is fairly common with an 'atypical' drug – clozapine which can also cause a myocarditis
- 'Neuroleptic malignant syndrome' is a rare but serious effect leading to extrapyramidal rigidity, autonomic instability and hyperthermia

Other effects

Type	Manifestations	Mechanism
Autonomic nervous system	Loss of accommodation, dry mouth, difficulty urinating, constipation	Muscarinic cholinoceptor blockade
	Orthostatic hypotension, impotence, failure to ejaculate	Alpha adrenoceptor blockade
Central nervous system	Parkinson's syndrome, akathisia, dystonias	Dopamine receptor blockade
	Tardive dyskinesia	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

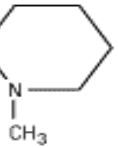
PHENOTHIAZINE DERIVATIVES



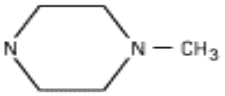
Phenothiazine nucleus

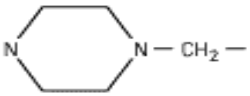
Aliphatic side chain

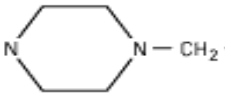
Chlorpromazine (2) — Cl (10) — $CH_2 - CH_2 - CH_2 - N - (CH_3)_2$

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

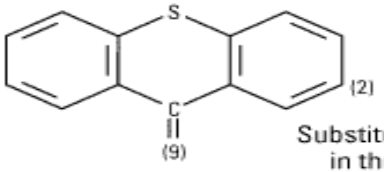
Piperazine side chain

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) — $CH_2 - CH_2 - CH_2 - N$  $N - CH_2 - CH_2 - OH$

THIOXANTHENE DERIVATIVE

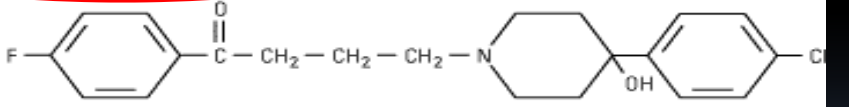


Substituting C for N in the nucleus

Thiothixene (2) — $SO_2N(CH_3)_2$

(9) = CH — $CH_2 - CH_2 - N$  $N - CH_3$

BUTYROPHENONE



Haloperidol

Typical Antipsychotics

- **Phenothiazines**
  - **chlorpromazine** (Chlorpromazine Mixture, Chlorpromazine Mixture Forte, Largactil, Hibernal)
  - **Levomepromazine (methotrimeprazine)** (Tisercin)
  - **fluphenazine** (Moditen, Anatensol, Modecate)
  - **pipotiazine** (Piportil)
  - **flupenthixol** (Fluanxol depot)
  - **chlorprothixene** (Truxal)
  - **zuclopenthixol** (Cisordinol, Clopixol)
  - **sertindole** (Serdolect)
  - **ziprasidone** (Zeldox, Zeldox, Zipwell)
  - **pimozide** (Orap) n.a.
  - **thioridazine** (Aldazine)
  - **trifluoperazine** (Stelazine)

Butyrophenones

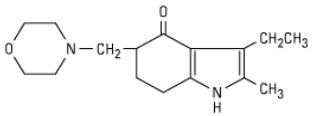
droperidol (Xomolix, Droleptan Injection)
haloperidol (Haldol, Serenace)
Benperidol (Anquil) (to control hypersexuality syndromes

- Thioxanthene derivatives
  - **Flupentixol (FLUANXOL DEPOT 20 mg/ml)**
  - **Clopenthixol**
  - **Chlorprothixene (TRUXAL)**
  - **Tiotixene**
  - **Zuclopenthixol (CISORDINOL)**

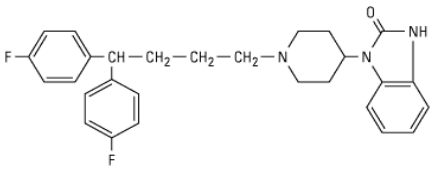
Newer Antipsychotics

- **Atypical agents**
  - **aripiprazole** (Abilify) (D2 partial agonist)
  - **clozapine** (Leponex, Clopine, Clozaril)
  - **olanzapine** (Zyprexa)
  - **risperidone** (Risperdal)
  - **quetiapine** (Seroquel, Kventiax)
  - **sulpride** (Depral)
  - **tiapride** (Tiapridal)
  - **amisulpride** (Solian, Amitrex)
  - **paliperidone** (Invega)
  - **loxapine** (Adasuve)
  - **Cariprazine** (Reagila) (D3>>>D2 partial agonist)

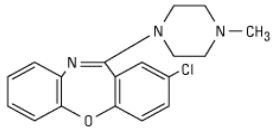
Rapidly dissociates from D2 receptors



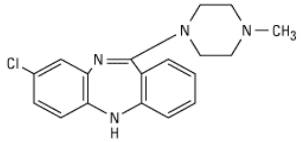
Molindone



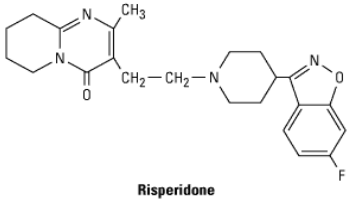
Pimozide



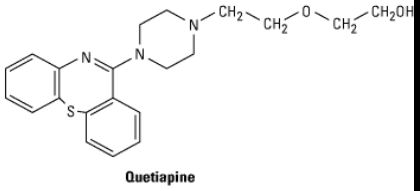
Loxapine



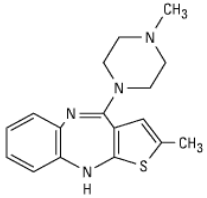
Clozapine



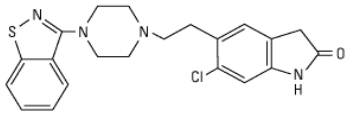
Risperidone



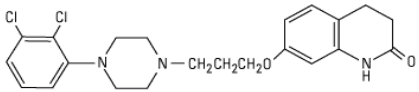
Quetiapine



Olanzapine



Ziprasidone



Aripiprazole

List of approved antipsychotics around the world

Typical or conventional or first-generation antipsychotics (FGAs) *N*=51			
Phenothiazines (N=23)			
Acetophenazine	Butaperazine	Chlorproethazine	Chlorpromazine
Cyamemazine	Dixyrazine	Fluphenazine	Mesoridazine
Methotrimeprazine	Perazine	Periciazine	Perphenazine
Piperacetazine	Pipoptiazine	Prochlorperazine	Promazine
Propericiazine	Sulforidazine	Thioridazine	Thiopropazate
Thioproperazine	Trifluoperazine	Triflupromazine	
Non-Phenothiazines (N=28)			
Benperidol	Bromperidol	Chlorprothixene	Clocapramine
Clopenthixol	Clothiapine	Droperidol	Fluanisone
Flupenthixol	Fluspirilene	Haloperidol	Loxapine
Melperone	Molindone	Moperone	Mosapramine
Nemonapride	Oxypertine	Penfluridol	Pimozide
Pipamperone	Sulpiride	Sultopride	Thiothixene
Tiapride	Timiperone	Trifluperidol	Zuclopenthixol
ATYPICAL OR SECOND GENERATION ANTIPSYCHOTICS (SGAs) *N*=11			
Amisulpride	Aripiprazole	Clozapine	Olanzapine
Paliperidone	Perospirone	Quetiapine	Risperidone
Sertindole	Ziprasidone	Zotepine	

Antipsychotics

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

[1]At dosages below 8 mg/d.

- Indole derivatives
  - **Oxypertine**
  - **Molindone**
  - **Sertindole**
  - **Ziprasidone**
  - **Lurasidone**

Differences among Antipsychotic Drugs

- Chlorpromazine: $\alpha_1 = 5\text{-}HT_2 > D_2 > D_1$
- Haloperidol: $D_2 > D_1 = D_4 > \alpha_1 > 5\text{-}HT_2$
- Clozapine: $D_4 = \alpha_1 > 5\text{-}HT_2 > D_2 = D_1$

Adverse effects of antipsychotics

- Extrapyramidal effects
  - Dsytonia (oculogyric crisis, glossospasm, torticollis, tongue protrusion)
  - Akathisia
  - Pseudoparkinsonism
  - Tardive dyskinesia
- Sedation
- Anticholinergic effects
- Orthostatic hypotension
- Obstructive jaundice with phenothiazines

Acute, reversible

Chronic, irreversible

Clinical Trials (~1600 RCTs) with Atypical Antipsychotics

- Claims
  - lower doses
  - reduced side effects
  - more effective (especially negative symptoms)
  - better compliance
- Evidence (questionable, because company sponsored trials)
  - trials have been quite small and involved patients previously heavily treated and somewhat 'resistant'
  - trials have tended to show equivalent efficacy and better side effect profiles with newer drugs
  - head to head trials claimed superiority of olanzapine over risperidone (but company sponsored and controversial); some "parallel publications"
- Government sponsored trials:
  - Clinical Antipsychotic Trial of Intervention Effectiveness in schizophrenia in the U.S.A. (CATIE)
  - Cost Utility of the Latest Antipsychotics in Severe Schizophrenia in the U.K. (CUtLASS)
- Costs
  - Much higher with new drugs (10-40 times higher)
  - Global direct expenditures on antipsychotic medications multiplied over 20-fold over the past decade from approximately $ 0.5 billion/year to more than $ 15 billion/year

Metabolic effects

Weight gain over 1 year (kg)	
aripiprazole	1
amisulpride	1.5
quetiapine	2 – 3
risperidone	2 – 3
olanzapine	> 6
clozapine	> 6

Insulin resistance

- Prediabetes (impaired fasting glycaemia) has ~ 10% chance / year of converting to Type 2 diabetes
- Prediabetes plus olanzapine has a 6-fold increased risk of conversion
- If olanzapine is stopped 70% will revert back to prediabetes

Stroke in the elderly

- Risperidone and olanzapine associated with increased risk of stroke when used for behavioural control in dementia
- Risperidone 3.3% *vs* 1.2% for placebo
- Olanzapine 1.3% *vs* 0.4% for placebo
- However, large observational database studies
  - Show no increased risk of stroke compared with typical antipsychotics or untreated dementia patients

Conclusions

- Atypical antipsychotics have serotonin blocking effects as well as dopamine blockade
- As a group have less chance of extrapyramidal side effects
- Most have weight gain and insulin resistance as a side effect (except perhaps aripiprazole and maybe amisulpride)
- May be associated with stroke when used for behavioural control in dementia
- Many have idiosyncratic toxicities

	D_1	D_2	α-adr	H_1	mACh	5-HT_2	EPS	Sed.	Hypo.	Other	
Classical											
Chlorpromazine	++	+++	+++	++	++	++	++	++	++	Increased prolactin (gynaecomastia) Hypothermia Anticholinergic effects Hypersensitivity reactions Obstructive jaundice	Phenothiazine class **Fluphenazine, trifluperazine** are similar, but: • do not cause jaundice • less hypotension • more EPS Fluphenazine available as depot preparation
Thioridazine	+	++	+++	+	++	++	+	++	++	As chlorpromazine, but does not cause jaundice	Phenothiazine class First drug with lower EPS tendency
Haloperidol	+	+++	++	–	±	+	+++	—	++	As chlorpromazine, but does not cause jaundice Fewer anticholinergic side-effects	Butyrophenone class Widely used antipsychotic drug Strong EPS tendency
Flupenthixol	++	+++	++	++	–	+++	++	+	+	Increased prolactin (gynaecomastia) Restlessness	**Clopenthixol** is similar Available as depot preparations
Atypical											
Sulpiride	—	+++	—	—	—	—	+	+	—	Increased prolactin (gynaecomastia)	Benzamide class Selective D_2/D_3 antagonist Less EPS than haloperidol Poorly absorbed. **Remoxipride and pimozide** (long acting) are similar
Clozapine	++	++	++	++	++	+++	—	++	+	Risk of agranulocytosis (~1%): regular blood counts required Seizures Sedation Salivation Anticholinergic side-effects Weight gain	Dibenzodiazepine class Potent antagonist at D_4-receptors No EPS Shows efficacy in "treatment-resistant" patients Effective against negative and positive symptoms **Olanzapine** is similar, without risk of agranulocytosis
Risperidone	—	++	++	++	++	+++	+	++	+	Weight gain EPS at high doses Hypotension	Significant risk of EPS ? Effective against negative symptoms Potent on D_4-receptors
Sertindole	—	++	++	—	—	+++	+	+	++	Ventricular arrhythmias (ECG checks advisable) Weight gain Nasal congestion	Long plasma half-life (~3 days) ? Effective against negative symptoms
Quetiapine	—	+	+++	—	+	+	+	++	++	Tachycardia Agitation Dry mouth Weight gain	Novel type, acting mainly on α-adrenoceptors Not yet fully evaluated

$D_{1/2}$, types of dopamine receptor; EPS, extrapyramidal side-effects; Sed., sedation; Hypo., hypotension; adr, adrenoceptor; mACh, muscarine acetylcholine; ECG, electrocardiograph.

Pharmacokinetic and metabolic properties of atypical antipsychotic drugs

Drug and active (inactive) metabolite	Half-life (h) in plasma	Oral bioavailability (%)	Cytochrome P-450 substrate
Amisulpride	12	33–45	–
Aripiprazole	58–79*	87	3A4, 2D6
Dehydroaripiprazole	94		
Clozapine	8.1–13.7	50–60	1A2, 3A4, 2C19, (2D6)
Demethylclozapine	5.5–35		
(Clozapine N-oxide)			
Olanzapine	27–39	80	1A2, (2D6)
(N-glucuronide (main metab.))			
(N-oxide, demethylolanzapine)			
Paliperidone (9-OH-risperidone)	23	28	–
Quetiapine	5.8–6.8	9	3A4, (2D6)
(7-OH-quetiapine)			
(Quetiapine sulfoxide)			
Norquetiapine			
Risperidone	2.8 ± 0.5*	66	2D6, 3A4
9-OH-risperidone	20.5 ± 2.9		(3A4)
Sertindole	73–93	74	2D6, 3A4
Norsertindole	242 ± 222		
Ziprasidone	3–10	59	3A4, 2C19
S-methyl-dihydroziprasidone			
(Zipras. sulfoxide and sulfone)			
Zotepine	15–24	10	1A2, 3A4, 2D6
Norzotepine	19		

*In extensive metabolisers (EM CYP2D6).

Differences among Antipsychotic Drugs

- All effective antipsychotic drugs block D2 receptors
- Chlorpromazine and thioridazine
  - block α1 adrenoceptors more potently than D2 receptors
  - block serotonin 5-HT2 receptors relatively strongly
  - affinity for D1 receptors is relatively weak
- Haloperidol
  - acts mainly on D2 receptors
  - some effect on 5-HT2 and α1 receptors
  - negligible effects on D1 receptors
  - Used in the treatment of Gilles de la Tourette sy. (facial, vocal tics, coprolalia, echolalia)
- Pimozide and amisulpride[†]
  - act almost exclusively on D2 receptors

Differences among Antipsychotic Drugs

- Clozapine
  - binds more to D4, 5-HT2, α1, and histamine H1 receptors than to either D2 or D1 receptors
- Risperidone
  - about equally potent in blocking D2 and 5-HT2 receptors
- Olanzapine
  - more potent as an antagonist of 5-HT2 receptors
  - lesser potency at D1, D2, and α1 receptors
- Quetiapine
  - lower-potency compound with relatively similar antagonism of 5-HT2, D2, α1, and α2 receptors

Differences among Antipsychotic Drugs

- Clozapine, olanzapine and quetiapine
  - potent inhibitors of H1 histamine receptors
  - consistent with their sedative properties
- Aripiprazole
  - partial agonist effects at D2 and 5-HT1A receptors
  - Blocks 5-HT2A receptors
  - In case of autistic children good for the treatment of irritability

Features of clozapine

- Advantage
  - Effective in schizophrenia refractory to other drugs
  - Reduce the risk of suicide
- Disadvantage
  - Relaps after discontinuation is rapid and severe
  - Myocarditis
  - Agranulocytosis (1-2 % in the 6-18th week of the therapy. First 6 month weekly, after three weekly blood count is necessary
  - Can provoke seizures
  - Weight gain (>6 kg/year)
  - Insulin resistance and diabetes

Quetiapine (KETILEPT, KVENTIAX, SEROQUEL

- Schizophrenia, maniac disorder
- Side effects

Features of thioridazine

- Ventricular arrhythmias (TdP)
- Anti-muscarinic effect
- Quinidine-like effect
- Causes retineal deposits (resembling to retinitis pigmentosa) „browning vision”

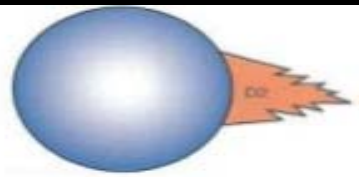
A „receptorome” for several antipsychotics regarding some dopaminergic, serotonergic, adrenergic, muscarinic and histaminic receptors.

Loxapine (ADASUVE)

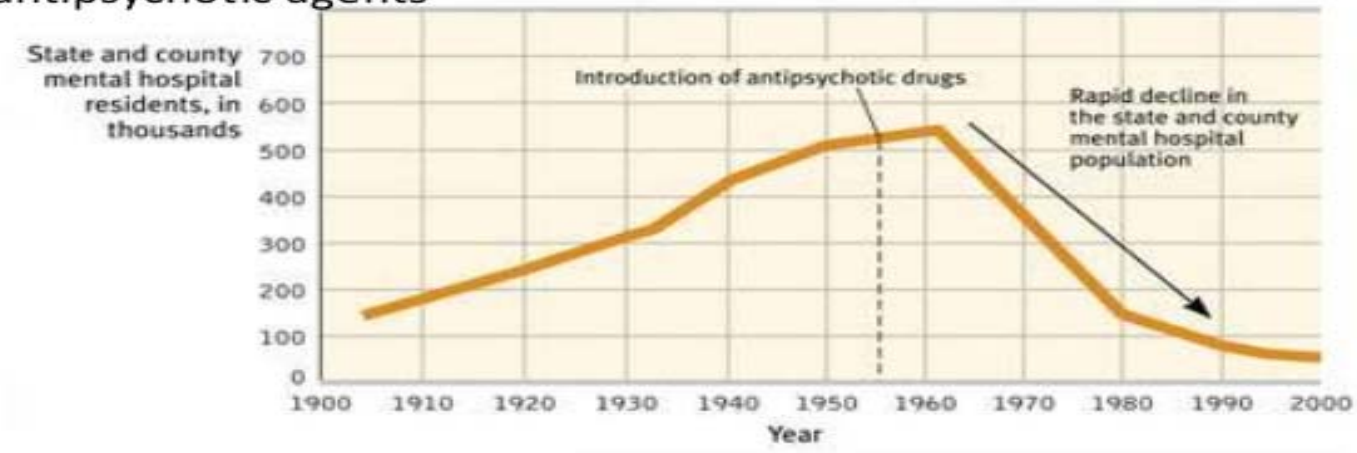
- D2 and 5-HT2A antagonist (beta antagonist, M blocking))
- Side effects:
  - Bronchospams
  - Hypoventilation
  - Extrapyramidal signs
  - Tardive dyskinesia
  - Neurolept malignant syndrome
  - Hypotony
  - QT prolongation
  - Convulsions
  - Anticholinerg actions

	SEDATION	WEIGHT GAIN	EPS
Best choice	Aripiprazole	Aripiprazole	Clozapine
	Iloperidone	Lurasidone	Iloperidone
	Lurasidone	Ziprasidone	Quetiapine
	Paliperidone	Asenapine	Aripiprazole
	Risperidone	Iloperidone	Asenapine
	Ziprasidone	Paliperidone	Lurasidone
	Asenapine	Risperidone	Olanzapine
	Olanzapine	Quetiapine	Ziprasidone
	Clozapine	Clozapine	Paliperidone
Worst choice	Quetiapine	Olanzapine	Risperidone

History of Antipsychotics



- **1953**: an antihistamine agent (cholpromazine) is found to improve psychosis in schizophrenics
- **1960-1970**: identification of D_2 blockade as the key mechanism, development of these first-generation of antipsychotic agents



Other uses of antipsychotic substances

- Bipolar disorder
- Psychomotor agitation, severe anxiety (chlorpromazine, haloperidol)
- Agitation and restlessness in elderly (risperidone)
- Parkinson's related psychosis (halucinations, delusions) (atypical primavanserin (NUPLAZID) inverse agonist/antagonist on 5-HT2A and 5-HT2C)
- Restlessnes and pain in palliative care (levomepromazine (methotrimeprazine))
- Nausea and vomiting (Chlorpromazine, haloperidol)
- Motor tics, intractable hiccup (chlorpromazine, haloperidol)
- Antisocial sexual behaviour (benperidol)
- Involuntary movements in Huntington's disease (haloperidol)

Aspirin in the treatment of schizophrenia

Aspirin given as adjuvant therapy to regular antipsychotic treatment reduces the symptoms of schizophrenia spectrum disorders. The reduction is more pronounced in those with the more altered immune function. Inflammation may constitute a potential new target for antipsychotic drug development.

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Future perspectives

- PDE10A inhibitors: activates cAMP/PKA signalling in basal ganglia → inhibition of D2 and potentiation of D1 rec mechanisms (control of negative symptoms)
- α7 nicotinic receptor agonists
- H3 antagonists
- 5-HT6 antagonists
- Xanomeline: M1 and M4 agonist and M5 antagonist

Lithium (LITHICARB 500mg)

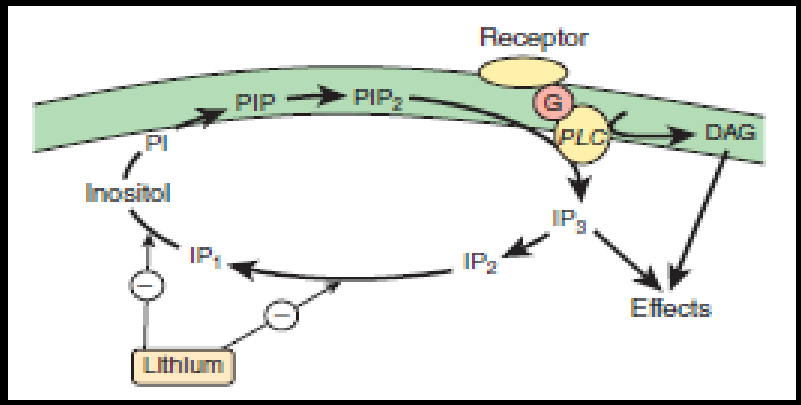
PK

- A: 6-8 h (peak 30-120 min)
- D: Body water (Vd: 0,5 L/kg), no p.b.
  Th: 0,5-1,0 mM (above 2-3 mM convulsions, coma)
- M: ---
- E: urine

Side effects

•Neurological: tremor, choroathetosis, ataxia, aphasia
•Thyroid: ↓
•Renal: polyuria, polydipsia
•Edema: Na^+ retention (frequent)
•Cardiac: SSS
•Pregnancy: Newborn: lethargy, poor suck, cyanosis, Moro reflex ↓, hepatomegaly
•Misc: Acneiform eruptions, leukocytosis,

MOA



Uncouple vasopressin rec → polyuria
Uncouple TSH rec → hypothyreoidism
Na^+K^+ATPase
Choline uptake ↑
Enhance serotonin/dopamine turnover

Dose: 600-3600 mg for profilaxis

Enzymes effected by lithium

Enzyme	Enzyme Function; Action of Lithium
Inositol monophospha-tase	The rate-limiting enzyme in inositol recycling; inhibited by lithium, resulting in depletion of substrate for IP_3 production (Figure 29–4)
Inositol polyphosphate 1-phosphatase	Another enzyme in inositol recycling; inhibited by lithium, resulting in depletion of substrate for IP_3 production (Figure 29–4)
Bisphosphate nucleotidase	Involved in AMP production; inhibited by lithium; may be target that results in lithium-induced nephrogenic diabetes insipidus
Fructose 1,6-biphosphatase	Involved in gluconeogenesis; inhibition by lithium of unknown relevance
Phosphoglucomutase	Involved in glycogenolysis; inhibition by lithium of unknown relevance
Glycogen synthase kinase-3	Constitutively active enzyme that appears to limit neurotrophic and neuroprotective processes; lithium inhibits

AMP, adenosine monophosphate; IP_3, inositol 1,4,5-trisphosphate.