Antidepressants

The optimal use of antidepressant required a clear understanding of their mechanism of action, pharmacokinetics, potential drug interaction and the deferential diagnosis of psychiatric illnesses.

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Depression

A World Health Organization (WHO) Prediction

- **Depression is currently the FOURTH most significant cause of suffering and disability worldwide**

- **and, sadly, It will be the SECOND most debilitating human condition by the year 2020.**

Myths

- 54% believe depression is a weakness not an illness.
- 62% believe depression is not a health problem.
- >50% believe depression is “normal” and will not seek treatment.

Chemical "Jobs"

Dopamine

- Attention
- Pleasure
- Emotions
- Reward
- Motivation
- Movement

Norepinephrine

- alertness
- Observance
- Daydreaming
- Heart/BP rates
- Stress

Serotonin

- Regulates mood
- sleep
- emesis
- sexuality
- Appetite
- impulsiveness/ aggression

Depression

- **Symptoms**
  - **Cognitive**
    - **Thoughts of hopelessness, poor confidence, negative thoughts.**
  - **Emotional**

    Feeling sad, unable to feel pleasure, irritability
  - **Psychomotor/Physical**
    - **Decreased libido, energy**
    - **Sleep changes (70% less, 30% more)**
    - **Appetite changes (70 % less, 30 % more)**

Depression: Treatment

- **Antidepressant Medications**

- **Psychotherapy**
  - **Usually individual psychotherapy**
  - **Cognitive behavioral therapy has most evidence for efficacy of treatment.**

- **Sometimes exercise or body awareness has been found to helpful**

Drug	Brand	Class	2007 Prescriptions (in millions)
Sertraline	Zoloft	SSRI	29.652
Escitalopram	Lexapro	SSRI	27.023
Fluoxetine	Prozac	SSRI	22.266
Bupropion	Wellbutrin	NDRI	20.184
Paroxetine	Paxil	SSRI	18.141
Venlafaxine	Effexor	SNRI	17.200
Citalopram	Celexa	SSRI	16.246
Trazodone	Desyrel	SRI	15.473
Amitriptyline	Elavil	TCA	13.462
Duloxetine	Cymbalta	SNRI	12.551
Mirtazapine	Remeron	TeCA	5.129
Nortriptyline	Pamelor	TCA	3.105
Imipramine	Tofranil	TCA	1.524

Tricycle antidepressant (Amitriptyline)

- **TCAs inhibit serotonin, norepinephrine, and dopamine transporters, slowing reuptake.**

- **with a resultant increase in activity.**

- **Muscarinic acetylcholine receptors, alpha-adrenoceptors, and certain histamine (H1) receptors are blocked.**

Side effects:

(1) drug-induced Sedation

(2) Orthostatic hypotension

(2) Cardiac effects

(3) Anticholinergeric effects dry mouth, constipation,blurred vision, urinary retention

SSRIs (Serotonin-specific reuptake inhibitors)

inhibits the reuptake of serotonin without seriously effecting the reuptake of dopamine & norepinephrine.

- **Most common side effects include GI upset, sexual dysfunction (30%+!), anxiety, restlessness, nervousness, insomnia, fatigue or sedation, dizziness**

- **Can develop a discontinuation syndrome with agitation, nausea, disequilibrium and dysphoria**

SSRI/SNRI Discontinuation Syndrome in **Adults**

F.I.N.I.S.H.

- **F**lu-like symptoms: fatigue, muscle aches, headache, diarrhea
- **I**nsomnia: vivid or disturbing dreams
- **N**ausea
- **I**mbalance: gait instability, dizziness, lightheadedness, vertigo
- **S**ensory disturbance: paresthesia, “electric shock” sensation, visual disturbance
- **H**yperarousal: anxiety, agitation
- Onset: 24-72 hours + Resolution: 1-14 days
- Incidence: ~ 20 - 40 % (who have been treated at least 6 weeks)

Why there are many of them

Paroxetine:

- Sedating properties (dose at night) offers good initial relief from anxiety and insomnia
  - Significant CYP2D6 inhibition

Sertraline:

- Increased number of GI adverse drug reactions

Fluoxetine

- Secondary to long half life, less Discontinuation Syndrome
- Significant P450 interactions so this may not be a good choice in pts already on a number of meds
- Initial activation may increase anxiety and insomnia
- More likely to induce mania than some of the other SSRIs

Serotonin syndrome

- At high doses or combined with other drugs an exaggerated response can occur
  - This is due to increased amounts of serotonin
  - Alters cognitive function, autonomic function and neuromuscular function
  - Potentially fatal

Serotonin/Norepinephrine reuptake inhibitors (SNRIs)

- Slightly greater efficacy than SSRIs
- Slightly fewer adverse effects than SSRIs
  - Venlafaxine
  - Duloxetine

1. Can cause a 10-15 mmHG dose dependent increase in diastolic BP.
2. May cause significant nausea,
3. Can cause a bad discontinuation syndrome, and taper recommended after 2 weeks of administration

Monoamine oxidase inhibitors (MAOI) (Phenelzine) for atypical depression

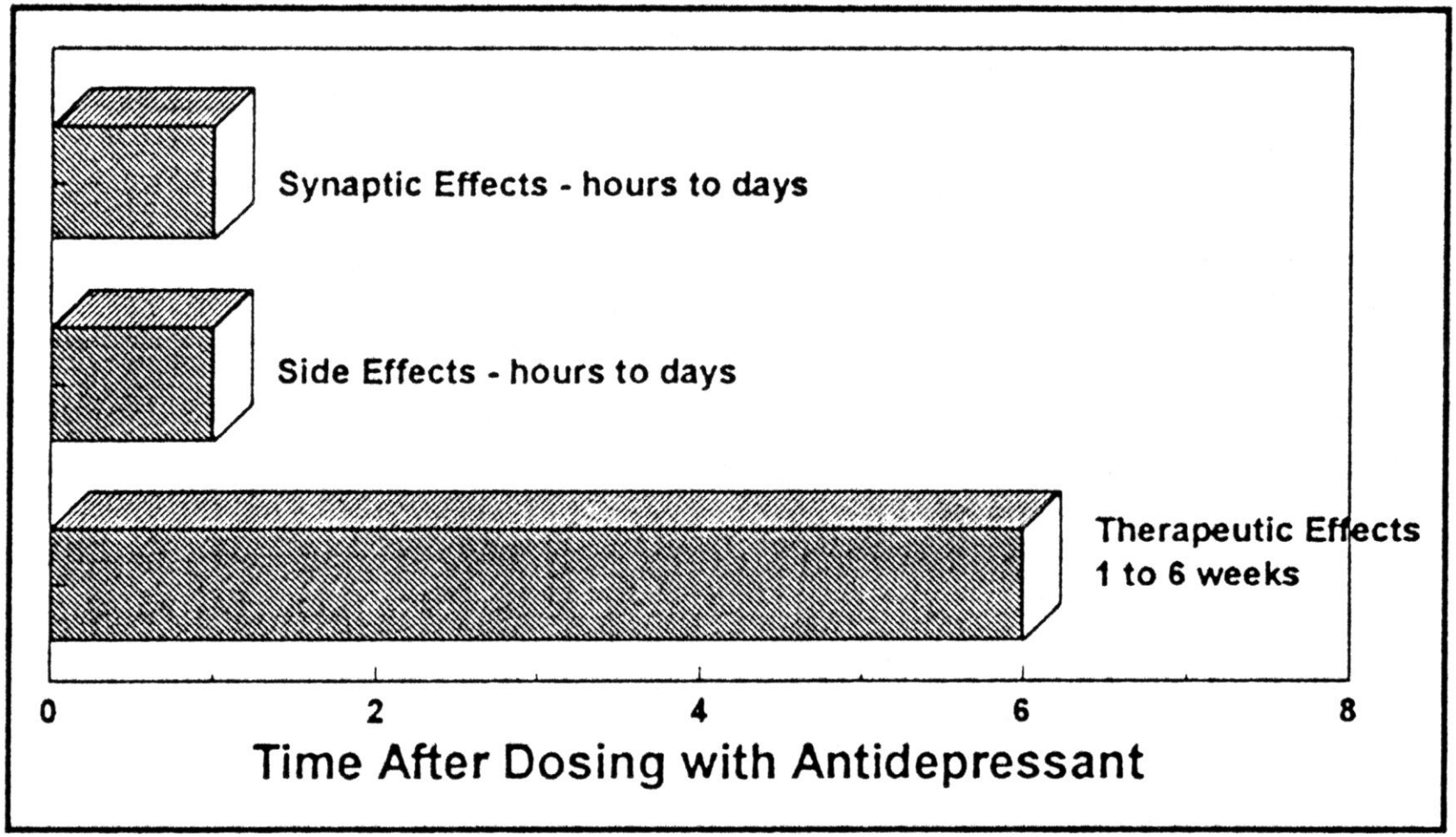
- **Inhibition of intra-neuronal degradation of serotonin and norepinephrine causes an increase in extracellular amine levels.**

- **Side effects:**

Blood pressure problems, Dietary requirements, Weight gain, Insomnia, Edema.

Selective MAO-A Inhibitors

- **Moclobemide**
- **No dietary restrictions, except in high-dosage treatment, wherein they lose their selectivity**.



Onset of action of antidepressants. Synaptic effects and side effects of antidepressants begin before therapeutic effects are observed.

Important

- **Following the initiation of the antideppresant drug treatment there is generally a therapeutic lag lasting for 3-4 weeks.**

- **8 weeks trial, then you allow to switch to another antidepressant.**

- **Partial response then add one another drug from different class.**

Important

- **if the initial treatment was successful then 6-12 maintenance periods.**

- **If the patient has experience two episodes of major depression, then it is advisable to give an anti depressant life long.**

- **All antidepressants now carry a "black box" warning that they may lead to suicidal thoughts/behavior**

Schizophrenia

- Pathogenesis is unknown.
- Onset of schizophrenia is in the late teens - early ‘20s.
- Genetic predisposition -- Familial incidence.
- Multiple genes are involved.
- Afflicts 1% of the population worldwide.
- Athought disorder

Schizophrenia

Positive Symptoms.

Hallucinations, delusions, paranoia, ideas of reference.

Negative Symptoms.

Apathy, social withdrawal, anhedonia, emotional blunting, cognitive deficits, lack of motivation to interact with the environment.

These symptoms are progressive and non-responsive to medication**.**

Schizophrenia

- Drugs currently used in the prevention of psychosis.

** These drugs are not a cure **

- Schizophrenics must be treated with medications indefinitely, as the disease in lifelong and it is preferable to prevent the psychotic episodes than to treat them.

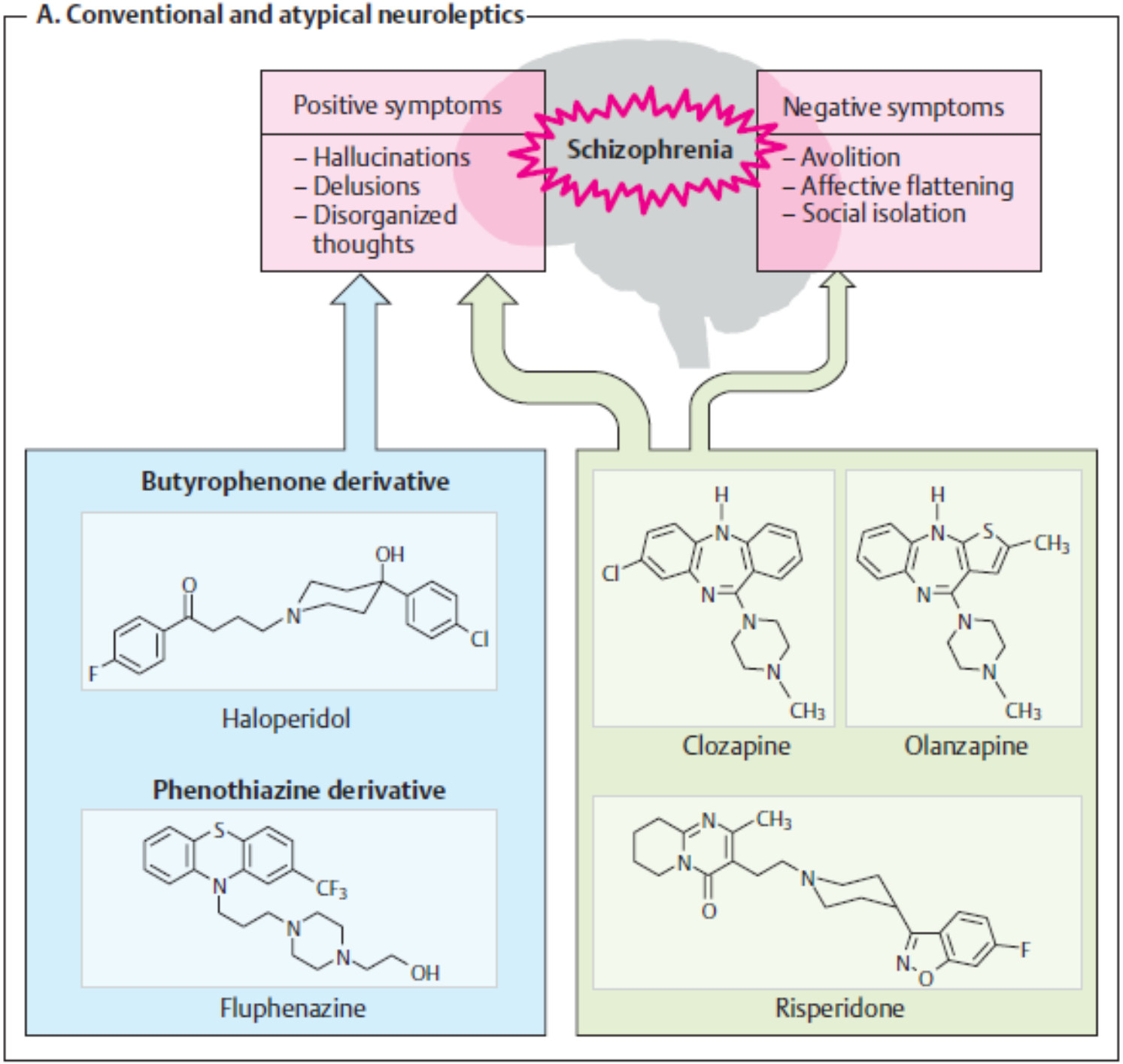
SCHIZOPHRENIA IS FOR LIFE

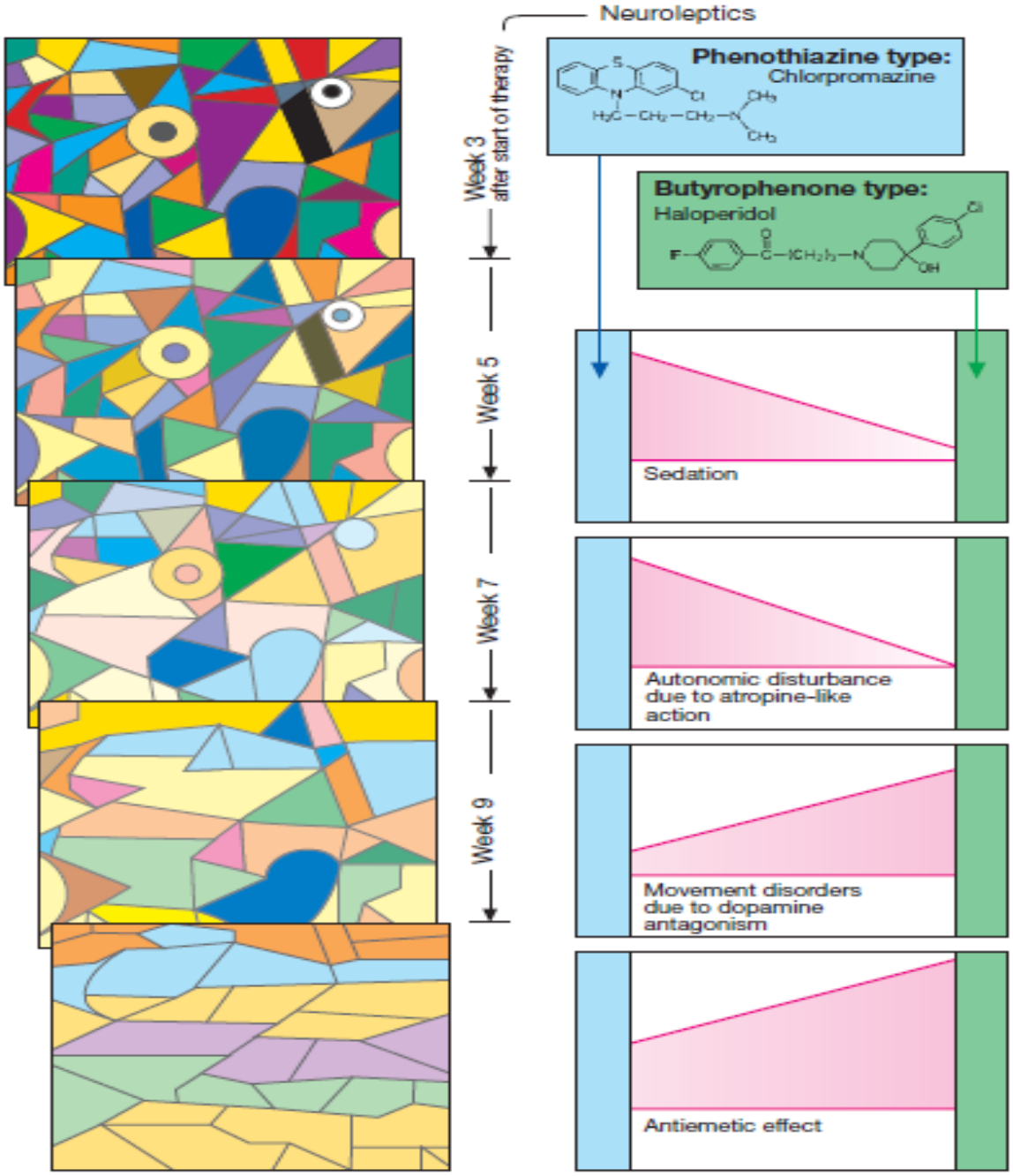
There is no remission

Dopamine Theory of Schizophrenia

Many lines of evidence point to the aberrant increased activity of the dopaminergic system as being critical in the symptomatology of schizophrenia.

There is a greater occupancy of D2 receptors by dopamine => greater dopaminergic stimulation


A. Conventional and atypical neuroleptics
Positive symptoms
– Hallucinations
– Delusions
– Disorganized thoughts
Schizophrenia
Negative symptoms
– Avolition
– Affective flattening
– Social isolation
Butyrophenone derivative
Haloperidol
Phenothiazine derivative
Fluphenazine
Clozapine
Olanzapine
Risperidone


Neuroleptics
Phenothiazine type:
Chlorpromazine
Butyrophenone type:
Haloperidol
Week 3
after start of therapy
Week 5
Week 7
Week 9
Sedation
Autonomic disturbance due to atropine-like action
Movement disorders due to dopamine antagonism
Antiemetic effect

Classification of Antipsychotic drugs

- Main categories are:
  - *Typical antipsychotics*
    - Phenothiazines (**chlorpromazine, perphenazine, fluphenazine, thioridazine et al**)
    - Thioxanthenes (**flupenthixol**, **clopenthixol**)
    - Butyrophenones (**haloperidol, droperidol**)
  - *Atypical antipsychotics* (e.g. **clozapine**, **risperidone**, **sulpiride**, **olanzapine**)

Classification of Antipsychotic drugs

- Distinction between ‘typical’ and ‘atypical’ groups is not clearly defined, but rests on:
  - Incidence of extrapyramidal side-effects (less in ‘atypical’ group)
  - Efficacy in treatment-resistant group of patients
  - Efficacy against negative symptoms.

First Generation Antipsychotic Drugs

Compound	Seda-tion	Hypo-tension	Motor (EP) Effects
Phenothiazines			
Chlorpromazine	+++	++	++
Fluphenazine	+	+	++++
Haloperidol	+	+	++++

Second Generation Antipsychotic Drugs

Compound	Sedation	Hypo-tension	Motor effects
Risperidone Risperdal	++	+++	+/++ Dose dependent
Clozapine Clozaril	++	++	-
Aripiprazole Abilify	0/+	0/+	0/+

Tolerance and dependence to antipsychotic drugs

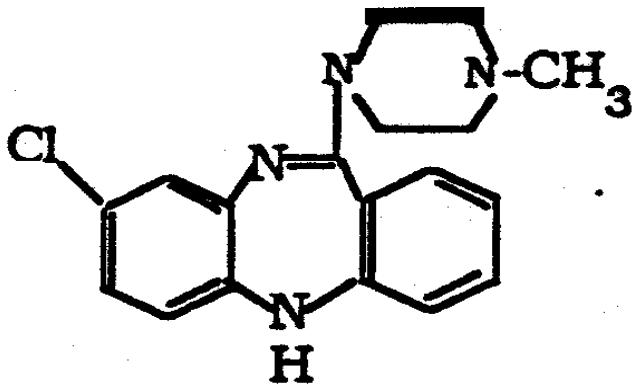
- Not addicting
- Relapse in psychosis if discontinued abruptly

- Tolerance develops to sedative effects
- No tolerance to antipsychotic effect

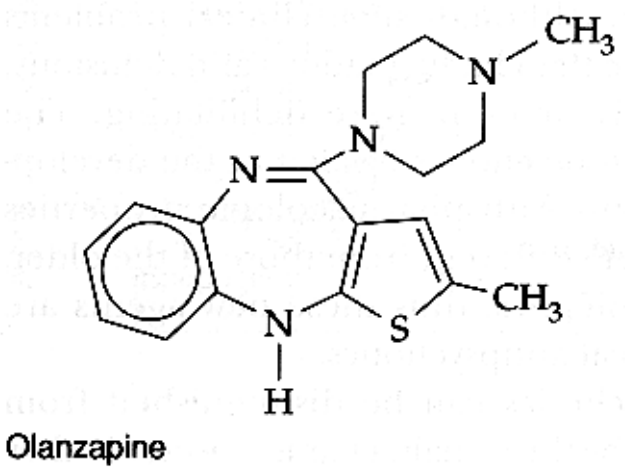
Withdrawal-like syndrome

1. **Symptoms: nausea, vomiting, insomnia, and headache**
2. **Symptoms may persist for up to 2 weeks.**
3. **Symptoms can be minimized with a tapered reduction of drug dosage.**

Clozapine and olanzapine



- VERY low EPS
- Blocks D1, D2, D4, α-adrenergic, 5HT2, muscarinic, and histamine H1 receptors
- May show greater efficacy against negative symptoms than other antipsychotic drugs
- Agranulocytosis is a potentially fatal side effect for clozapine



Olanzapine

Both drugs have high efficacy, but cause significant weight gain and diabetes

Aripiprazole

- **Partial agonist at D2 receptor**
- Affinity for muscarinic, α_1-adrenergic, serotonin and histamine receptors
- Few extrapyramidal side effects
- Weight gain

Tardive dyskinesia

comprises mainly involuntary movements of face and tongue, but also of trunk and limbs, appearing after months or years of antipsychotic treatment due to accumulation of the drug.

Risperidone
Endocrine effect

- One of the most prescribed drugs in Jordan.
- In **women**, these disturbances include:
  - **galactorrhea**
  - **loss of libido**
  - delayed ovulation and menstruation or amenorrhea.

- In **men**, these disturbances include:
  - **gynecomastia**
  - **impotence.**