Antidepressants

- Depression
  - major (endogenous)
    - **MDD (major depressive disorder)**
  - reactive
  - bipolar disease (manic-depressive)
- Antidepressants
  - CDC 2007: most commonly prescribed in the USA
  - **used NOT only in MDD**
    - e.g. panic disorder / GAD / PTSD / OCD / pain /

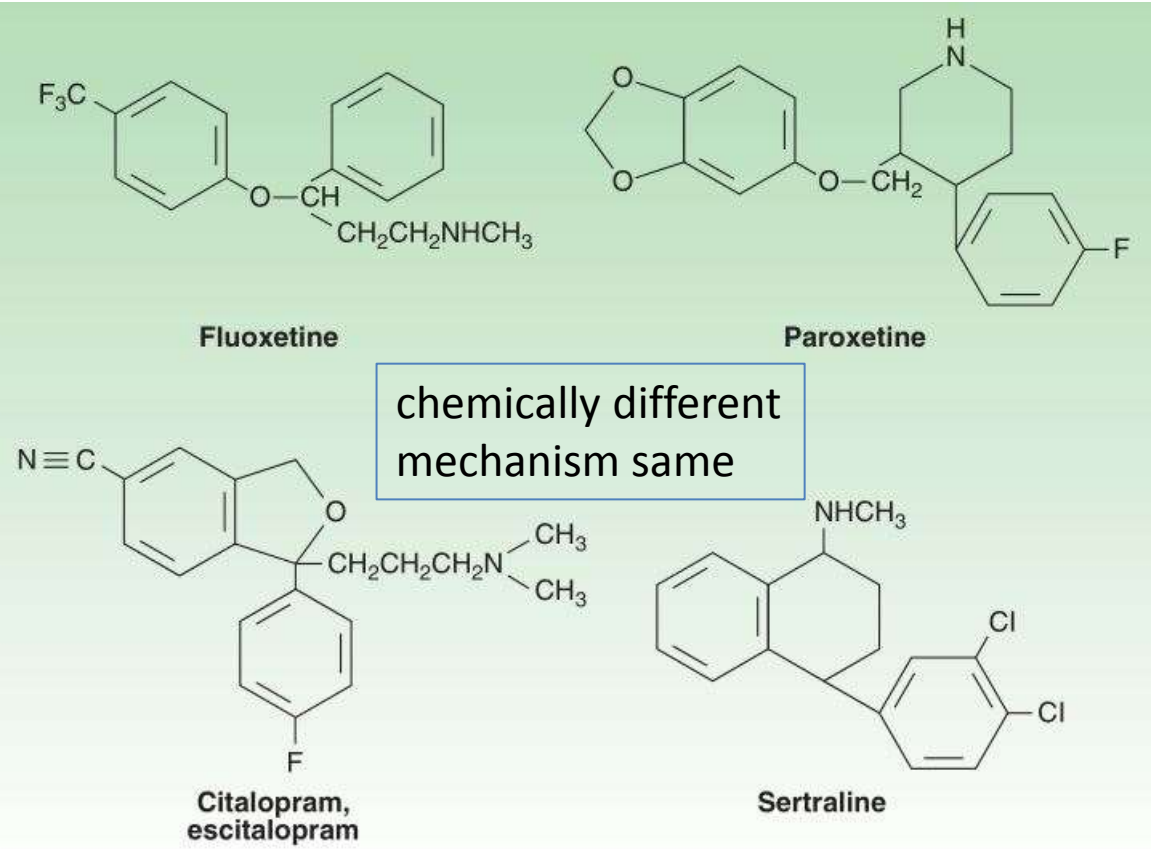
Pathophysiology of depression

- **monoamines** (↓ NE and 5-HT, see reserpine)
  - clinically effective drugs ↑ NE/5-HT
  - BUT there are problems:
    - post mortem no decrease
    - molecular/clinical onset time does not correlate
    - in the long run: receptor downregulation
    - not all drugs influence NE and 5-HT levels (see bupropion)
- **neurotrophic**
  - BDNF (**B**rain-**D**erived **N**eurotrophic **F**actor)
  - therapy: ↑ neurogenesis, synaptic connectivity
- **neuroendocrine**
  - HPA axis abnormalities / thyroid dysregulation / sexual steroids

Classification

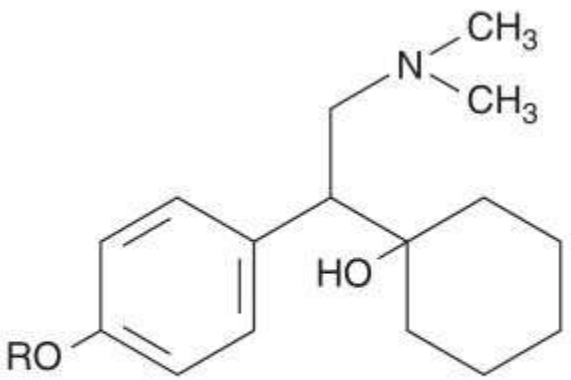
- **SSRI** (selective 5-HT)
  - **fluoxetin** / citalopram / fluvoxamine / sertraline / paroxetine
- Serotonin-norepinephrine reuptake inhibitors (5-HT and NE)
  - sSNRI
    - duloxetine / venlafaxine / desvenlafaxine / milnacipran
  - tricyclic antidepressants
    - imipramin → desipramin / amitryptilin → nortriptylin / clomipramin
- 5-HT_{2A} antagonists
  - trazodone / nefazodone
- Tetracyclic and unicyclic antidepressants (miscellaneous)
  - bupropion / mirtazapine / amoxapine / maprotiline
- MAO inhibitors
  - *phenelzine / tranylcypromine* / selegiline / moclobemide

Selective serotonin reuptake inhibitors (SSRI)

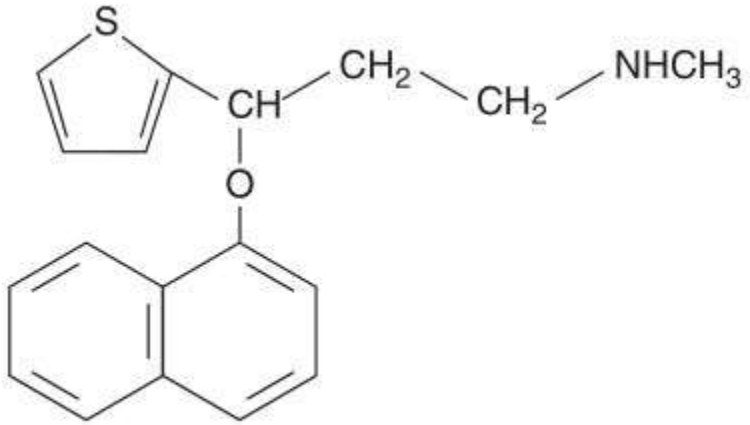


- commonly used
  - overdose is safe
  - rare adverse effects
  - low cost

Selective SNRI



R = CH_3 : **Venlafaxine**
R = H : **Desvenlafaxine**

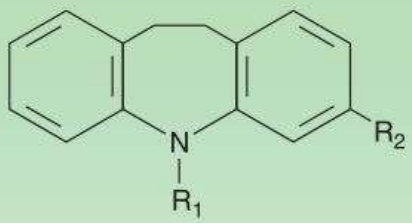


Duloxetine

chemically different
mechanism same
better tolerated than TCA

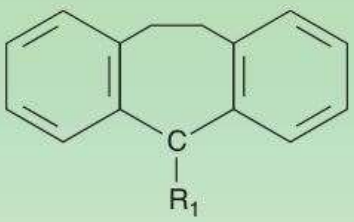
- less commonly used
  - overdose is dangerous
  - adverse effects

Tricyclic antidepressants



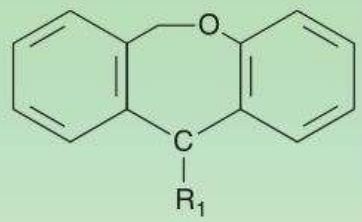
R_1:–$(CH_2)_3N(CH_3)_2$
R_2: H

Imipramine



R_1: = $CH(CH_2)_2N(CH_3)_2$

Amitriptyline



R_1: = $CH(CH_2)_2N(CH_3)_2$

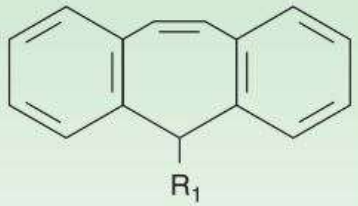
Doxepin

R_1: = $(CH_2)_3NHCH_3$
R_2: H

Desipramine

R_1: = $CH(CH_2)_2NHCH_3$

Nortriptyline



R_1: = $(CH_2)_3NCH_3$

Protriptyline

R_1: = $(CH_2)_3N(CH_3)_2$
R_2: – Cl

Clomipramine

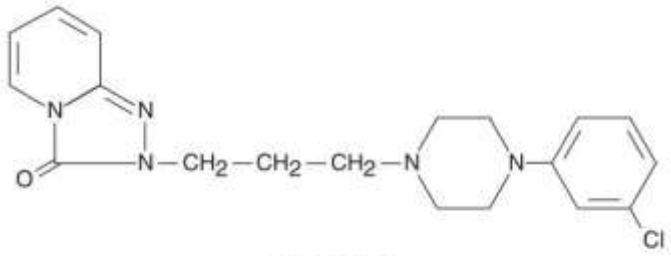
chemically similar
mechanism same
older than SSRI

R_1: = $CH_2CH(CH)_3CH_2N(CH_3)_2$
R_2: – H

Trimipramine

- less commonly used
  - overdose is dangerous
  - adverse effects

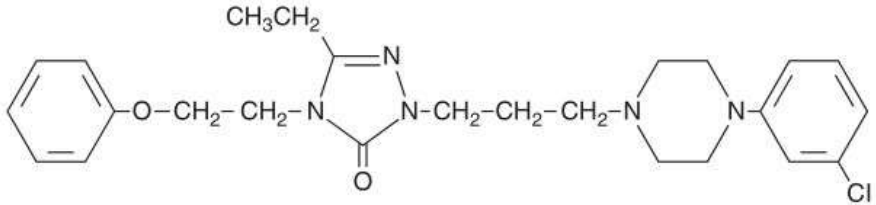
5-HT_2 antagonists



Trazodone

- its use ↓ in MDD
- unlabeled hypnotic
- no tolerance / dependence

chemically related
mechanism same
older than SSRI



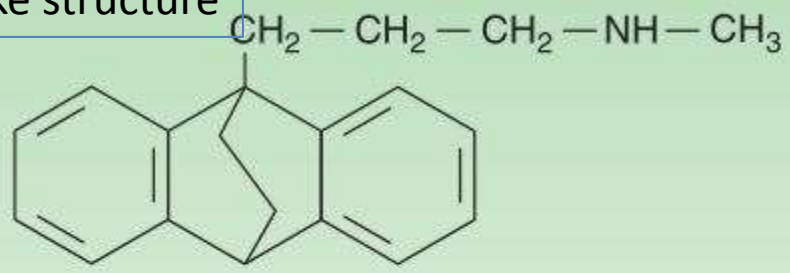
Nefazodone

hepatotoxicity !

Tetracyclic and unicyclic antidepressants

Amoxapine

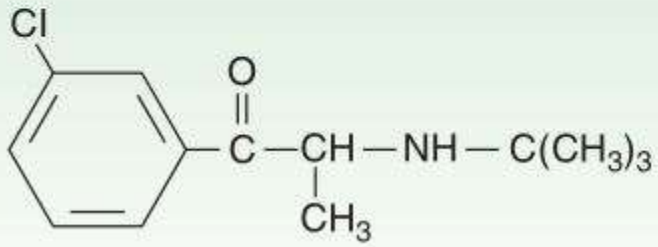
TCA like structure



Maprotiline

do not fit into other groups
"special" mechanism

Mirtazapine



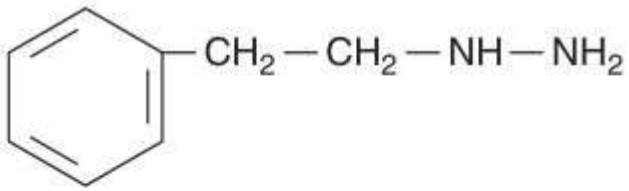
Bupropion

α_2 antagonist
no sexual dysfunction

amphetamine like, dopamine uptake↓
stimulant
no sexual dysfunction

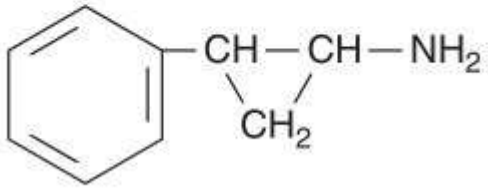
Monoamine oxidase inhibitors

oldest group
now rarely used



Phenelzine

irreversible
non-selective



Tranylcypromine

amphetamine like
stimulant

selegiline
moclobemide

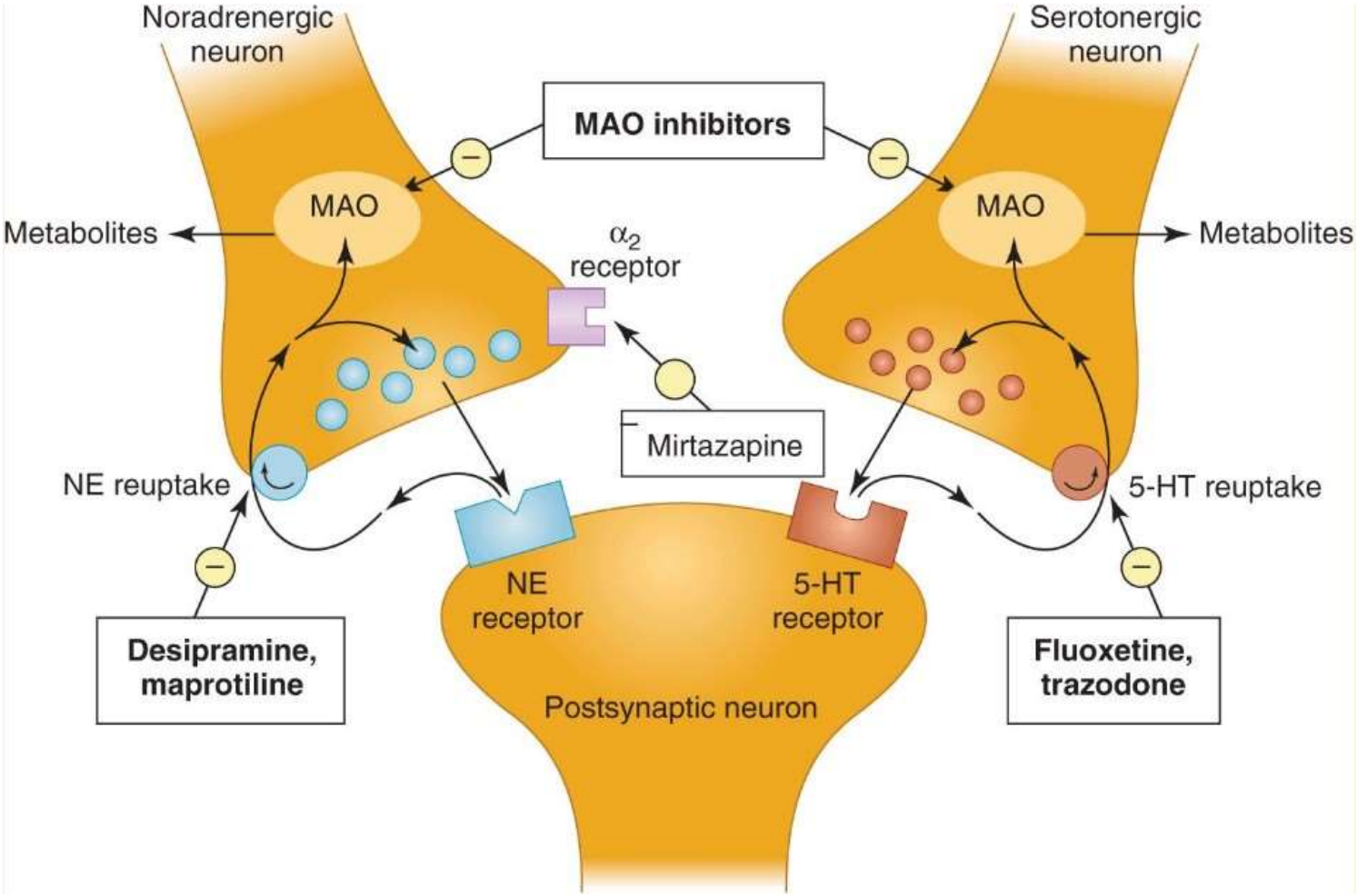
reversible
MAO-B selective

Pharmacokinetics

(of antidepressants)

- good oral absorption
- large V_d ($\rightarrow$ hemodialysis not effective)
- metabolism
  - significant metabolism („first pass” too)
  - active metabolites (e.g. TCAs, fluoxetin)
  - interactions (e.g. MAOIs inhibit cP450 too)
- generally long half-life (12-24 h)
  - exceptions:
    - 5-HT_2 antagonists – short
    - fluoxetin’s metabolite – very long (a few days)
    - MAOIs – very long (weeks)

Mechanism of action



Drug	Sedation	Muscarinic Receptor Block	NE Reuptake Block	5-HT Reuptake Block
Tricyclics				
Amitriptyline[a]	+++	+++	+	++
Desipramine	+	+	+++	+
Doxepin[a]	+	++	+++	+
Imipramine	++	++	+	++
Nortriptyline	++	+	++	+
SSRIs				
Citalopram, etc	0	0	0	+++
Heterocyclics—SNRIs				
Duloxetine	0	0	++	+++
Venlafaxine	0	0	+	+++
Heterocyclics—5-HT_2 antagonists				
Nefazodone	++	+	0/+	+
Trazodone	++	0	0	+
Heterocyclics—other				
Amoxapine	++	++	++	+
Bupropion	0	0	0	0
Maprotiline	+	+	++	0
Mirtazapine[b]	++	++	+	0

SNRI, serotonin-norepinephrine reuptake inhibitor.

[a]Significant α_1 antagonism.

[b]Significant H_1 and α_2 antagonism.

0/+, minimal activity; +, mild activity; ++, moderate activity; +++, high activity.

Clinical use of antidepressants

- major depressive disorder
  - individual drug selection (efficacy is similar)
  - generally the newer drugs (safety, less adverse effects)
  - SSRI: in case of overweight patients
  - TCAs: in case of insomnia, decreased appetite, weight loss
  - MAOI: in case of anxiety, phobias, hypochondria
- other use of TCAs
  - bipolar disease
  - acute panic attacks / phobias
  - enuresis / ADHD
  - chronic pain
- SNRI
  - neuropathies (e.g. diabetic neuropathy (duloxetin))
- SSRI
  - generalized anxiety disorder/ panic / phobias / post-traumatic stress
  - bulimia / premenstrual dysphoric disorder (PMDD)
- bupropion
  - nicotin withdrawal

Adverse effects, toxicity

- TCA
  - sedation
  - sympathomimetic effects
  - atropin like effects
  - ortostatic hypotension
  - weight gain
  - **overdose is very dangerous**
    - see 3Cs (**c**oma, **c**onvulsions, **c**ardiotoxicity)
- SSRI
  - nausea / diarrhea
  - anxiety / agitation
  - insomnia / bruxism
  - weight loss / sexual dysfunct.
  - initially extrapyr. symptoms
    - e.g. akathisia, dystonia
  - **serotonin syndrome**
- mirtazapine
  - weight gain, sedation
- trazodone
  - sedation
- nefazodone
  - hepatotoxicity
- bupropion
  - anxiety, dizziness, psychosis
- venlafaxine
  - blood pressure increase
  - CNS stimulant
  - withdrawal symptoms
- MAOI
  - hypertension – see cheese react
  - CNS stimulant
  - **serotonin syndrome**

Interactions

- MAO inhibitors
  - ↑ NE: hypertensive crisis
    - tyramine (see cheese reaction) / TCAs / levodopa
  - ↑ 5-HT: serotonin syndrome
    - SSRIs / TCAs / meperidine / dextromethorphan
- TCAs
  - hypertensive crisis
    - MAO inhibitors (see above)
  - serotonin syndrome
    - MAO inhibitors (see above) / SSRIs
  - prevent antihypertensive effect of
    - guanethidine / clonidine
  - ↑ CNS depression
    - e.g. BZD / ethanol
- SSRIs
  - serotonin syndrome
    - MAO inhibitors / TCAs / meperidine / dextromethorphan
  - PK interaction: CYP450 **inhibition**
    - e.g. fluoxetine – **CYP2D6**, CYP3A4 -
    - least for citalopram

Serotonin syndrome

- severe, life threatening
- in classic form after the adminstration of two „serotoninergic" drugs (within hours)
  - e.g. MAO inhibitor + SSRI
- **symptoms**
  - change in mental state (delirium, coma)
  - **muscle rigidity,** ***myoclonus****,* tremor, **hyeprthemia**, hyperreflexia
  - increased blood pressure, diarrhea
- **treatment**
    - **discontinue serotoninergic drug / sedation (BZD)**
    - cyproheptadine
    - intubation, paralysis
    - cooling / iv. fluids / other supportive treatment

Drugs involved in serotonin syndrome

Mechanism	Drugs
increased release of serotonin	amphetamines (including: dextroamphetamine, methamphetamine) MDMA (ecstasy)
impaired reuptake from the synaptic cleft into the presynaptic neuron	cocaine / meperidine / tramadol **Selective Serotonin Reuptake Inhibitors (SSRIs)** (e.g. citalopram, fluoxetine, fluvoxamine) Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs) (e.g. venlafaxine) tricyclic antidepressants (TCAs) (pl. amitriptyline, imipramine)
inhibited serotonin metabolism	**MAOIs** (pl. phenelzine, moclobemide, selegiline)
direct serotonin agonist	buspirone triptans (pl. sumatriptan) ergot derivatives (pl. ergotamine, methylergonovine) fentanyl LSD

Schizophrenia

- **positive symptoms**
  - thought disturbances / delusions / hallucinations / paranoia
- **negative symptoms**
  - amotivation / social withdrawal / poor speech / emotional blunting
- dopamine hypothesis
  - excessive DA in mesolimbic system
  - DA agnoists → psychosis
  - DA antagonists have antipsychotic actions
  - but 5-HT seems also important in etiology

Antipsychotics: classification

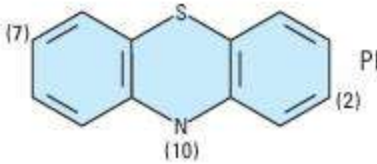
- classic drugs (neuroleptics)
  - antagonism of D_2 dopamine receptors
  - adverse extrapyramidal neurological effects
  - increased release of prolactin
  - NO effect on negative symptoms
- atypical antipsychotics - newer (2^{nd} generation) drugs
  - greater efficacy for reducing negative symptoms
  - lower risks of extrapyramidal effects
  - combine 5-HT_{2A}/5-HT_{2C} and D_2-receptor blocking actions
  - BUT hypotension, seizures, weight gain, and increased risk of type 2 diabetes mellitus and hyperlipidemia

Antipsychotics: classic drugs 1.

- phenothiazines
  - **chlorpromazine** (aliphatic derivatives)
  - thioridazine, mesoridazine (piperidine derivatives)
  - trifluoperazine, fluphenazine (piperazine derivatives)
- thioxanthenes
  - thiotixene
- butyrophenones
  - **haloperidol**

Antipsychotics: classic drugs 2.

PHENOTHIAZINE DERIVATIVES



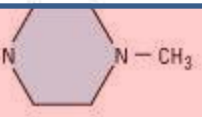
Phenothiazine nucleus

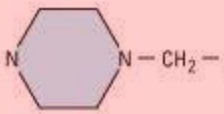
Aliphatic side chain

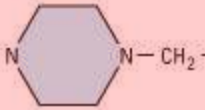
Chlorpromazine (2) – Cl (10) – $CH_2 – CH_2 – CH_2 – N – (CH_3)_2$

Thioridazine (2) – SCH_3 (10) – $CH_2 – CH_2$ – 

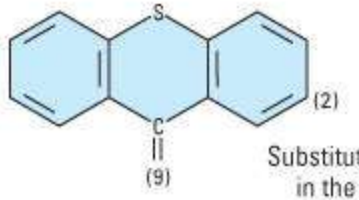
Piperazine side chain

Trifluoperazine (2) – CF_3 (10) – $CH_2 – CH_2 – CH_2 – N$  $N – CH_3$

Perphenazine (2) – Cl (10) – $CH_2 – CH_2 – CH_2 – N$  $N – CH_2 – CH_2 – OH$

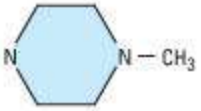
Fluphenazine (2) – CF_3 (10) – $CH_2 – CH_2 – CH_2 – N$  $N – CH_2 – CH_2 – OH$

THIOXANTHENE DERIVATIVE

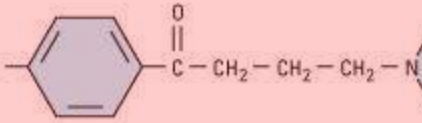
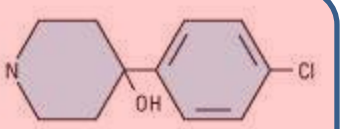


Substituting C for N in the nucleus

Thiothixene (2) – $SO_2N(CH_3)_2$

(9) = CH – $CH_2 – CH_2 – N$  $N – CH_3$

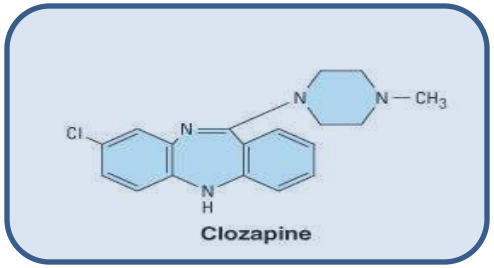
BUTYROPHENONE

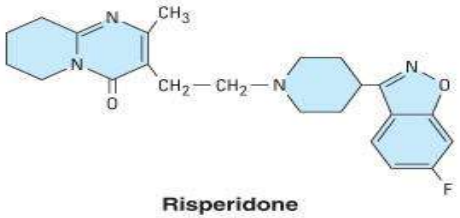
F –  $C – CH_2 – CH_2 – CH_2 – N$  – Cl

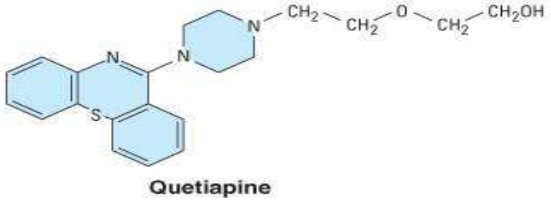
Haloperidol

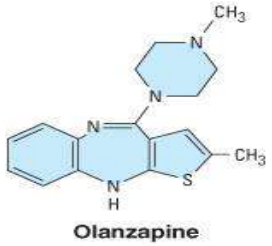
Antipsychotics: atypical antipsychotics

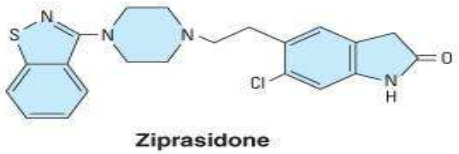
paliperidone
(9-OH-risperidone)

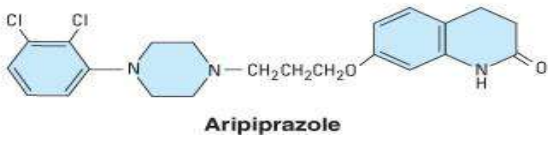








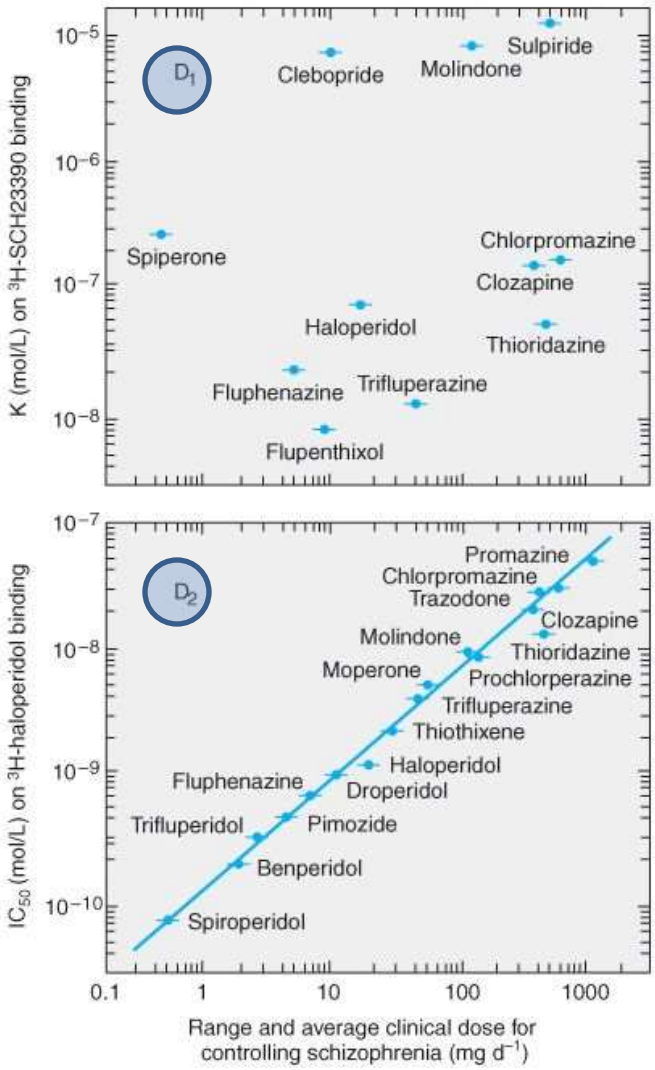




Antipsychotics: pharmacokinetics

- high lipid solubility
  - good (but incomplete) oral absorption
  - significant metabolism (first-pass effect, low F)
- highly protein protein bound (92-99%)
- large V_d (> 7 L/kg)
- duration of action >> t½
  - sequestered in lipid compartments
  - very high affinity to CNS receptors
- almost complete metabolism
  - usually metabolites are not important (except mesoridazine)
- parenteral forms available
  - prompt initiation or “depot” treatment

Correlation between therapeutic potency and D_1 or D_2 receptor binding



Antipsychotics: correlation between receptor affinity and adverse effects

drug	D_2 block	$5HT_{2A}$ block	α_1 block	M block	H_1 block	EPS	sedative	hypotension
phenothiazines	++	+	++	+	+	++	+++/++	+++/+
haloperidol	+++	-	+	-	-	+++	+	-
clozapine	-	++	++	++	+	-	+	++
olanzapine	+	++	+	+	+	-	++	+
risperidone	++	++	+	+	+	+	+	+
ziprasidone	++	++	++	-	+	-	+	-
aripiprazole	+	++	+	-	+	-	-	+

Haloperidol: **D_2** > α_1 > D_4 > $5\text{-}HT_{2A}$ > D_1 > H_1
Clozapine: $D_4 = \alpha_1$ > **$5\text{-}HT_{2A}$** > $D_2 = D_1$
Olanzapine: **$5\text{-}HT_{2A}$** > H_1 > D_4 > D_2 > α_1 > D_1
Aripiprazole: **$D_2 = 5\text{-}HT_{2A}$** > D_4 > $\alpha_1 = H_1$ >> D_1

- **athethosis**
  - continuous **slow**, sinusoidal, and flowing *involuntary* movements
- **chorea**
  - *involuntary*, forcible, **rapid, jerky** movements
- **dystonia**
  - an attitude or posture due to the co-contraction of agonists and antagonist muscles in one region of the body (e.g. **torticollis** ≈ "twisted neck")
- **hypokinesia**
  - slow or **diminished** movement of body musculature
- **tics**
  - habitual, **repeated, rapid** contraction of certain muscles, resulting in stereotyped individualized actions that can be voluntarily suppressed for only brief periods (face, neck, vocal cords – e.g. repetitive **throat clearing**, vocalizations, **sniffing** and excessive **blinking**)
- **tremor**
  - cyclical movement of a body part (e.g. intentional tremor – cerebellar diseases, resting tremor – Parkinson's disease)
- **akathisia**
  - psychomotor agitation, feeling of restlessness

Adverse effects of antipsychotics 1.

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

Adverse effects of antipsychotics 2.

- reversible neurologic effects
    - Parkinson-like syndrome, acute dystonia, akathisia
- ***tardive dyskinesia*** (haloperidol)
- autonomic effects
- endocrine effects
- ***metabolic effects***
    - weight gain, hyperglycemia, diabetes
- ***neuroleptic malignant syndrome***
- sedation
- miscellaneous
    - retinal deposits, QT prolongation (thioridazine → mesoridazine)
    - **agranulocytosis** (clozapine)
- ***overdosage toxicity***

Tardive dyskinesia

- a **late-occurring** (months / years) syndrome of **abnormal** choreoathetoid **movements**
  - oral-facial dyskinesia; widespread choreoathetosis or dystonia
- **the most important unwanted effect of antipsychotics**
  - occurred in **20-40%** of chronically treated patients prior to the introduction of the newer atypical antipsychotics
- **early recognition / prevention** is important
- mechanism ???
  - supersensitivity of dopamine receptors in the caudate-putamen ? → relative cholinergic deficiency
- treatment ???
  - dose reduction / discontinuation
  - switch to atypical (quetiapine/clozapine)
  - leave central anticholinergics
  - high dose diazepam ?

Metabolic effects

- weight gain
  - clozapine, olanzapine > quetiapine > fluphenazine, haloperidol, risperidone > aripiprazole, ziprasidone
- type 2 diabetes (secondary ?)
- hyperlipidemia
- hypertension
- sleep apnea

Neuroleptic malignant syndrome

- severe, life threatening (mortality ≈10-20%)
- after high dose parenteral administration (in a few days)
  - any **neuroleptic** but mostly the **typical potent** (eg. haloperidol, fluphenazine)
- in patients more sensitive to extrapyramidal effects
- basically not dose dependent (idiosyncratic)
- **symptoms**
  - mental state change (delirium, catatonia, stupor, coma)
  - **muscle rigidity**, **hyperthermia**, stress leukocytosis
  - unstable blood pressure, increased CK, myoglobinemia
- **treatment**
    - discontinuation of any neuroleptic agent
    - diphenhydramine
    - diazepam
    - cooling / iv. fluids / other supportive treatment

Overdose

- overdose is rarely fatal
  - in contrast with tricyclic antidepressants
  - except: thioridazine and mesoridazine – ventricular arrhythmias
- drowsiness → (agitation) → coma
- neuromuscular excitability → convulsions
- supportive therapy (ABCD)

Serotonin syndrome / neuroleptic malignant syndrome / malignant hyperthermia

	SS	NMS	MH
onset	within 24 hours	days – weeks	in minutes
causative agents	serotonin agonist	dopamin antagonist	inhalational anesthetics, succinylcholine
treatment	**diazepam**, *(cyproheptadine)*	diphenhydramine	**dantrolene**
resolution	within 24 hours	days – weeks	within 24 hours

Bipolar disorder

- lithium
  - PK: plasma level monitoring / also altered by changes in body water
  - PD: block recycling of membrane phosphoinositides / slow onset of action
  - AEs
    - reversible nephrogenic diabetes insipidus
    - tremor / sedation / ataxia
- other drugs
  - olanzapine / quetiapine
  - valproic acid / carbamazepine / lamotrigine