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Review Article

DRUGS USED IN MENTAL DISORDER: AN OVERVIEW

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Abstract

Brain is the central processing unit of human body. Most of the conditions afflicting people are related to mental function. Some of them are transient and some are longer lasting affecting their day to day life. If mental function is hampered; drugs are used to control them. These drugs can alter the mind and behavior of people so that they can get a hold of the unusual imbalance happening due to mental imbalance or dysfunction. These drugs not only control the symptomatic manifestations and problems associated to the behavior but also facilitate the patient's tendency towards to cope up with the society.

Keywords: Anxiolytic, Barbiturate, Phenothiazine, Psychosis.

Introduction:

All of us are aware of the many different states of brain activity, including sleep, wakefulness, extreme excitement, and even different levels of mood such as exhilaration, depression, psychosis and fear. All these states result from different activating or inhibiting forces generated usually within the brain itself. When any kind of brain disorder occurs due to change in such forces we call it mental disorder. It can be of various kinds. Drugs used in these disorders are either called antipsychotic, anxiolytic, antidepressant, antimanic or sedative hypnotic depending on the severity and extent of the disorder.

Mental disorders can be of various kinds. It can be psychosis, anxiety, schizophrenia, delusion or hallucination.

Psychosis: A variety of mental disorder is known as psychosis. It has following symptoms-

1. Inappropriate emotional response
2. Bizarre behavior
3. Agitation
4. Aggressiveness
5. Hostility
6. Social withdrawal
7. Hallucination
8. Paranoid delusion
9. Deterioration in occupational and social functioning

Hallucination: A false sense of perception having no relation to reality and not accounted by any exterior stimulation is known as hallucination. It may be visual or auditory in nature (an imaginary perception of sound or voice). The sensation of seeing objects that are not really there is known as visual hallucination.

Delusion: A false belief (e.g. that one can send radio messages directly to god) brought about without appropriate external stimulation and inconsistent with the individuals own knowledge and experience is called delusion. The most serious delusion is those that cause patients to hurt others or themselves. For example-fear of being poisoned may cause refusal of food. Delusion may lead to suicidal tendency or self injury. Delusion differs from hallucination in the way that hallucination involves the false excitation of one or more senses.

Schizophrenia: A particular kind of psychosis (thought disorder) marked by delusion and hallucination. The common etiology of schizophrenia and related psychosis is over activity of dopaminergic receptors. When the activity of dopamine activity increases in the nerve endings such kind of mental disorder is observed. Dopamine is a neurotransmitter which is mainly inhibitory in nature.

Anxiety: Anxiety is an unpleasant state of tension, apprehension, or uneasiness- a fear that seems to arise from an unknown source. Disorders involving anxiety are the most common mental disturbances. The symptoms of severe anxiety are similar to those of fear (such as tachycardia, sweating, trembling, and palpitations) and involve sympathetic activation.

Treatment:

Medications used to treat such mental disorders include antipsychotic, anxiolytic, sedative and hypnotic drugs. These kind of drugs act on dopaminergic receptors in the brain such as-

- Chlorpromazine
- Fluphenazine
- Haloperidol

These drugs are mainly divided into two classes-1) antipsychotic drugs (major tranquilizers) & 2) anxiolytic drugs (minor tranquilizers).

Major classes of antipsychotic drugs are classified in following ways:

A.**1st generation agents**

1. Phenothiazine derivative.

   a) aliphatic; e.g. chlorpromazine (Figure 1)

   b) piperidine; e.g. thioridazine (Figure 2)

   c) piperazine; e.g. fluphenazine (Figure 3)
2. Rauwolfia alkaloids; e.g. reserpine (Figure 4)
3. Butyrophenone derivatives; e.g. haloperidol (Figure 5)
4. Thioxanthene derivatives; e.g. chlorprothixene (Figure 6)

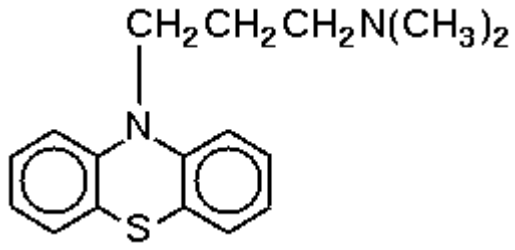


Figure 1: Chlorpromazine

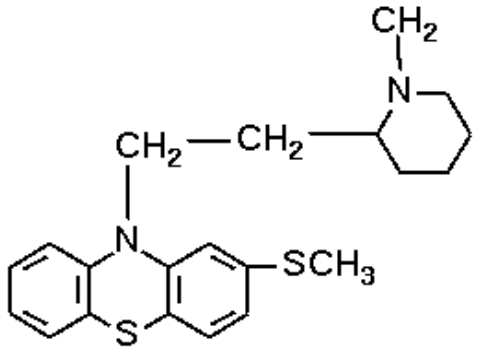


Figure 2: Thioridazine

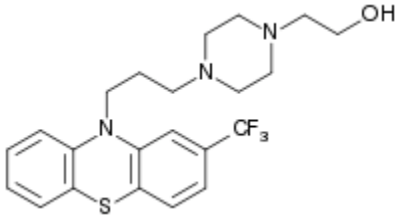


Figure 3: Fluphenazine

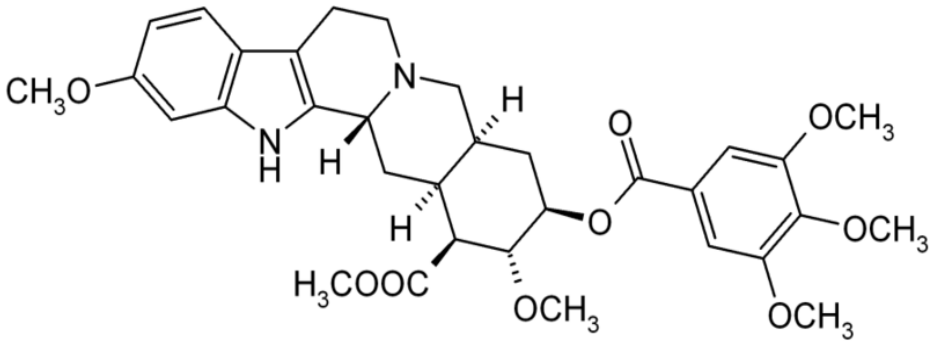


Figure 4: Reserpine

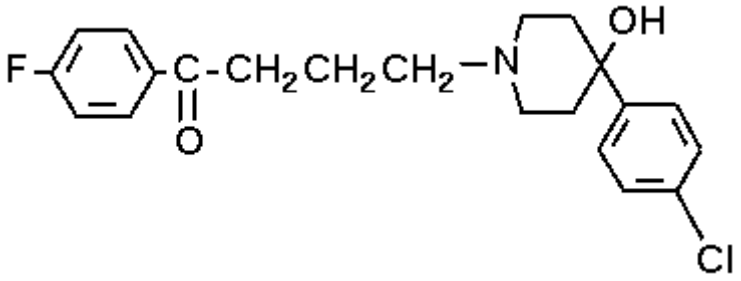


Figure 5: Haloperidol

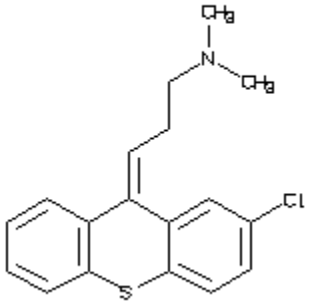


Figure 6: Chlorprothixene

B.**2nd generation agents**

1. Benzoquinolizine; e.g. tetrabenazine (Figure 7)
2. Dibenzoxazepine; e.g. loxapine (Figure 8)
3. Dihydroindolone; e.g. molindone (Figure 9)

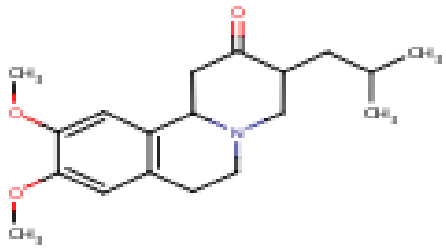


Figure 7: Tetrabenazine

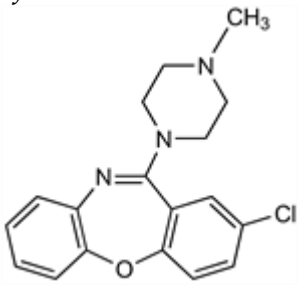


Figure 8: Loxapine

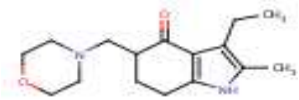


Figure 9: Molindone

Minor classes of anxiolytic drugs are classified in following ways:

1. Benzodiazepine; e.g. diazepam (Figure 10)
2. Propanediol derivatives; e.g. meprobamate (Figure 11)
3. Barbiturates; e.g. phenobarbitone (Figure 12)
4. Miscellaneous; e.g. chlormazazone (Figure 13)

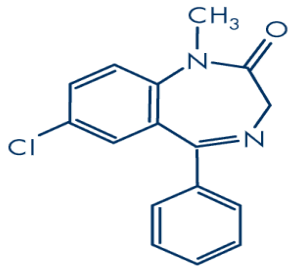


Figure 10: Diazepam

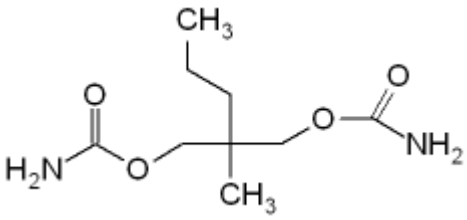


Figure 11: Meprobamate

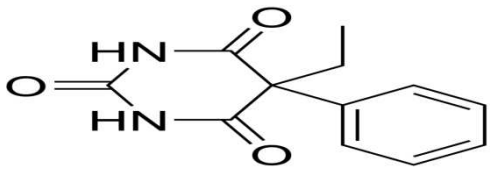


Figure 12: Phenobarbitone

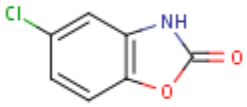


Figure 13: Chlormazazone

Antipsychotic drugs

Phenothiazine: (Figure 14)

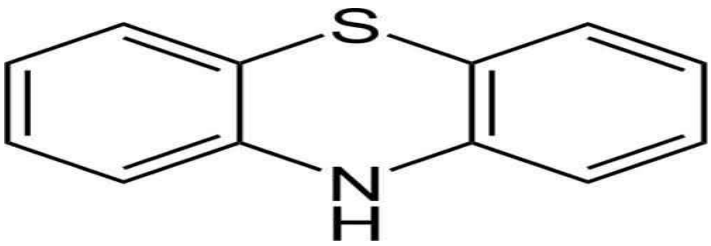


Figure 14: Phenothiazine

Phenothiazine is one of the most widely used antipsychotic drugs. The structure activity relationship (SAR) of phenothiazine is as follows:

1. Modification of basic ring

Phenothiazine has a three ring structure in which two benzene rings are linked by a sulfur and nitrogen atom. If the nitrogen atom at position 10 is replaced by a carbon atom with a double bond to the side chain, the resulting compound is thioxanthene which is also active. Generally, these compounds are slightly less potent than that of phenothiazine analogue.

2. Substitution at different positions

2.1. The best position for substitution is position 2. Substitution at position 2 with electron withdrawing group increases the efficacy of phenothiazines.

2.2. Position 3 can be substituted. But the substitution does not give results as good as substitution at position.

2.3. Any substitution at position 1 gives deleterious effect to antipsychotic activity.

2.4. Substitution at position 4 interferes with receptor binding by sulfur atom.

3. The nature of substitution at position 10 influences pharmacological activity

3.1. Those with an aliphatic side chain are relatively low in potency but not in clinical efficacy.

e.g. cholrpromazine,triflupromazine.

3.2. Those with a piperidine ring in the side chain show lower incidence of extrapyramidal side effects (e.g. parkinsonism) possibly due to increased central antimuscarinic activity.

e.g. thioridazine.

3.3. Those with a piperizine ring in the side chain are potent antipsychotic compounds.

e.g. fluphenazine. These compounds have relatively weak anticholinergic activity and entail a greater risk of inducing extrapyramidal side effects but less tendency to produce sedation and autonomic side effects such as hypotension.

3.4. The three carbon atom chain between position 10 of the central ring and the amino nitrogen is required . Shortening or lengthening the chain at this position drastically decreases activity.

Butyrophenone (phenylbutylpiperidine) derivatives: (Figure 15)

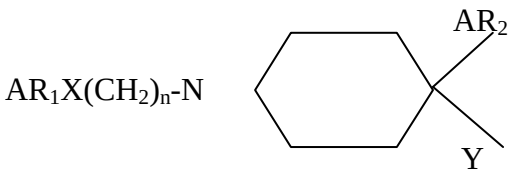


Figure 15: Butyrophenone

This group has very different structure. Most widely used butyrophenone derivative is haloperidol. These compounds are closely related to each other. They tend to be more potent and have fewer autonomic side effects such as hypotension. The structure activity relationship (SAR) of butyrophenone is as follows:

1. Optimal activity is seen when AR_1 is an aromatic system.
2. A p-fluoro substituent aids activity. e.g. haloperidol.
3. When X is equal to C=O, optimal activity is seen, although other groups such as C(H)OH and C(H)aryl, also give good activity.
4. When n=3, activity is optimal. Longer or shorter chains decrease activity.
5. The aliphatic amino nitrogen is required and highest activity is seen when it is incorporated into a cyclic form.
6. AR_2 is an aromatic ring and is needed. It should be attached directly to the position 4 or occasionally separated from it by one intervening atom. e.g. droperidol. (Figure 16).

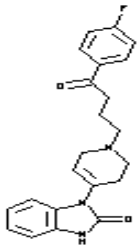


Figure 16: Droperidol

7. The Y group can vary and assist activity. An example is the hydroxyl group of haloperidol.

Thioxanthenes:

Thioxanthenes are classified as follows:-

1. Aliphatic substituent; e.g. chlorprothixene (Figure17)

2. Piperazine substituent; e.g. thiothixene (Figure 18)

Synthesis of chlorpromazine: (Figure 19)

Compound 1 in the presence of sulfur and heat produces a three ring structure containing the sulfur atom in the middle ring. Then the produced compound reacts with the compound 2 and produces chlorpromazine.

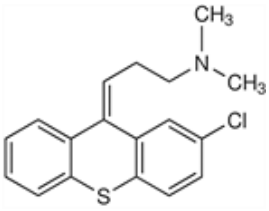


Figure 17: Chlorprothixene

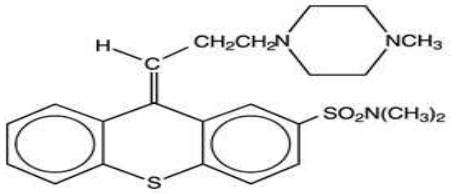


Figure 18: Thiothixene

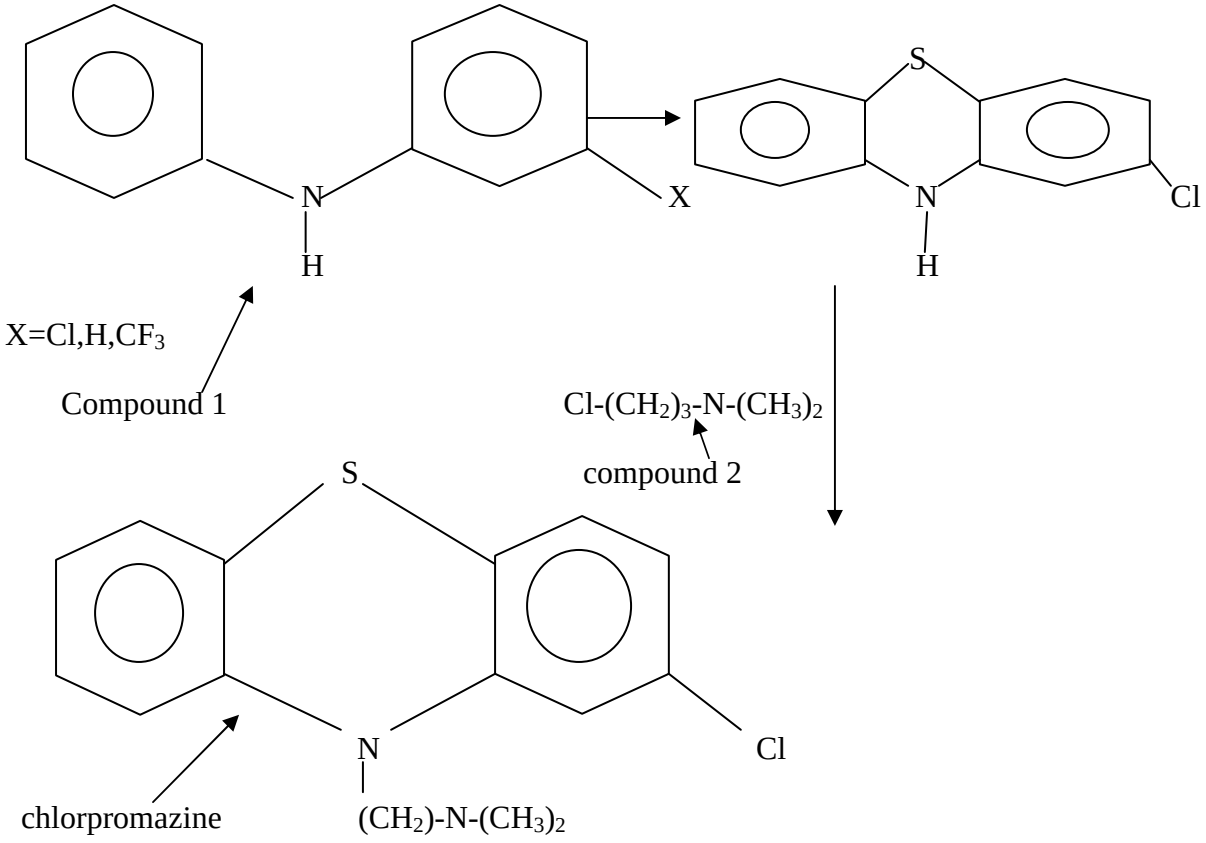


Figure 19: Synthesis of chlorpromazine

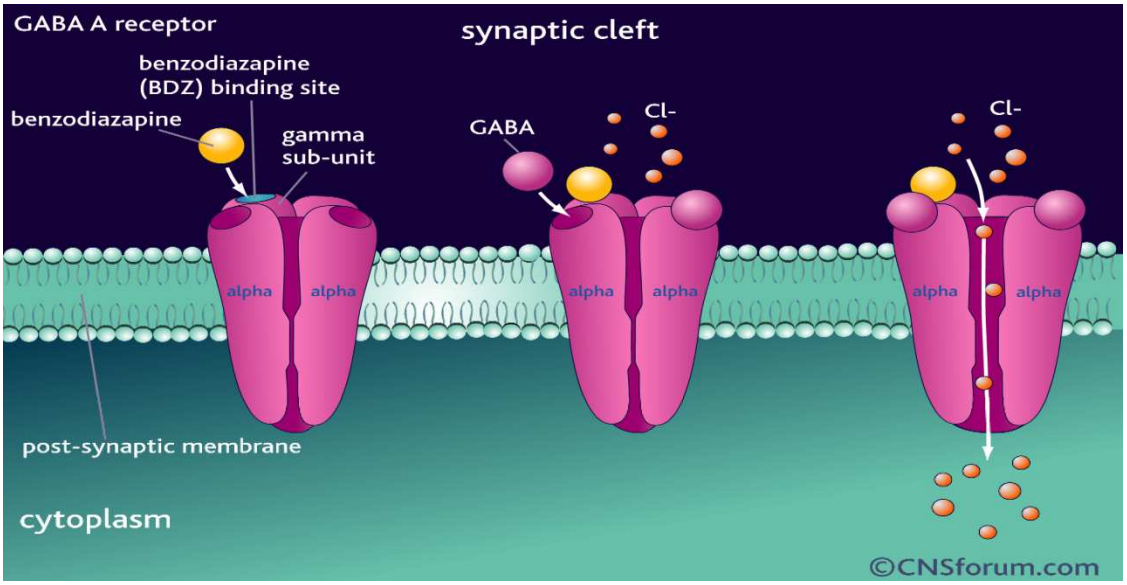
Anxiolytic and hypnotic drugs

Benzodiazepine:

Benzodiazepines are the most widely used anxiolytic drugs. They have largely replaced barbituraters and meprobamate in the treatment of anxiety, because they are safer and more effective.

Mechanism of action:

Benzodiazepines (BDZs) bind to the gamma sub-unit of the GABA-A receptor. Their binding causes an allosteric (structural) modification of the receptor that results in an increase in GABA A receptor activity. BDZs do not substitute for GABA, which bind at the alpha sub-unit, but increase the frequency of channel opening events which leads to an increase in chloride ion conductance and inhibition of the action potential. (Figure 20).



(http://www.cnsforum.com/imagebank/item/drug_benzo/default.aspx)

Figure 20: Empty receptor is inactive and Cl^- channel is closed. Binding of GABA causes the Cl^- ion channel to open, leading to hyperpolarization of the cell. Binding of GABA is enhanced by benzodiazepine, resulting in a greater entry of chloride ion. Entry of chloride ion hyperpolarizes the cell, making it more difficult to depolarize, and therefore reduces neural excitability.

Classification of benzodiazepine:

1. Short acting

   Alprazolam

2. Intermediate acting

   Oxazepam

3. Long acting

   Diazepam

Table-1: Distinctions among several benzodiazepines including alprazolam, oxazepam & diazepam.

Available preparation	Oral dosage equivalency(MG)	Time to peak plasma level(H)	Protein bindin g (%)	Eliminatio n half life (H) parent compared	Active metaboli te	Metabolic pathway
alprazolam	0.5	1-2	80	12-15	one	Oxidation
oxazepam	15	2-4	97	5-20	none	conjugation
diazepam	5	0.5-2	98	20-80	two	oxidation
chlordiazepoxide	10	1-4	96	5-30	four	N-dealkylation oxidation
clonazepam	0.25	1-4	85	30-40	none	notroreduction
clorazepate	7.5	1-2	97	prodrug	two	oxidation
lorazepam	1	2-4	85	10-20	none	conjugation

Pharmacological action of benzodiazepines:

1. Reduction of anxiety: Anxiolytic effect is seen at low doses. They might reduce anxiety by selectively enhancing GABAergic transmission in neurons.

2. Sedative and hypnotic action: All of them have some sedative and hypnotic action and produce hypnosis (artificially-produced sleep) at higher doses.
3. Anterograde amnesia: Temporary impairment of memory may be mediated by GABA receptors.
4. Anticonvulsant: Some of them are used in epilepsy and other seizure disorders as anti convulsant.
5. Muscle relaxant: At higher doses they relax the spascity of skeletal muscles, probably by increasing presynaptic inhibition in the spinal cord.

Therapeutic use of benzodiazepines:

1. Anxiety disorders
2. Muscular disorders
3. Amnesia
4. Seizures
5. Sleep disorder

Adverse effects:

1. Drowsiness
2. Confusion
3. Ataxia
4. Cognitive impairment

Barbiturates:

Barbiturates were previously used to sedate the patients and produce sleep. But today they have been replaced by the benzodiazepines. At toxic doses they cause coma.

Mechanism of action of barbiturates:

Most likely site of action: gamma-aminobutyric acid (GABA) receptor complex, $GABA_A$. Effects on $GABA_A$ occur at clinical drug concentrations, correlate with anesthetic potency and arestereospecific.

GABA is the principal inhibitory neurotransmitter in the mammalian CNS $GABA_A$ complex: 1. Oligomeric complex of 4 to 6 glycoprotein subunits assembled to form a ligand-gated chloride ion channel. 2. Activation (e.g. by GABA) leads to increased chloride conductance causing hyperpolarization, hence inhibition or decreased excitability, of the postsynaptic neuronBarbiturates enhance and mimic the action of GABA at the $GABA_A$ receptor complex. Barbiturate binding to this receptor decreases the rate of GABA dissociation and increases the duration of GABA-activated chloride channel opening. At slightly higher concentrations, barbiturates directly activate chloride channel opening even in the absence of GABA, leading to "barbiturate anesthesia."

(http://www.metrohealthanesthesia.com/edu/ivanes/barbiturates1.htm)

Pharmacological action of barbiturate:

1. Depression of CNS: At low doses they produce sedation. At higher doses they cause hypnosis followed by anesthesia.
2. Respiratory depression: Barbiturates suppress the hypoxic and chemoreceptor response to CO_2 and overdosage is followed by respiratory depression and death.
3. Enzyme induction: They induce p450 microsomal enzyme in the liver. Therefore chronic barbiturate administration diminishes the action of many drugs dependant on enzyme p450.

Therapeutic use:

1. Anesthesia
2. Anticonvulsant
3. Anxiolytic

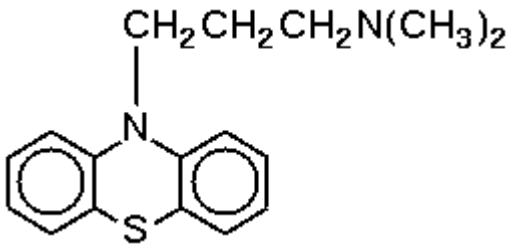
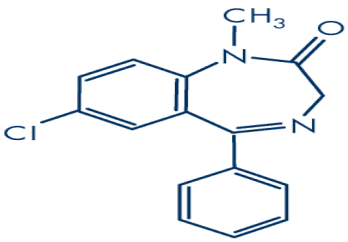
Adverse effect:

1. Drowsiness
2. Impaired concentration

3. Nausea
4. Dizziness
5. Anxiety
6. Tremor
7. Weakness
8. Restlessness
9. Delirium
10. Vomiting
11. Cardiac arrest etc.

Table-2: Differences between major and minor tranquilizers.

Points	Major tranquilizer	Minor tranquilizer
1.definition	Agents that reduce agitation and disturbed behavior associated with delusion and hallucination.	Agents that produce a calming effect in anxiety states associated with psychological disorders.
2.types of drug	Antipsychotic drug.	Anxiolytic drug.
3.therapeutic application	In schizophrenic patients or in bipolar disorders.	Can not be used in scizophrenic patients.it is used in insomnia.
4.sedative effect	No sedation is produced.	Sedation is produced.
5.safety	Unsafe.	Comparatively safe.
6.extent of adverse effects	More.	Less.
7.anticonvulsant effect	Absent.	Present.
8.axtrapyramidal effect	Present.	Absent.

9.example	 Figure:chlorpromazine	 Figure:diazepam
10.therapeutic window T_w	Low.	High.

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