Antiepiletpic Drugs (AEDs) and sedative hypnotics

- **Epilepsy is a chronic disorder characterized by recurrent seizures, which are finite episodes of brain dysfunction resulting from abnormal discharge of cerebral neurons**
- Epilepsy is the most prevalent neurological disorder affecting more than 0.5% of the world's population

Epilepsy

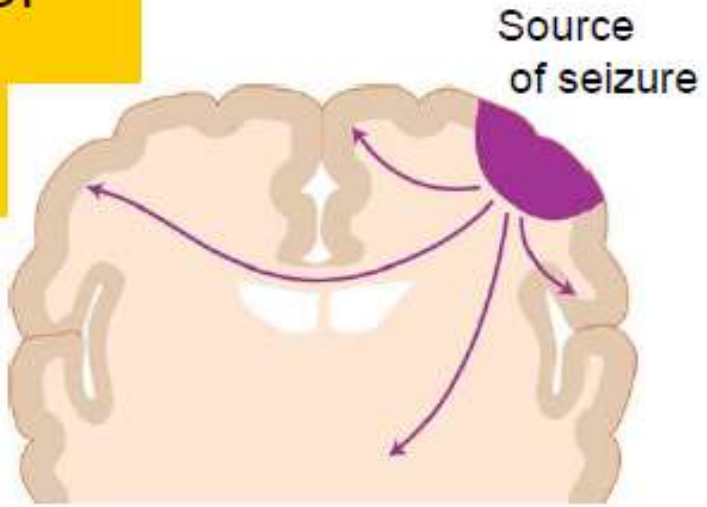
- The etiology of epilepsy is largely unknown even though recent evidence suggests that it may have a genetic component associated with its disease development.
- Seizures: are symptoms of disturbed electrical activity in the brain characterized by episodes of abnormal, excessive, and synchronous discharge of a group of neurons within the brain that cause involuntary movement, sensation, or thought.
- seizures may result from primary or acquired neurological disturbances of brain function as a result of an imbalance between excitatory and inhibitory processes in the brain.
- There are many possible causes of seizures including brain tumors or infections, head trauma, neurological diseases, systemic or metabolic disorders, alcohol abuse, drug overdose, or toxicities.

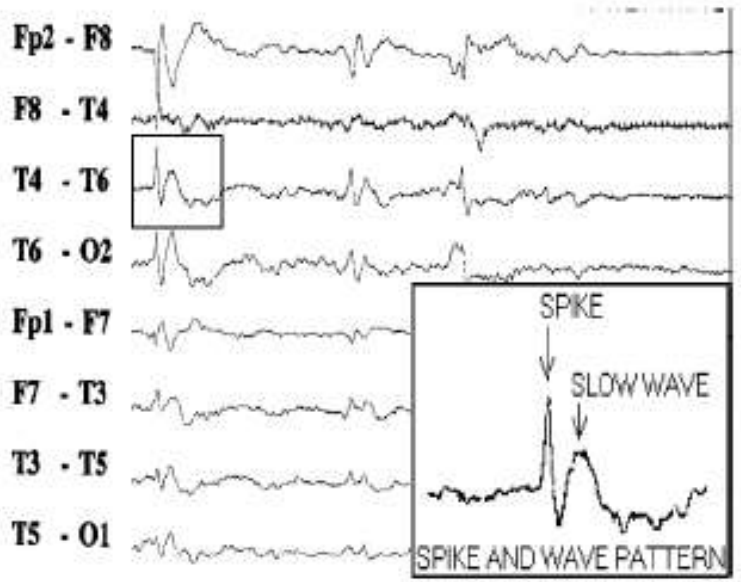
Classification of epileptic seizures

I. Partial (local, focal) seizures
   A. Simple (consciousness not impaired)
   B. Complex partial seizures (psychomotor seizures)
      1. Beginning as simple partial seizures, progressing to complex seizures
      2. With impairment of consciousness at onset
   C. Partial seizures evolving to secondarily generalized tonic-clonic convulsions
II. Generalized seizures (convulsive or nonconvulsive)
   A. Absence seizures
      Typical (petit mal)
      Atypical
   B. Myoclonic
   C. Clonic
   D. Tonic
   E. Tonic-clonic (grand mal)
   F. Atonic
III. Unclassified epileptic seizures (includes some neonatal seizures)

International Classification of Epileptic Seizures: Partial Onset Seizures

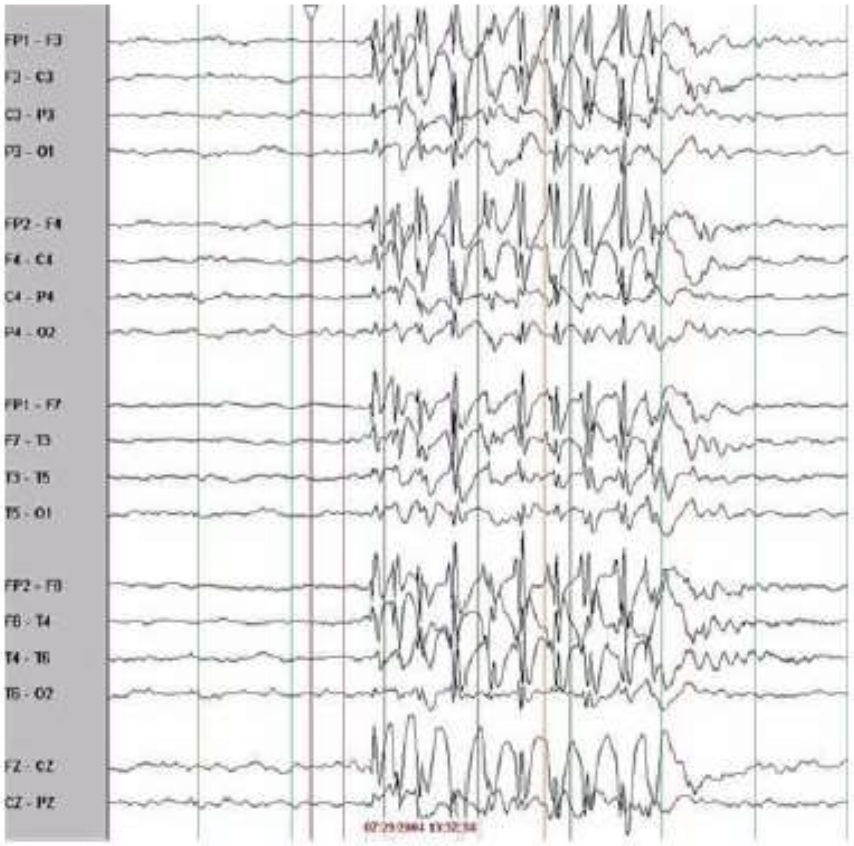
- Simple Partial
- Complex Partial (consciousness is affected)
- Partial Seizures with secondary generalization





International Classification of Epileptic Seizures: Primary Generalized Seizures

- Absence (Petit Mal)
- Generalized Tonic+Clonic (Grand Mal)
- Tonic
- Atonic
- Clonic and myoclonic



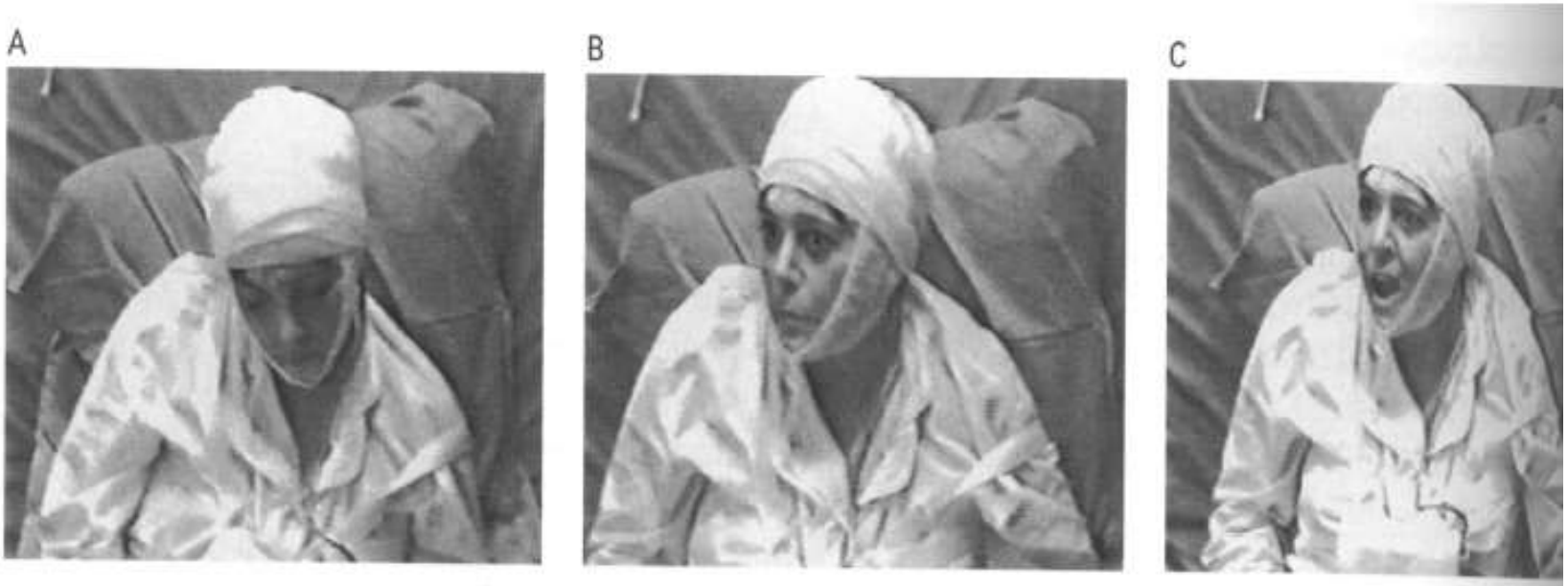
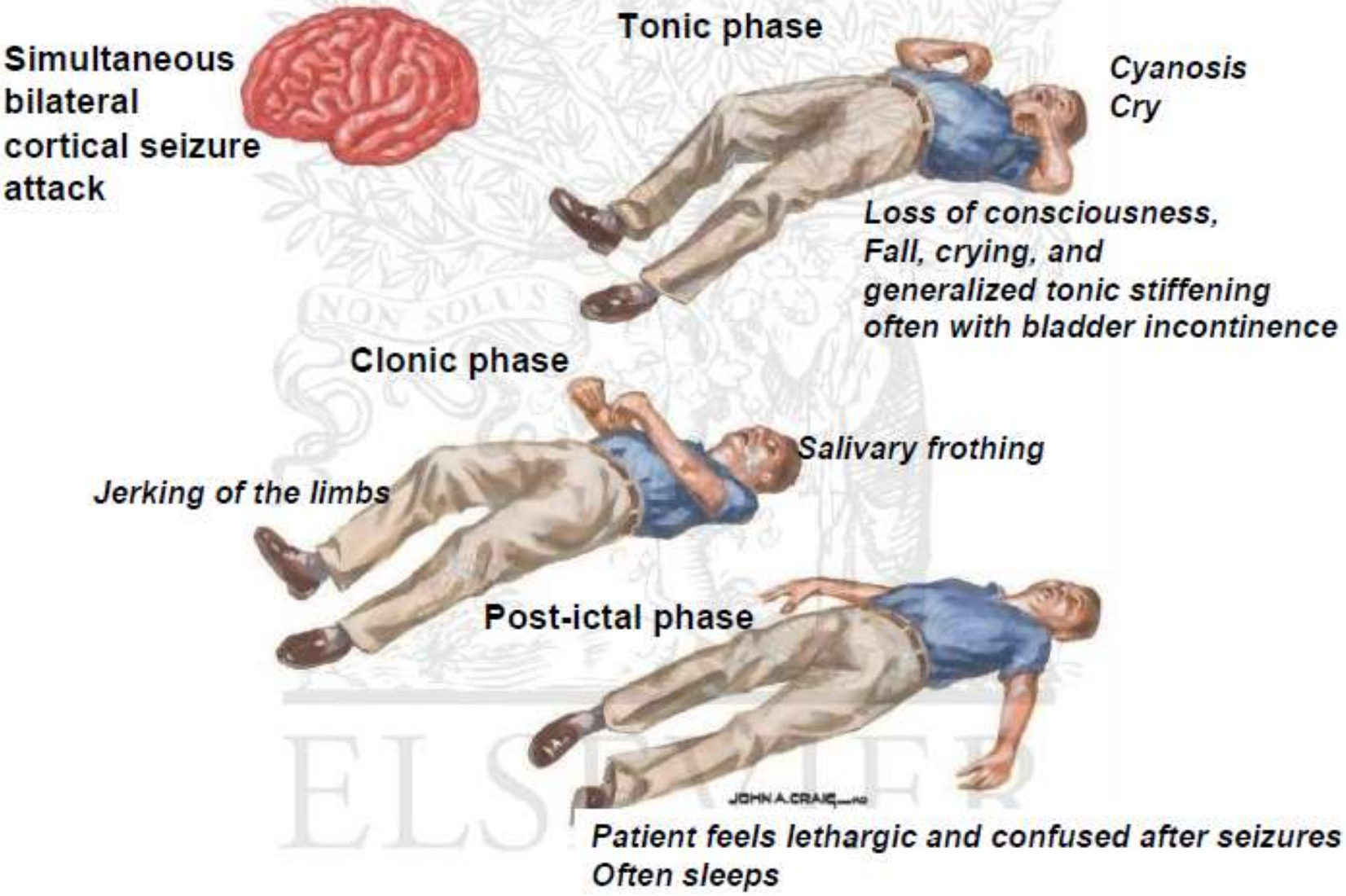


Figure 46-15 The patient was monitored with closed-circuit television simultaneous EEG and telemetry. The monitoring revealed stereotypical complex partial seizures. The patient is shown reading quietly in the period preceding the seizure (**A**), during the period when she reported a feeling of fea (**B**), and during the period when there was alteration of co sciousness and an audible scream (**C**). (Courtesy of Dr. M Salinsky, Oregon Health Sciences University Epilepsy Ce

Stereotypical complex partial seizures



Mechanisms of action of anticonvulsants

(a) modulation of voltage-gated ion channels (Na, Ca2, and K),

(b) Enhancement of -aminobutyric acid (GABA)-mediated inhibitory neurotransmission

(c) attenuation of excitatory (particularly glutamate-mediated) neurotransmission in the brain.

VOLTAGE-GATED SODIUM CHANNELS

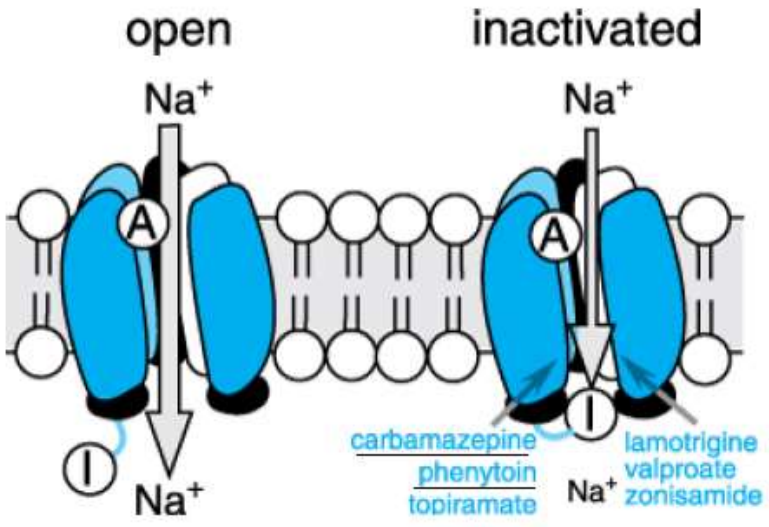
in the presynaptic nerve terminal of the excitatory glutamate receptors

1-Phenyl-substituted succinimide cause some Na^+-channel block

2-phenytoin, carbamazepine, oxacarbazepine, valproic acid, and felbamate is Phenobarbital, may also block voltage gated Na^+-channel

Drugs which act on Na+ channel

- Phenytoin
- Carbamazepine
- Oxcarbazepine
- Lamotrigine



(2) Interaction with $GABA_A$ receptor

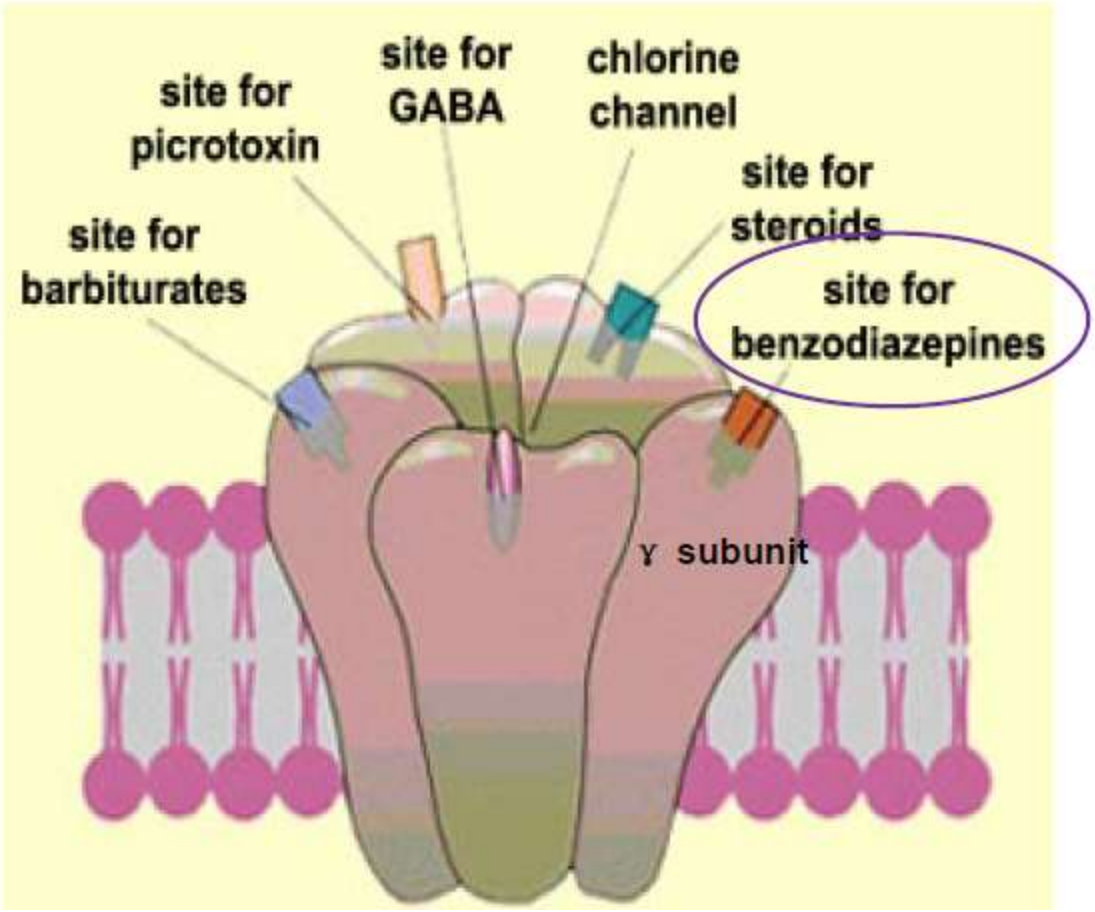
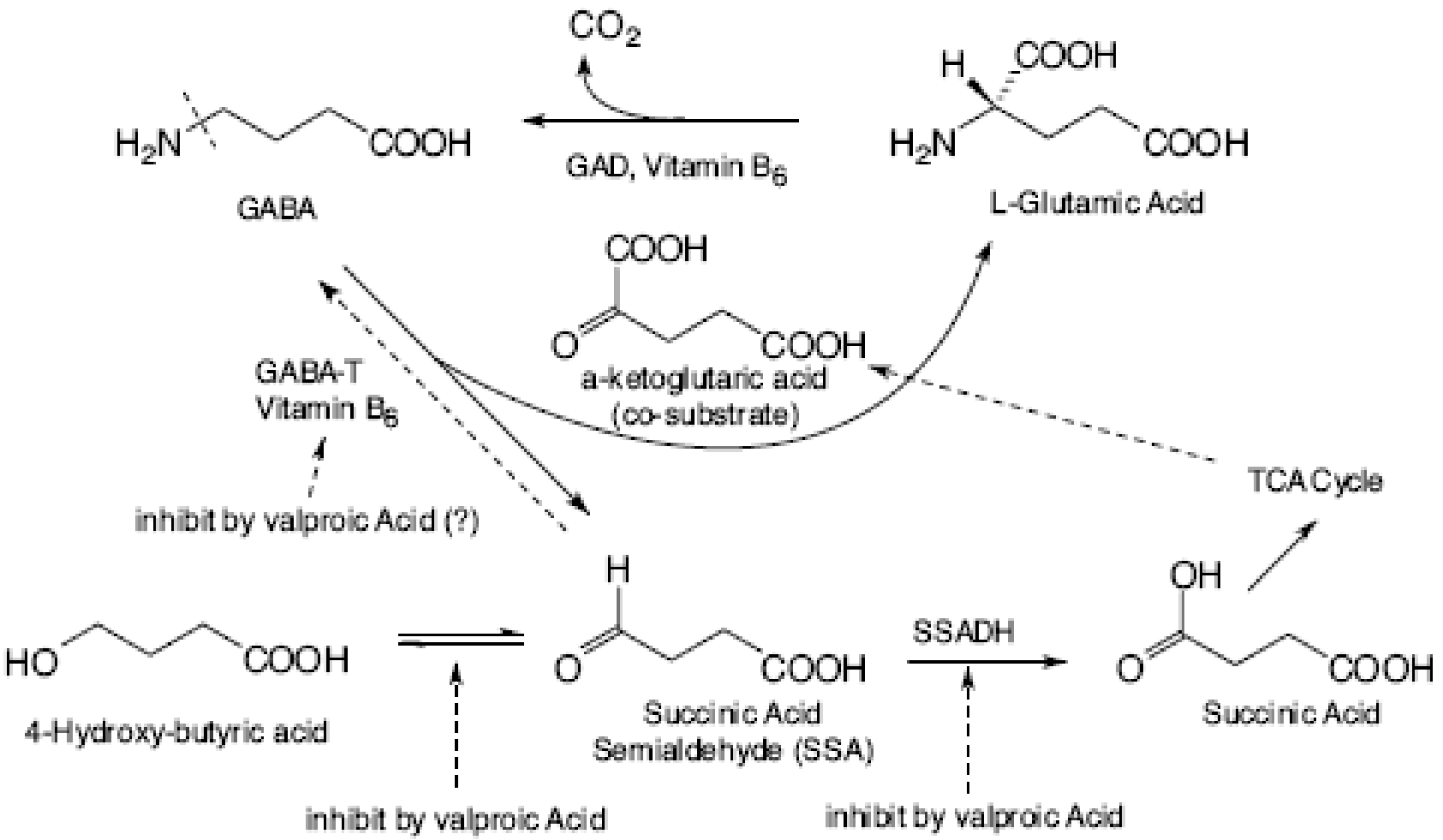
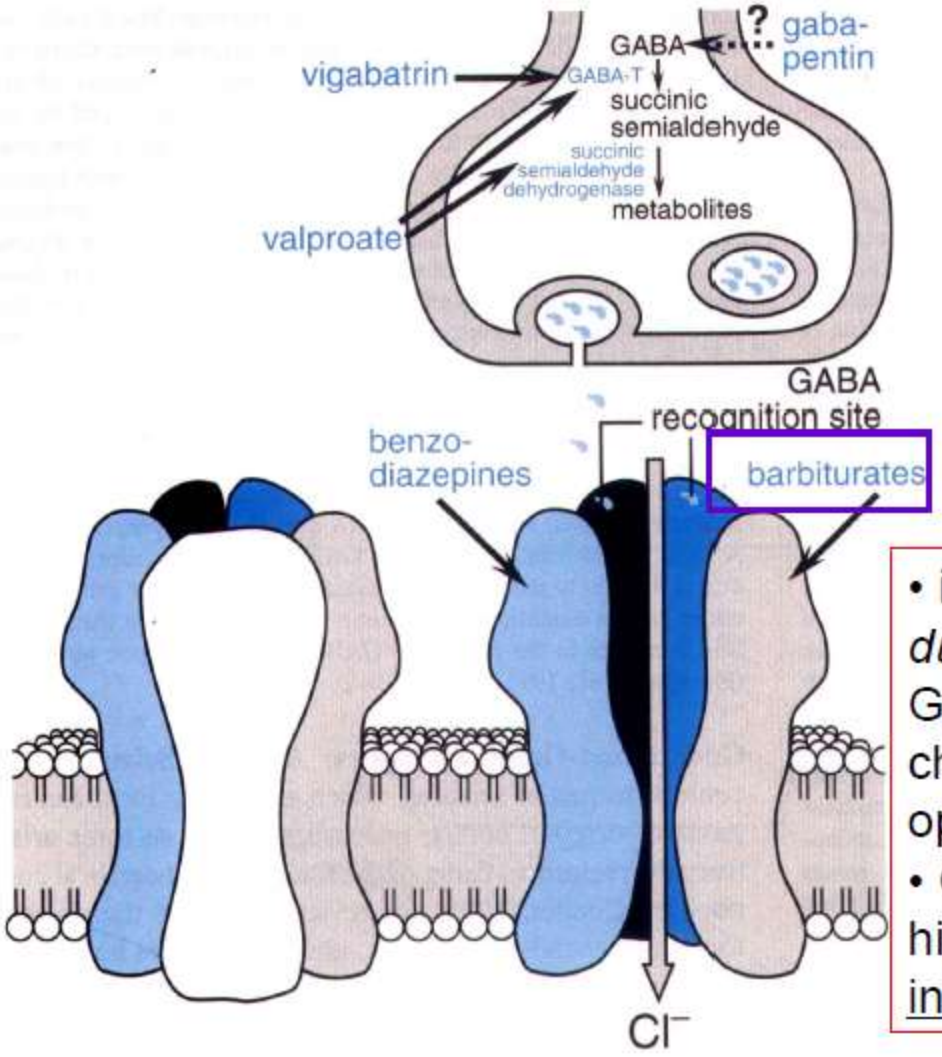


Figure 14.2 ● Biosynthesis and metabolism of GABA.





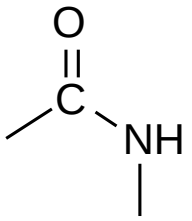
- increase the *duration* of the GABA-gated chloride ion channel openings
- GABA-mimetic at high dose – <u>GABA independent efficacy</u>

GABAA Receptors as Targets for Anticonvulsants

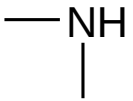
The potential targets for AED's action on the GABAergic inhibitory
synapses include:

(a)drugs that enhance the biosynthesis of GABA (gabapentin, pregabalin, and VPA),
(b) drugs that inhibit GABA degradation (vigabatrin),
(c) drugs that inhibit the reuptake of GABA (tiagabine), and
(d) drugs that bind to an allosteric site on the postsynaptic GABAA receptor complex that increase chloride conductance (barbiturates, BZDs, neurosteroids, felbamate FBM, Topiramate (TPM).

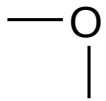
Antiepileptic General Structure



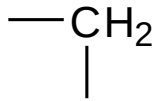
Barbiturates



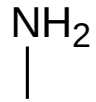
Hydantions



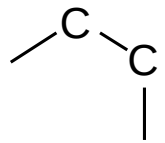
Oxazolidinediones



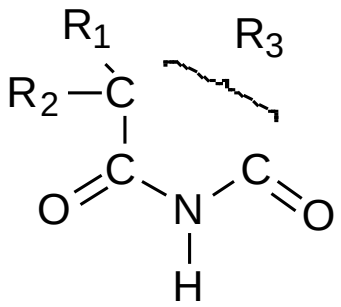
Succinimides

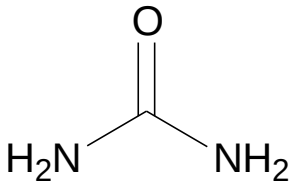


Phenacemide



Glutethimide

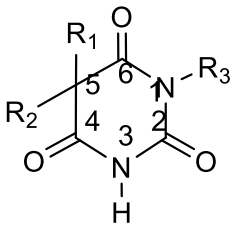


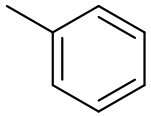
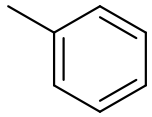
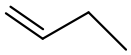
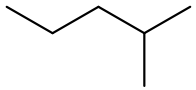


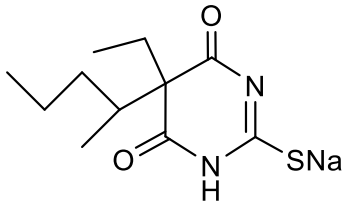
Urea

- Overall, R_1 and R_2 should be hydrocarbon
- Lower alkyls tend to be active against absence seizures and not active against generalized tonic-clonic or partial seizures
- If one of the hydrocarbon substituent is an aryl group activity tends to be directed toward generalized tonic-clonic and partial seizures and not absence seizures

Barbiturate

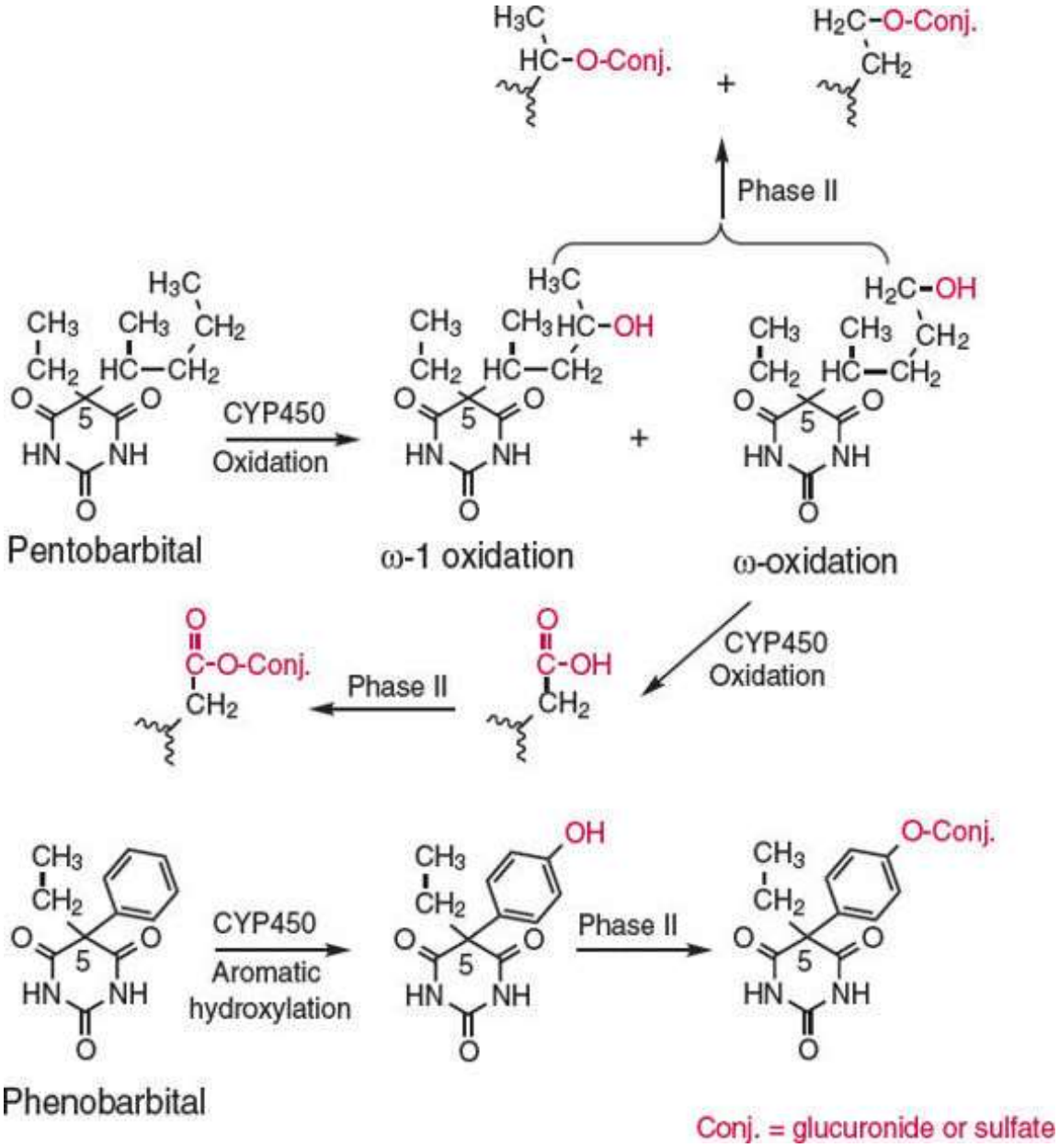


	R_3	R_1	R_2
Barbital	H	C_2H_5	C_2H_5
Phenobarbital	H	C_2H_5	
Mephobarbital	CH_3	C_2H_5	
Secobarbital	H		



Thiopental sodium

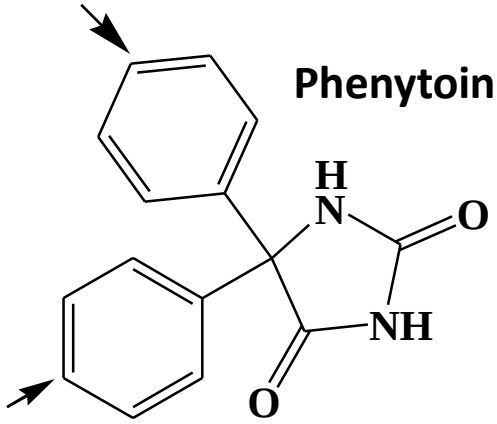
- The main antiepileptic drug is Phenobarbital major metabolite of which is the *p*-hydroxyl and/or the *p*-hydroxyglucuronide; about 25% excreted unchanged
- N^1 and N^3 are not distinguishable.
- Both drugs being substituted with an aromatic ring at R_2 are effective against generalized tonic-clonic and partial seizures.


H3C
HC-O-Conj.
+
H2C-O-Conj.
CH2
Phase II
H3C
H2C-OH
CH3 CH3 CH2
CH2 HC—CH2
O 5 O
HN NH
O
CYP450
Oxidation
+
Pentobarbital
ω-1 oxidation
ω-oxidation
O
C-O-Conj.
CH2
Phase II
O
C-OH
CH2
CYP450
Oxidation
CH3
CH2
OH
O-Conj.
CYP450
Aromatic
hydroxylation
Phase II
Phenobarbital
Conj. = glucuronide or sulfate

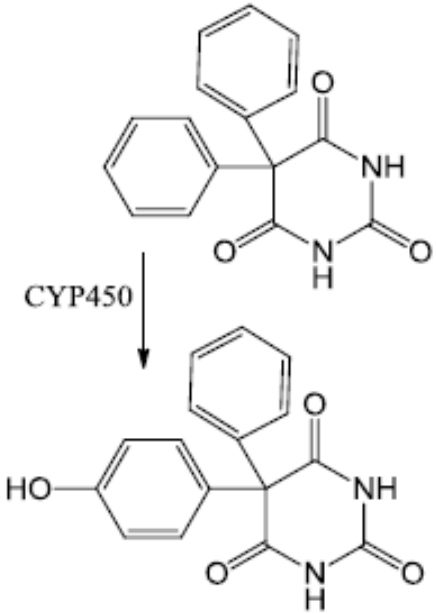
Example: Phenytoin

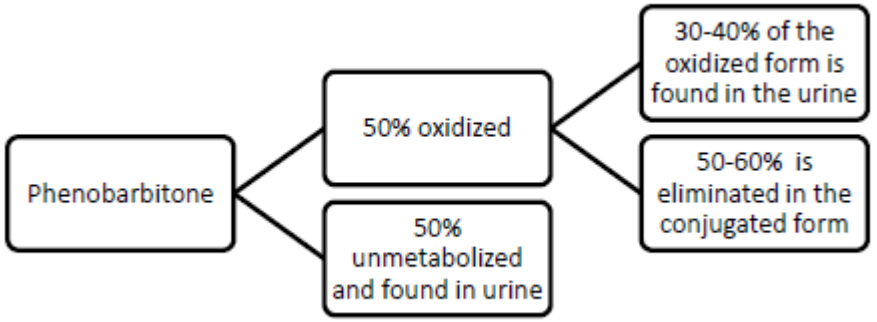
- Here the oxidation will occur only at one aromatic ring (it can be either)

Phenytoin

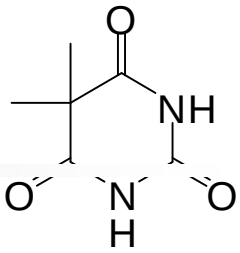


Phenobarbitone





SAR of Barbiturates



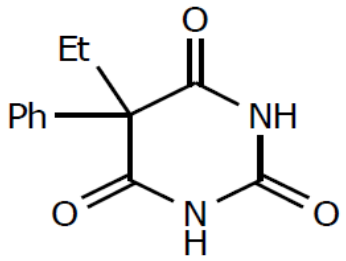
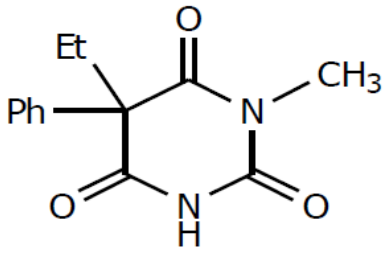
- Both hydrogen atoms at C^5 must be substituted
- There is a decrease in onset time and a decrease in duration as C^5 alkyl chain length increases.
- Due to increasing lipid solubility increases rate of CNS penetration for shorter onset and increases susceptibility to microsomal metabolism due to penetration into hepatic cells
- Common metabolic pathway is ω and ω-1 oxidation
- Except for those with very high lipid solubility (thiobarbiturates), the barbiturates have short duration
- Bulk on C^5 (i.e., aromatic ring) is a common feature for drugs with activity for generalized seizures and also for partial seizures and status epilepticus, but not good for absence seizures

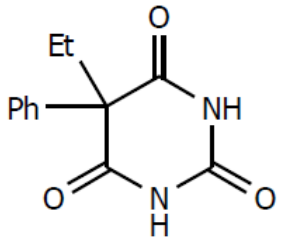
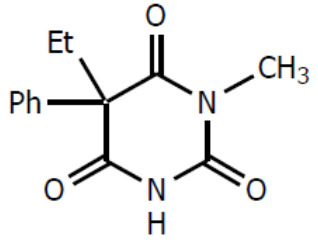
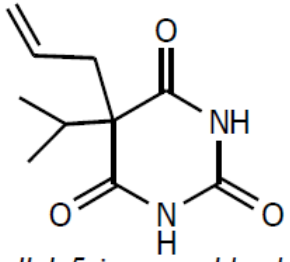
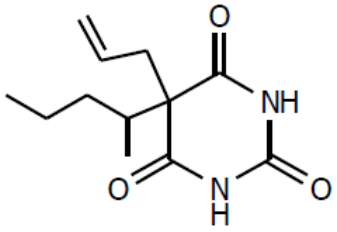
[i] Ureide derivatives

- **Classification**: A. Barbiturate. B. Hydantoins. C. Oxazolidinediones. D. Succinimides.
- **General Structure:**
- **The general SAR:**
- The substitution pattern at ***C_5 of the hydantoins & oxazolidinediones*** or ***C_2 of the succinimides*** determine the type of anti-convulsant activity.
- Hydantoins with ***at least one C_5 phenyl gp*** are the drug of choice in → ***generalized tonic-clonic seizures***

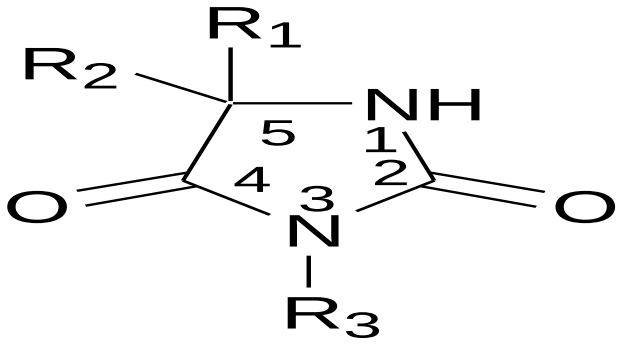
The ***diphenyl substitution*** pattern ***↑potency of anti-grand mal > single subs.*** •

A. Barbiturates

	
Phenobarbital	**Mephobarbital**
Mephobarbital by metabolism (N-dealkylation) → Phenobarbital (active form)	
Used in generalized & partial seizures	

Long acting (> 6 hr)	
Phenobarbital	Mephobarbital
 *5-Ethyl-5-phenyl barbituric acid*	 *5-Ethyl-1-methyl-5-phenyl barbituric acid*
Intermediate acting (3-6 hr)	**Short acting (< 3 hr)**
Aprobarbital	Secobarbital
 *5-allyl-5-isopropyl barbituric acid*	 *5-allyl-5-(1-methyl butyl) barbituric acid*

Hydantoins



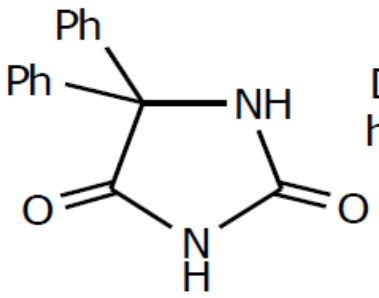
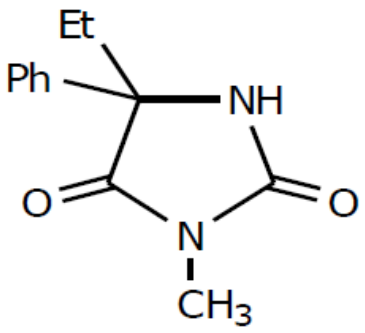
Hydantoins

1. Close structural relatives of barbiturates
2. **5-membered ring structure containing 2 nitrogen in ureide configuration**
3. Only lacking the 6-oxo group and are cyclic monoacylureas rather than diacylureas

SAR of Hydantoins

Most of the clinically used drugs in this class possess bulky aromatic ring in position C^5 that confers usefulness in generalized seizures, partial seizures and status epilepticus but not well for absence seizures

B. Hydantoins (imidazolidine-2,4-diones)

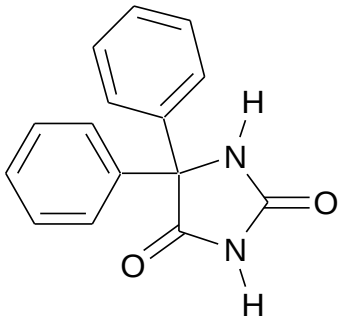
Phenytoin	Mephenytoin
 Diphenyl hydantoin	
5,5-Diphenyl imidazilidine-2,4-dione	*5-Ethyl-3-mehtyl-5-phenyl hydantoin*

- ***Structurally close to barbiturates*** (differ in lacking of the 6-oxo moiety)
- With ***anti-generalized tonic clonic >>> Anti-absence.***

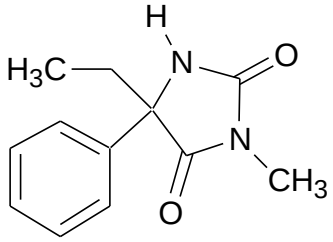
Hydantoin Drugs

Phenytoin is metabolized by *p*-hydroxylation followed by conjugation similar to Phenobarbital.

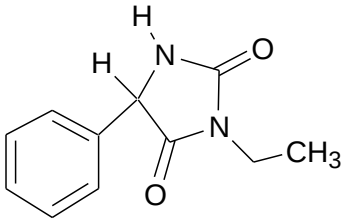
- **Mephenytoin** is the hydantoin analogue of mephobarbital which is also a prodrug, converted into the dealkylated derivative. Metabolism is also by *p*-hydroxylation and then glucuronidation



Phenytoin



Mephenytoin



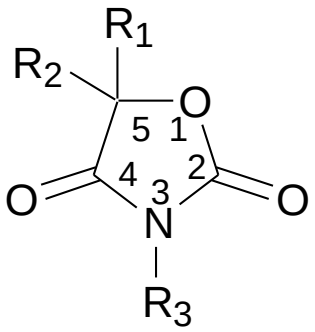
Ethotoin

- Ethotoin is dealkylated to the active drug. In this case there is free hydrogen at C_5, which explains its very low potency. Metabolism is also by *p*-hydroxylation and then glucuronidation

Hypersensitivity reactions (idiosyncratic toxicity) to phenytoin and other aromatic AEDs in susceptible individuals are believed to stem from the reactions of these reactive intermediates(i.e., arene oxide, catechol, or *o*-quinone) with hepatic enzymes or other cellular proteins forming covalently bonded haptens.

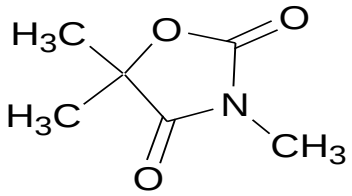
- The reactive intermediate, arene oxide, is deactivated by either epoxide hydrolase to dihydrodiol (amajor urinary metabolite) or by the action of GSH and glutathione transferase.
- It has also been suspected that these reactive arene oxides or epoxides mediate the teratogenicity of phenytoin and other AEDs.

Oxazolidinediones

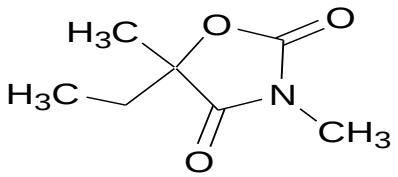


Oxazolidinedione

Replacement of the N-H group at position 1 of the hydantoin with an oxygen atom yields the oxazolidine-2,4-dione system



Trimethadione



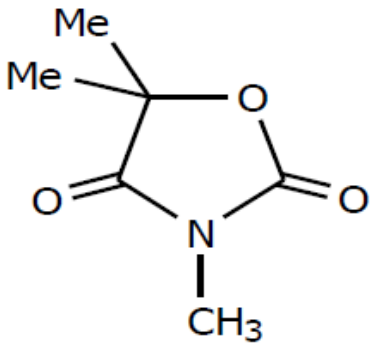
Paramethadione

- **Trimethadione** is useful for absence seizures. Note the absence of bulky substituents at the C_5 position which are useful in absence seizures.
- It is metabolized to 5,5 dimethyl oxazolidine 2,4 dione (dimethadione) which is also active. Both trimethadione and dimethadione are excreted in the urine and are very toxic

- **Paramethadione** is also N dealkylated, half life is 12-24 hours.

C. Oxazolidine2,4-Diones (Petit mal)

Trimethadione

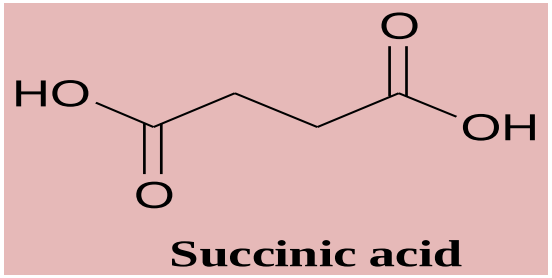


,5,5-Trimethyl-1,3-oxazolidine-2-4-dione

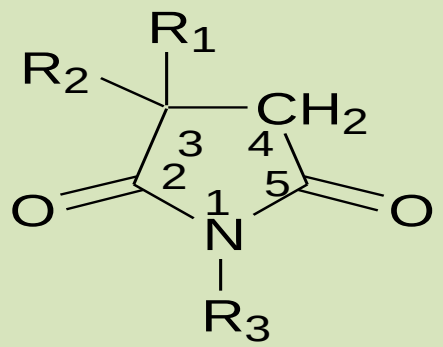
- ***Prototype of the Anti-absence***
- Produce ***Aplastic anemia & bone marrow depression*** → not used.

Succinimides

- This group of drugs resulted from a search for a less toxic version of the oxazolidinediones by replacing the “O” with CH_2
- work by blocking the low thresholdT-type calcium channels, thereby reducing the hyperexcitability of thalamic neurons that is specifically associated with absence seizure



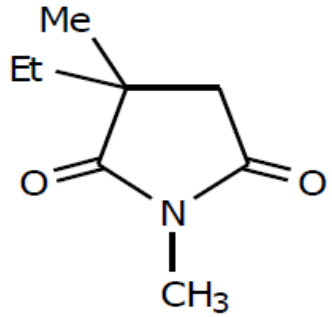
Succinic acid



Succinimides

D. Succinimides

Ethosuximide

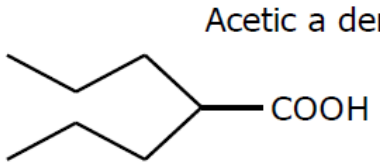


2-Ethyl-2-methyl succinimide

- ***More effective & less toxic than trimethadione*** → the ***drug of choice for typical absence*** seizures.

[ii] Miscellaneous

Valproic acid (Depakin®)



2-propyl petoic acid

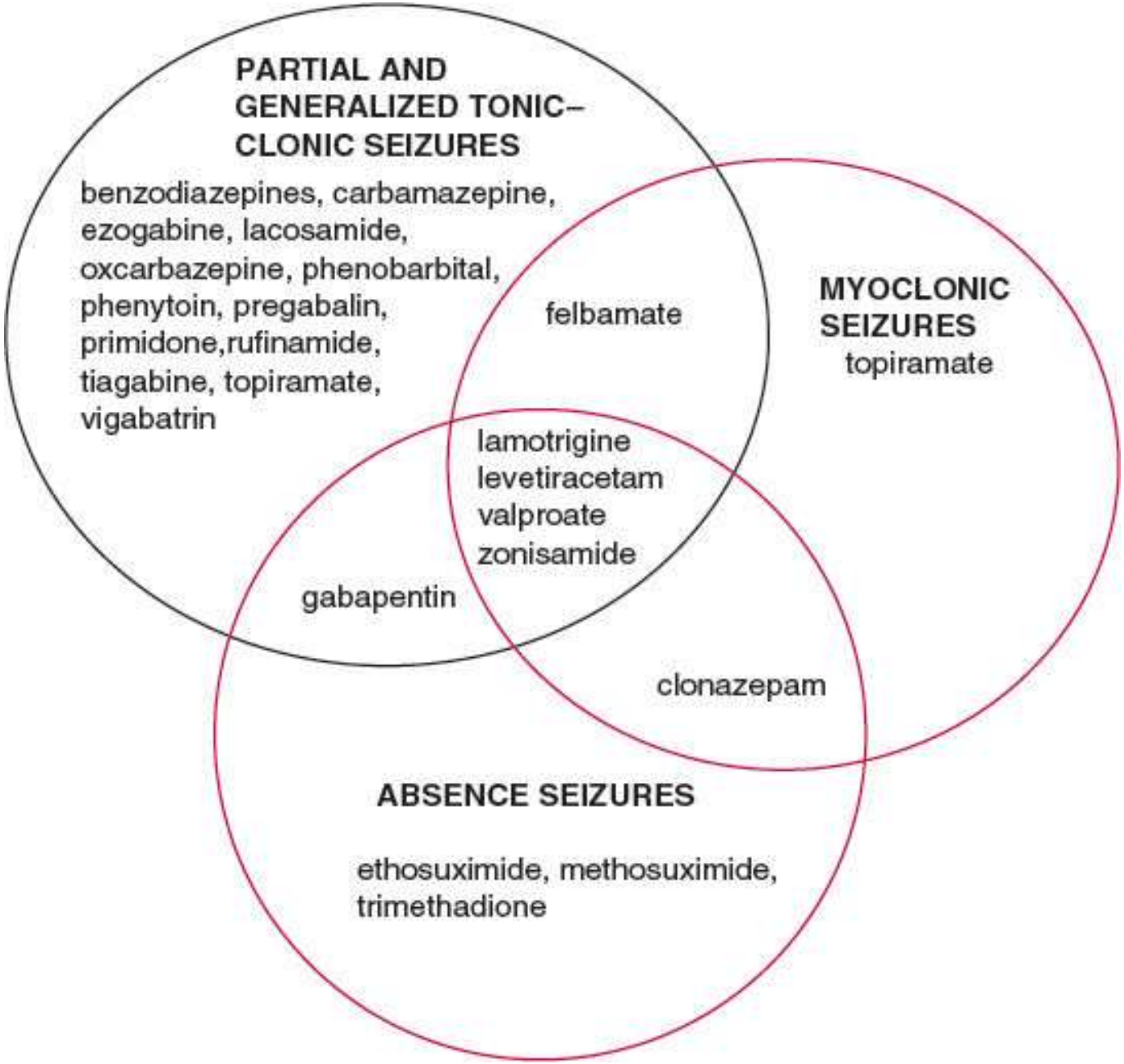
Metabolism:

① ***Direct conjugation*** (COOH)

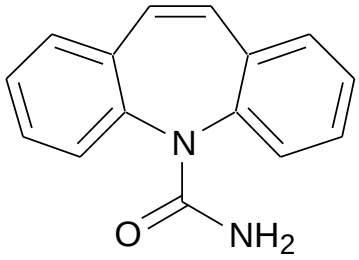
② ω or ω-1 oxidation → ***5-hydroxy*** & ***4- hydroxy derivative*** [5-Hydroxy → ***2-n-propyl glutamic acid.***

Drug of choice for absence

(Maybe used against grand mal)

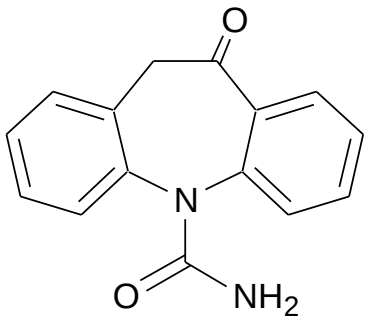

PARTIAL AND GENERALIZED TONIC–CLONIC SEIZURES
benzodiazepines, carbamazepine, ezogabine, lacosamide, oxcarbazepine, phenobarbital, phenytoin, pregabalin, primidone,rufinamide, tiagabine, topiramate, vigabatrin
felbamate
MYOCLONIC SEIZURES
topiramate
lamotrigine
levetiracetam
valproate
zonisamide
gabapentin
clonazepam
ABSENCE SEIZURES
ethosuximide, methosuximide, trimethadione

Miscellaneous -Iminostilbenes



Carbamazepine

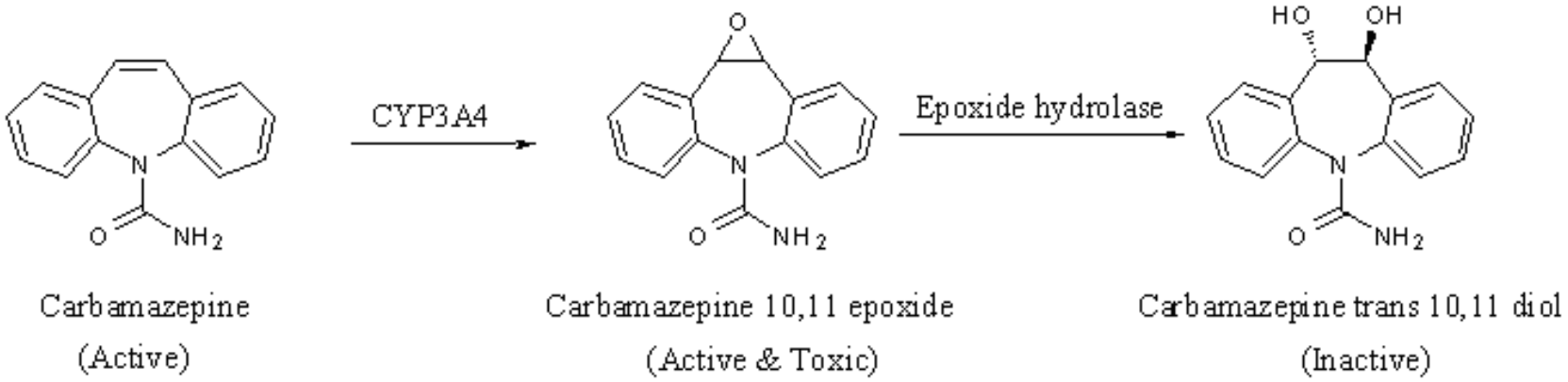
(Tegretol)



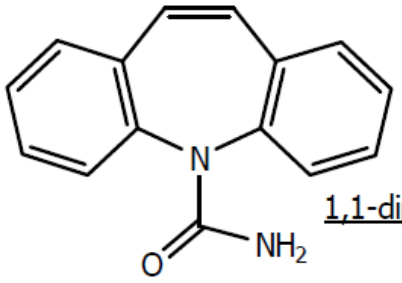
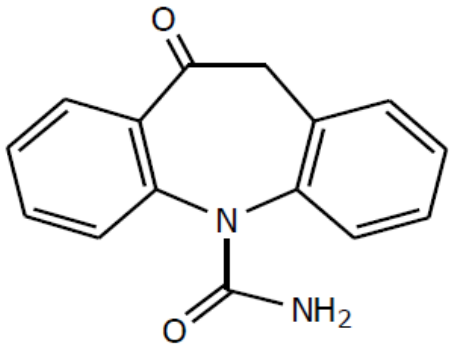
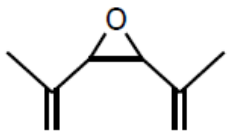
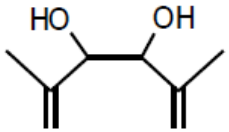
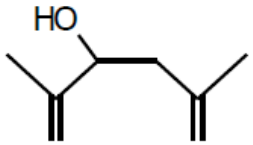
Oxacarbazepine

(Trileptal)

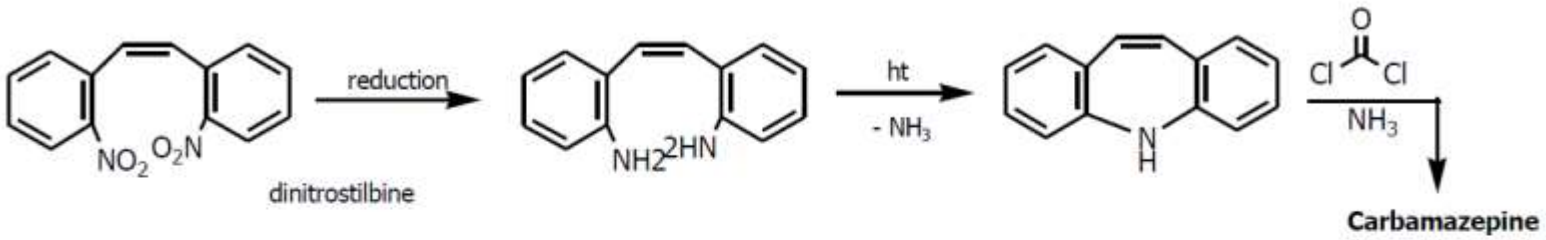
Dibenzazepines structurally related to the TCAs. The H_2NCO function is referred to as a carbamoyl or carboxamide. If the N in the ring is included we have a urea derivative. So it is also a ureide



Oxcarbazepine does not undergo such epoxidation so is expected to be less toxic

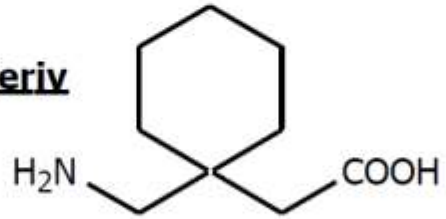
Carbamazepine (Tegretol®)	Oxacarbazepine (Trileptal)
 1,1-diphenyl urea	
Metab →  →  10,11-epoxide **active but toxic** trans 10,11-dihydroxy **inactice**	Metab →  excreted
Drug of choice for grand mal & used for partial not against petit	***Less side effect*** ***No epoxide formation***
S.E: ***Bone marrow depression*** & ***aplastic anemia***	

Synthesis of Carbamazepine



Gabapantin

acetic a deriv



GABA analogue but NOT acting on GABA receptors

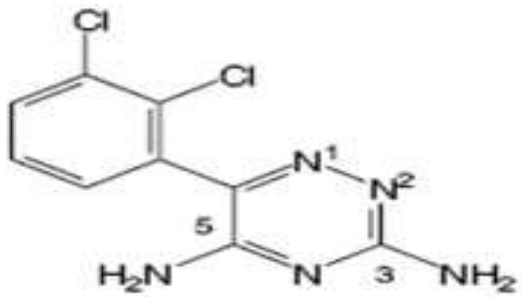
MOA: may involve ***L-amino acids transporter proteins.***

Novel Broad-Spectrum Anticonvulsants

LAMOTRIGINE (LAMICTAL):phenyltriazine class found effective against refractory partial seizures.

mechanism of action :blockade of sodium channels that is both voltage- and use dependent.

It also inhibits the high-threshold calcium channel, possibly through inhibition of presynaptic N-type calcium channels and also blocks glutamate release



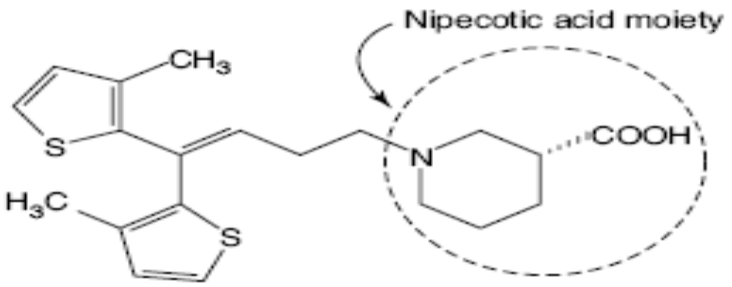
Lamotrigine

Anticonvulsants Acts on a Selective Molecular Target

TIAGABINE (GABITRIL)

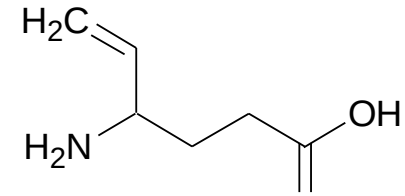
- A glance at tiagabine's structure suggests an uptake inhibitor.
- Reportedly, it blocks GABA reuptake as a major mode of its anticonvulsant activity

- Nipecotic acid is a potent inhibitor of GABA reuptake into synaptosomal membranes, neurons, and glial cells. However, nipecotic acid fails to cross the blood-brain barrier following systemic administration because of its high degree of ionization.



Tiagabine

Molecular Entity in 2009: Vigabatrin



VIGABATRIN
Sabril

- (±)-4-amino-5-hexenoic acid
- A GABA analog and is dosed as a racemic compound, with the S-enantiomer being the pharmacologically active form.
- The alkene group forms an irreversible, covalent bond with the gamma-aminobutyric acid transaminase (GABA-T) and irreversibly inhibits it.
- The enzyme (GABA-T) is responsible for the metabolism of the inhibitory neurotransmitter GABA; its blockade leads to increased levels of GABA in the central nervous system.
- Thus, it is an antiepileptic drug indicated as a monotherapy for pediatric patients 1 month to 2 years of age with infantile spasms (IS) and as an adjunctive therapy for adult patients with refractory complex partial seizures (CPS) who have inadequately responded to several alternative treatments.
- It is essentially completely orally absorbed and widely distributed throughout the body. It is not significantly metabolized (80% of a dose is recovered as parent drug), although it does induce CYP2C9, and it is eliminated primarily through renal .

CNS DEPRESSANTS

CNS Depression

Sedation

Hypnosis

General Anesthesia

Poisoning

Death

SEDATIVE

Drugs that have an inhibitory effect on the CNS to the degree that they reduce:

- Nervousness
- Excitability
- Irritability without causing sleep

(McKenry et al., 2003)

An effective **sedative** (anxiolytic) agent should reduce anxiety and exert a calming effect with little or no effect on motor or mental functions.

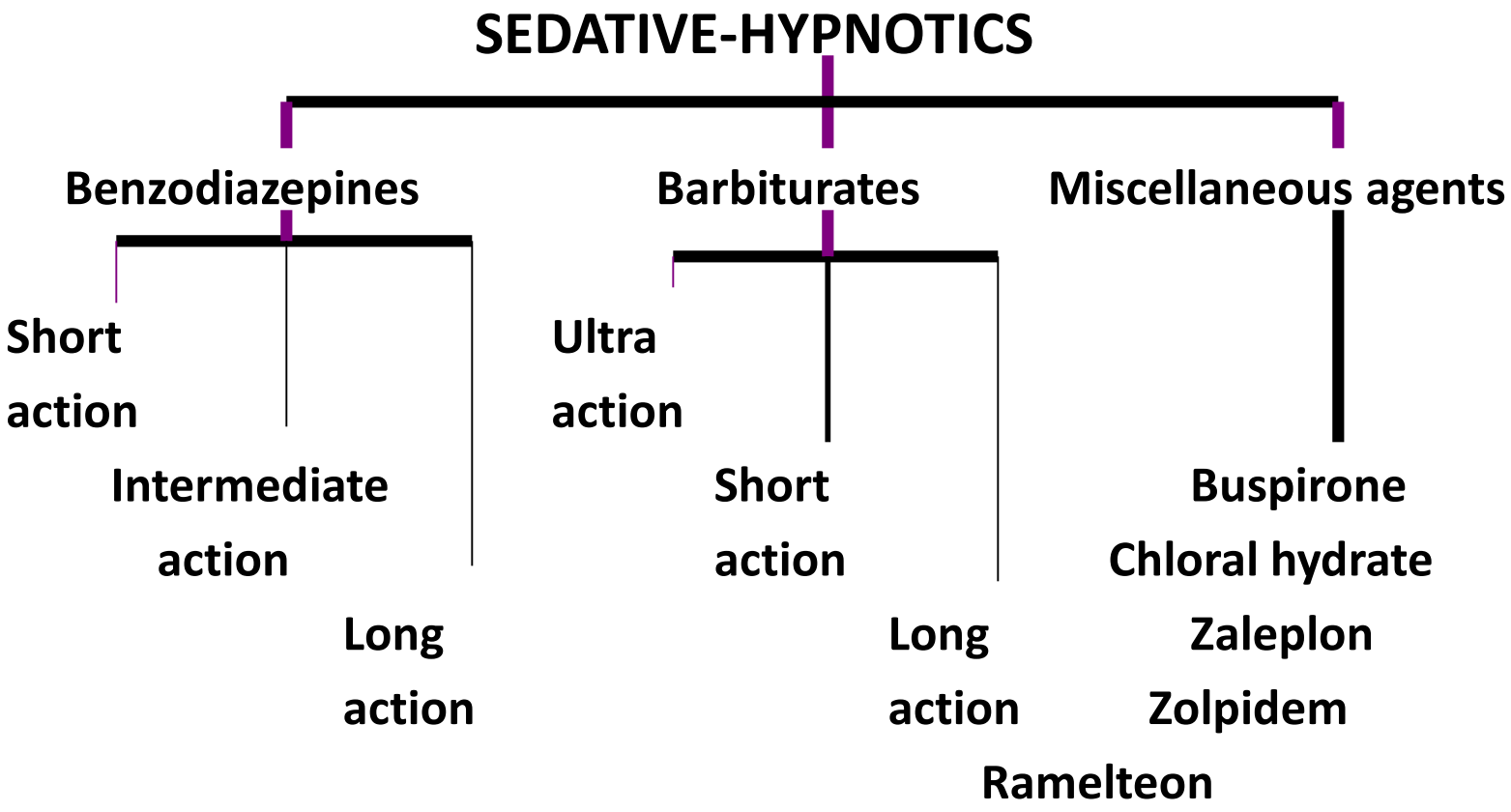
(Katzung et al., ed 11)

HYPNOTICS

- Calm or soothe the CNS to the point that they cause sleep
- A hypnotic drug should produce drowsiness and encourage the onset and maintenance of a state of sleep that as far as possible resembles the natural sleep state.
- A sedative can become a hypnotic if it is given in large enough doses → dose dependent

(Katzung; Goodman & Gilman)

SEDATIVE-HYPNOTIC DRUGS



[I] Sedative Hypnotics

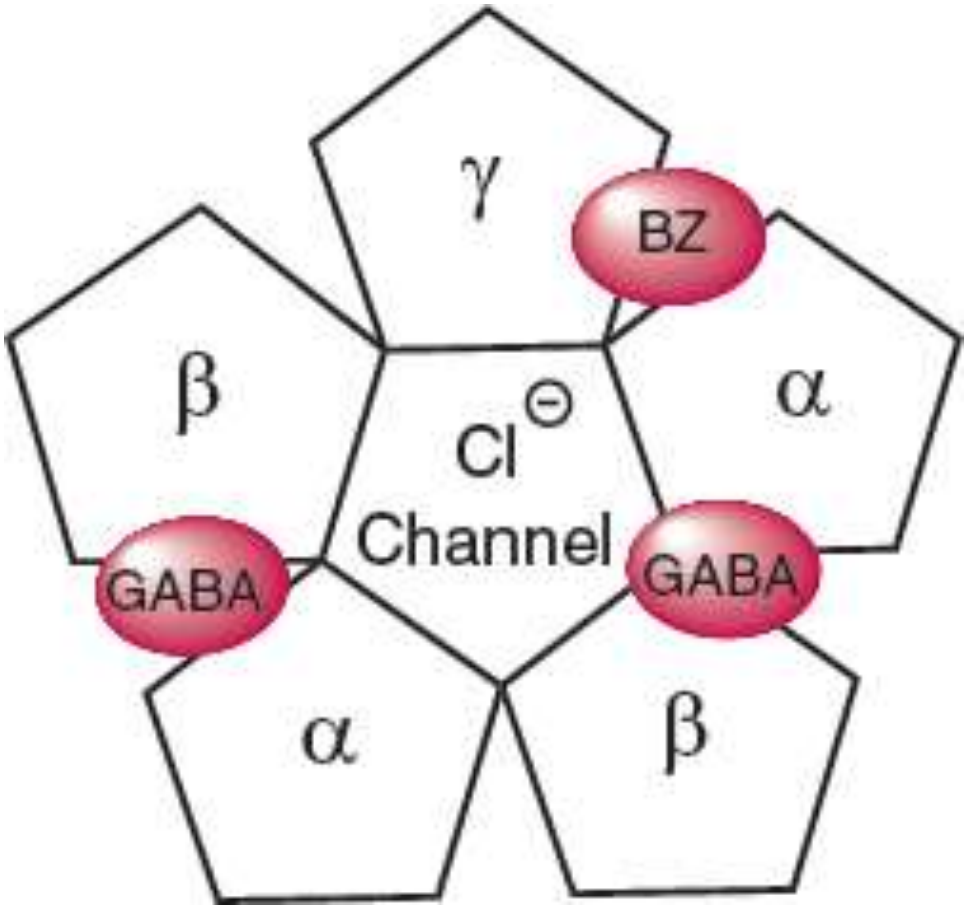
- Action ***from slight sedation to sleep*** according to the ***drug used, dose & its route of administration***
- **Uses of Sedatives**: *emotional stress*, *hypertension*, to control *convulsion* and adjunct to *anesthesia*.
- Uses of Hypnotics: To treat ***insomnia***.

[i] Barbiturates

- **Barbituric acid pKa = 4.12** (due to tautomerism→ ionized at physiological pH) → hydrophilic→ doesn't penetrate B.B.B.
- **Monosubstituted** barbituric acid at C5 has pKa =**4.75**
- Both barb.a'& monosubstituted barb.a' at physiological pH → found in ionic form→ doesn't penetrate B.B.B.→ inactive.
- ***Disubstitution* at C_5 has pKa= *7.6* + *N-methylation pKa=8.4***
- **So, for good hypnotic activity of barbiturates we need:**
- **1. Weak acid 2. ↑ Partition coefficient (to certain limit)**
- ***Prolonged use*** → habituation & tolerance.
- ***Phenobarbital → Hepatic Microsomal Enzyme Inducing Drug [HME Inducer]* → Tolerance + many Drug-Drug Interaction.**

[II] Anxiolytics
[i] Benzodiazepines (BZPs)

- **Uses (drug of choice):**
- Anxiolytics.
- Pre-anesthetic (induction of anesthesia)
- Hypnotic.
- Anticonvulsant.
- Central acting skeletal muscle relaxant.
- **Advantage over barbiturates:**
- ***More safe*** (overdose → ***no respiratory depression***)
- ***Low tendency of drug interaction.***
-
- **Disadvantage:**
- Slow eliminated from body → due to formation of ***active metabolite in brain & liver*** → ***hangover effect & accumulation*** ***on repeated dose.***


γ
BZ
β
α
Cl⊖
Channel
GABA
GABA
α
β

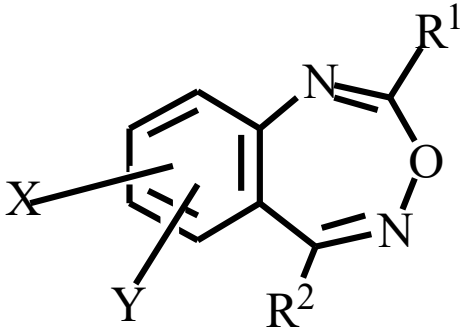
** ***BZPs potency*** ***depend on lipid solubility*** → ↑ lipophilicity will ↑ potency → (more distributed to the brain).

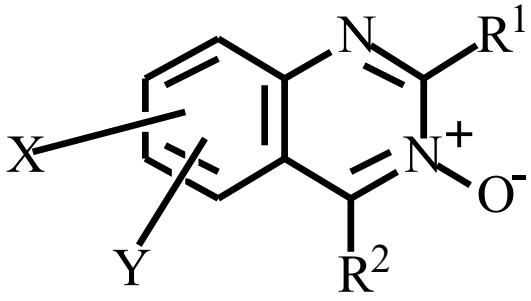
BZPs duration → depend on ***metabolism.

- MOA:
- Bind to ***BZPs recognition site on BZPs receptor*** → ***enhancing effect of $GABA_A$ receptors*** → ↑ Chloride ion flux into the neurons.

Serendipitous Discovery of Librium without a Lea

In 1955 Roche set out to prepare a series of benzheptoxdiazines as potential new tranquilizer drugs, but the actual structure was found to be that of a quinazoline 3-oxide.

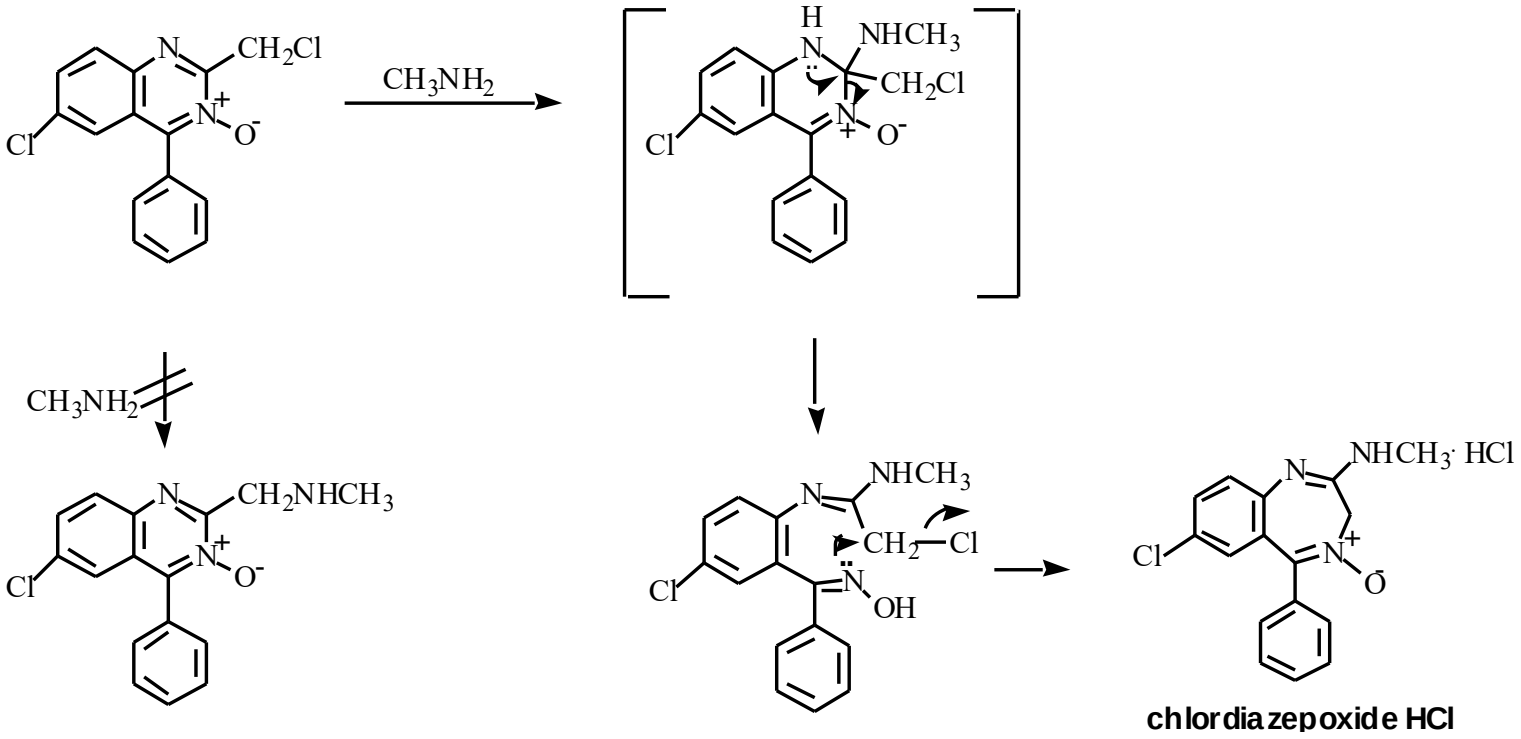




No active compounds were found, so the project was abandoned

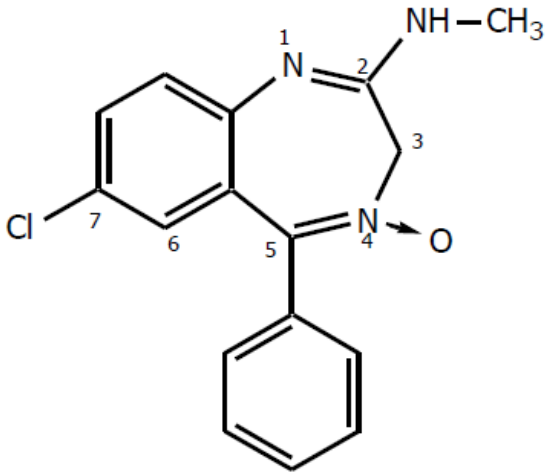
In 1957, during a lab cleanup, a vial containing what was thought to be the latter compound (X = 7-Cl, $R^1 = CH_2NHCH_3$, $R^2 = C_6H_5$) was sent for testing, and it was highly active.

Further analysis showed that the actual structure of the compound was the benzodiazepine 4-oxide, Librium, presumably produced in an unexpected reaction of the corresponding chloromethyl quinazoline 3-oxide with methylamine.

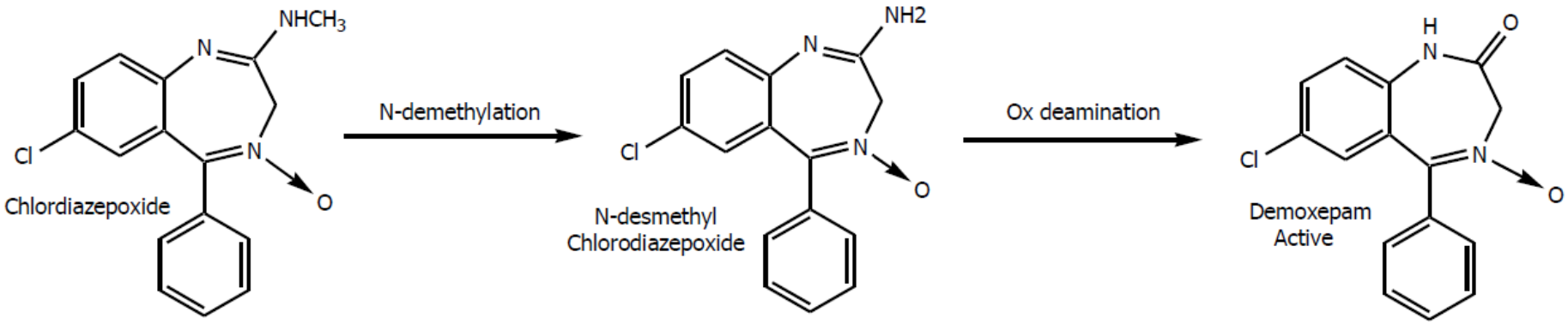


① 1,4-Benzodiazepine-4-oxides
Chlordiazepoxide

- Chlordiazepoxide is ***<u>the prototype & the most potent member</u>***

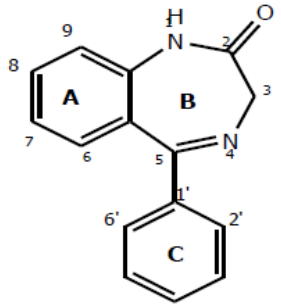


It's Long acting drug due to formation of several active metabolites



② 1,4-Benzodiazepine-2-ones

Ring System



5-Phenyl-1,4-benzodiazepin-2-one

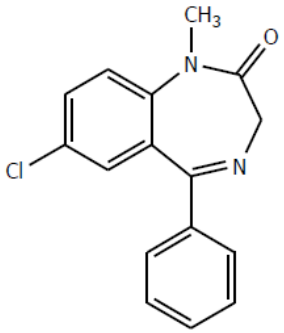
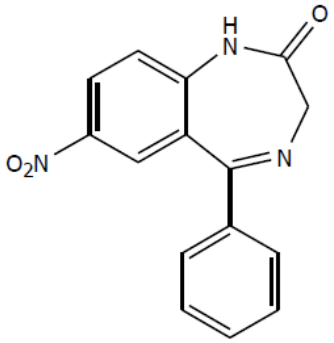
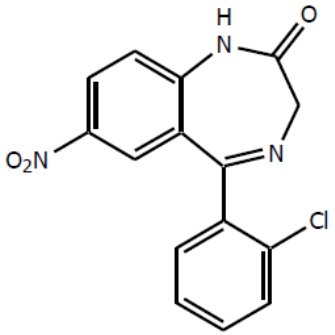
Ring A:

- ***Electron withdrawing gp at C_7*** is ***essential*** (Cl, Br, F, NO_2, CN) [the more electron attracting effect → the more activity].
- ***C_7 → NO_2*** (***intermediate duration***) → due to metabolism of NO_2 into NH_2 → Acetylation (inactive metabolites).
- ***Position 6,8,9*** should ***not subistituted***.

Ring B:

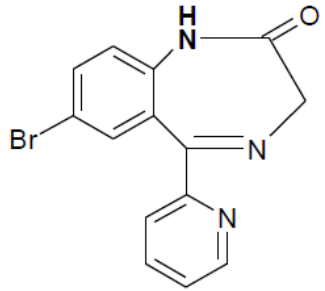
- The presence of ***7-membered imino-lactam ring*** is ***essential***.
- The ***2-carbonyl function*** is ***essential*** for activity.
- The ***N_1-substitution*** should be ***small*** → ***Xpt if active matabolits produced*** as (flurazepam & prazepam)
- Alkyl subs at C_3 → ↓ activity.
- The ***presence or absence of 3-OH*** is ***important pharmakokinetically.***
  - * ***Without 3-OH*** → ***non-polar*** (***long duration***).
  - * ***With 3-OH*** → ***more polar*** → ***more easily excreted*** as glucuronides → **short duration.**

- ***COOH at C_3*** → ***prodrug*** with ***long half life***.
- ***C_5 phenyl gp*** promotes activity.
- ***Saturation*** of double bond between C_4,C_5 **OR** its shift to C_3,C_4 → ↓ activity.
- Ring C:
- The presence of ***ortho or diortho substitution*** with electron-attracting effect → ***↑activity.***
- ***Para substitution*** → ***↓activity.***

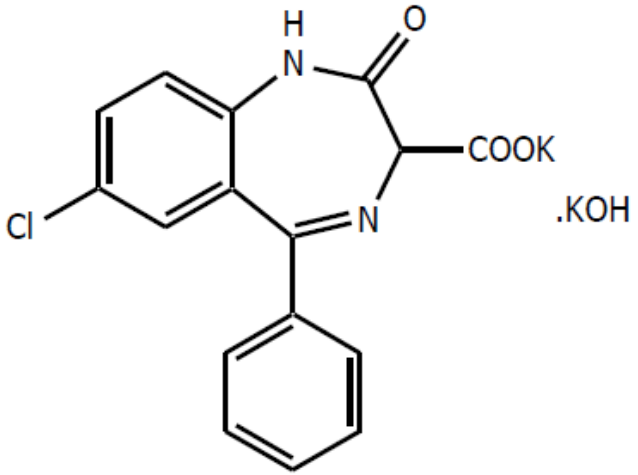
Diazepam (Valium®)	Nitrazepam	Clonazepam (Rivotril)
		 ***Anti-convulsant drug***

Diazepam:

- ***PROTOTYPE*** of this class. ***Very non-polar → rapidly absorbed → Very potent.***
- ***With long duration → active metabolites.***

Bromazepam (Calmipam)


Chlorazepate dipotassium

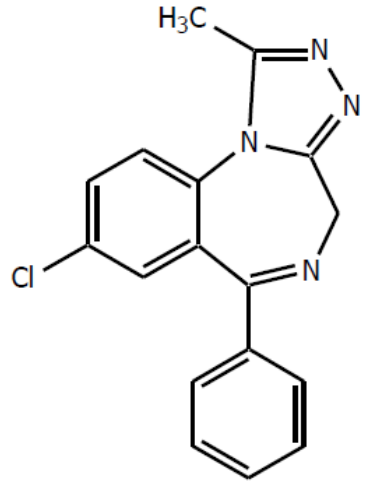


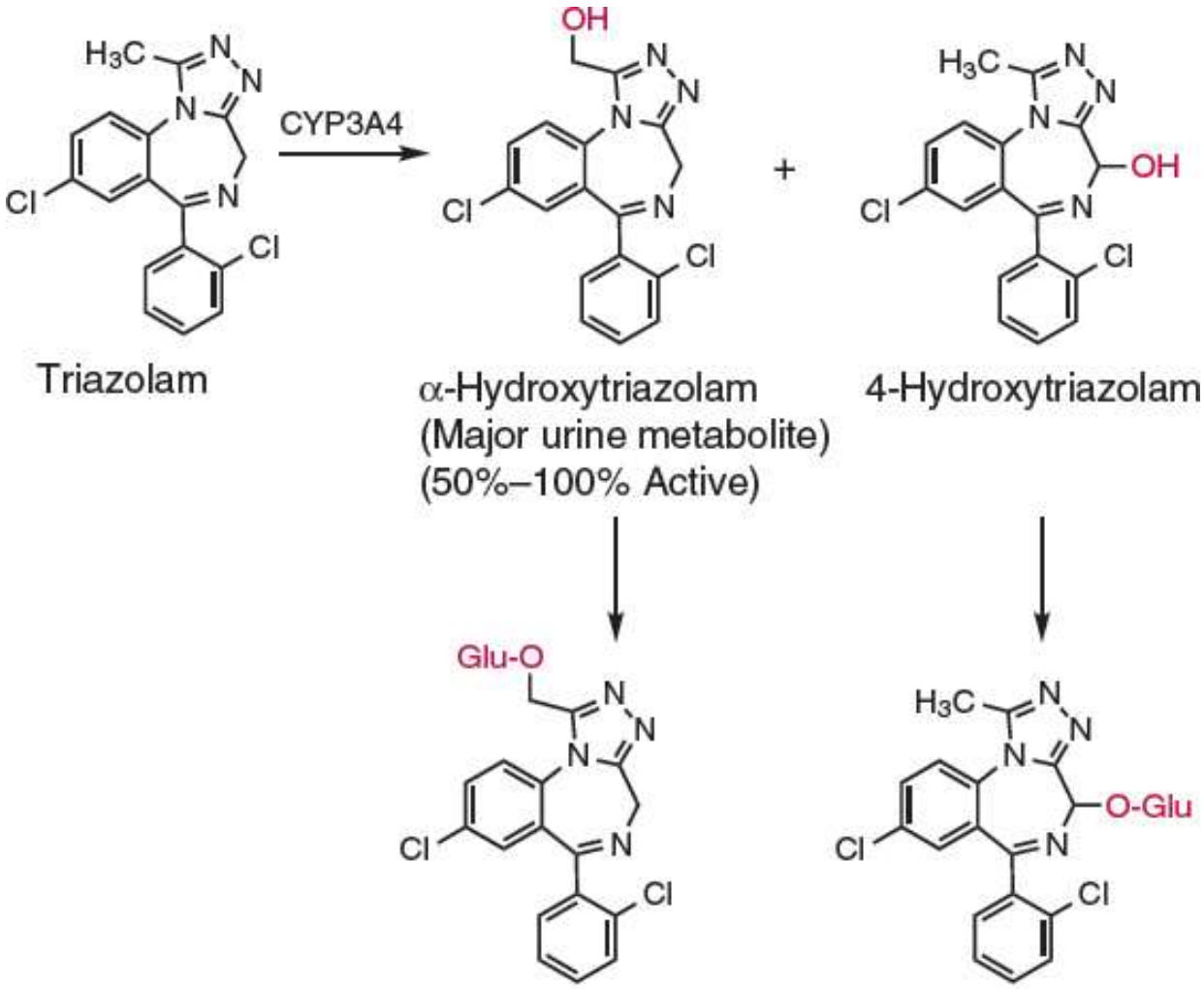
Prodrug → activated by decarboxylation in stomach to Nordiazepam (active) → with long $t_{1/2}$ (water sol → IV)

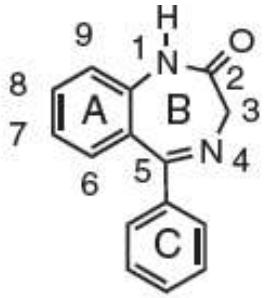
③ 1,2-Annealated 1,4-Benzodiazepaines

- **<u>Short duration</u>** → due to ***<u>rapid oxidation of -CH_3</u>*** → -CH_2OH → conjugation & excretion.

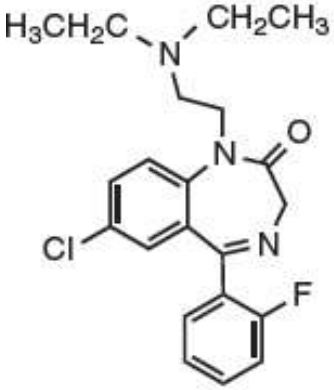
Alprazolam (Xanax)



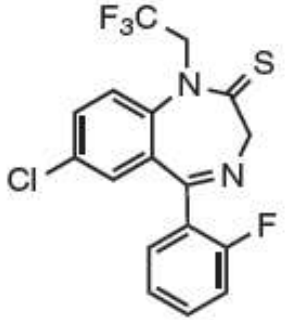

H3C
N
N
N
Cl
Cl
CYP3A4
OH
+
OH
Triazolam
α-Hydroxytriazolam
(Major urine metabolite)
(50%–100% Active)
4-Hydroxytriazolam
Glu-O
O-Glu



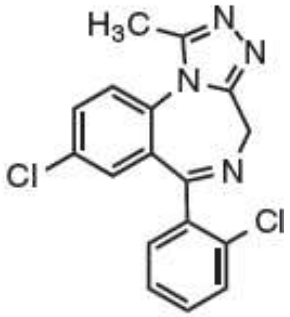
5-Phenyl-1,4-benzodiazepin-2-one
pharmacophore



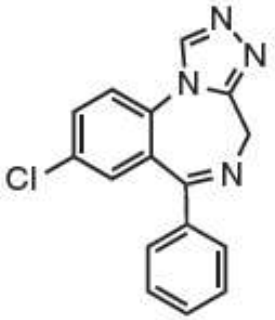
Flurazepam



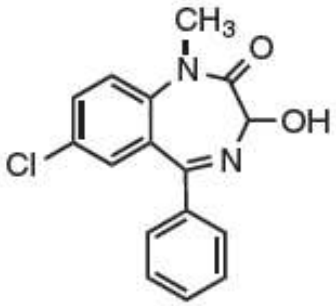
Quazepam



Triazolam

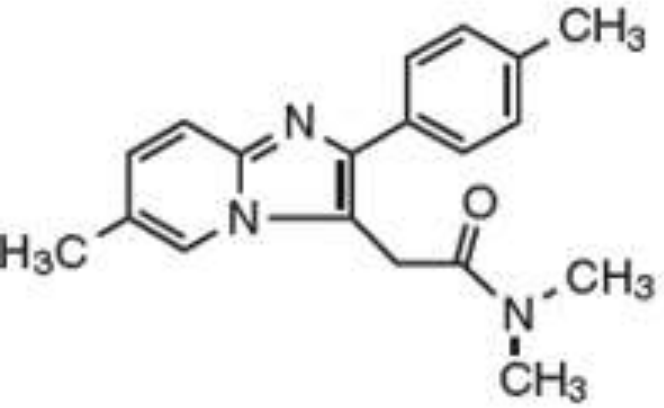


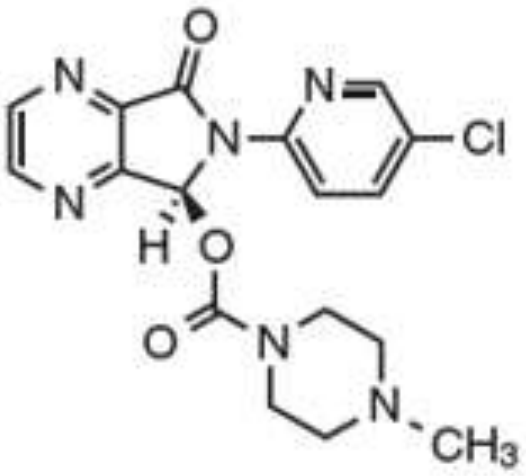
Estazolam

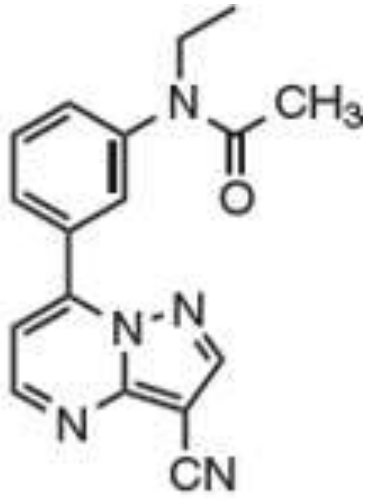


Temazepam

- **Nonbenzodiazepine $GABA_A$ Agonists**
- The discovery that there are several $GABA_A$ receptor subtypes (α_1, α_2, α_3, and α_5) and that the α_1-subtype is related most closely to benzodiazepine-induced sedation and hypnosis has led to the search for subtype-selective chemicals that would yield appropriate therapeutic outcomes. Currently there are three structurally distinct α_1-subtype selective nonbenzodiazepines: zolpidem, eszopiclone, and zaleplon.







Zolpidem, Eszopiclone, and Zaleplon

Zolpidem

- ***Effect:***
  - binds selectively to the BZ_1 subtype of BZ receptors and facilitates GABA-mediated neuronal inhibition
  - Useful for the short-term treatment of insomnia
  - Primarily a sedative (rather than an anxiolytic)
  - are antagonised by f l u m a z e n i l
  - risk of tolerance and dependence < BZ

- ***Pharmacokinetics:***
  - Rapidly absorbed in the GI tract following oral administration (75% reaches plasma)
  - Metabolized in the liver and excreted by the kidney's
  - Dosage reduction in hepatic dysfuction, elderly

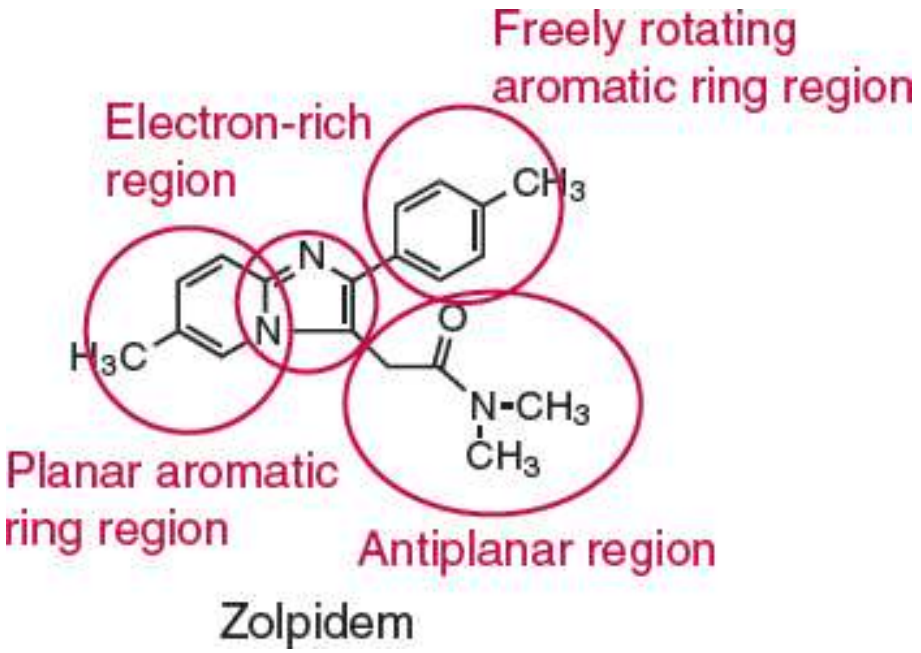
Structure–activity relationship studies revealed three activity regions necessary for binding to the $GABA_A$ receptor (Fig. 8.9).

An Electron-Rich Planar Aromatic Ring Region

- Substitution with electronegative groups (e.g., chloro) decreases selective affinity for the α_1 subtype.
- Imidazole ring is necessary for selectivity since conversion of either of the imidazole nitrogens to hydrogen bond donors leads to loss of $\alpha_1$subtype selectivity.

Freely Rotating Aromatic Ring

- Substitution with electronegative groups (e.g., chloro) decreases selective affinity for the α_1 subtype.



Zolpidem

Antiplanar Region

- The carbonyl group in this region can hydrogen bond with key residues in loop C of the α_1 subunit (Ser^{204} and Thr^{206}/Gly^{207}) and loop F of the γ_2 subuni

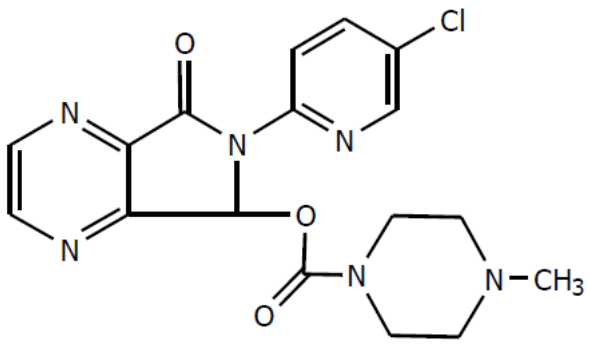
Zaleplon & Zopiclone

- Short half-life resembles zolpidem, $t_{1/2}$ = 1h
- Rapid onset and short duration of action are favorable properties for those patients who have difficulty falling asleep.
- Only approx. 30% of an orally administered dose reaches the plasma, and most of that undergoes first-pass elimination
- Half as potent as zolpidem
- Improves sleep quality w/o rebound insomnia, and little chance of developing dependency

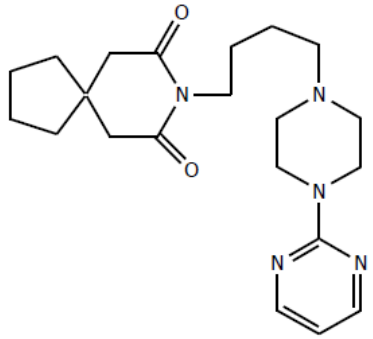
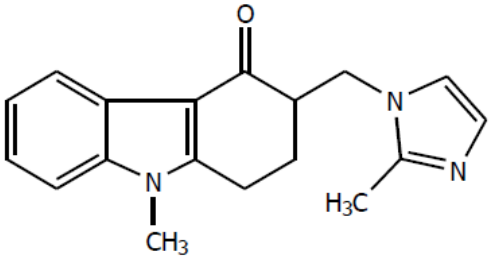
[ii] Cyclopyrolone derivatives

Zopiclone

- Advantage:
- 1. ***No withdrawal*** symptoms.
- 2. ***No accumulation*** after repeated doses.
- 3. ***Rapidly*** induce sleep.



[ii] Miscellaneous

Buspirone (Buspar®)	Ondansetron (Zofran®)
 **Aza spiro decane dione derivative**	
- **Uses**: Anxiolytic & Antidepressant - **M.O.A**: *5-HT_{1A} partial agonist*. - **S.E.**: *Block Dopamine receptors → (EPS)*	- **Uses**: Anxiolytic, Anti-depressant & Anti-emetic & anti-psychotic. - **M.O.A**: *5-HT_3 antagonist*.

Buspirone: 5 -HT1A -receptor agonists

- ***Pharmacokinetic:***
  - rapidly absorbed orally → extensive first-pass metabolism
  - The elimination half-life of buspirone is 2–4 hours, and liver dysfunction may slow its clearance.
  - Rifampin, an inducer of cytochrome P450, decreases the half-life of buspirone; inhibitors of CYP3A4 (eg, erythromycin, ketoconazole, grapefruit juice, nefazodone) can markedly increase its plasma levels.
- **A*dverse effect:***
  - causes less psychomotor impairment than benzodiazepines
  - does not potentiate effects of conventional sedative-hypnotic drugs
  - elderly patients do not appear to be more sensitive to its actions.
  - Nonspecific chest pain, tachycardia, palpitations, dizziness, nervousness, tinnitus, gastrointestinal distress, and paresthesias and a dose-dependent pupillary constriction
  - FDA category B drug in terms of its use in pregnancy.

Differences between buspirone and benzodiazepines:

1- The full anxiolytic effect of buspirone takes several weeks to develop, whereas the anxiolytic effect of the benzodiazepines is maximal after a few days of therapy.

2- In therapeutic doses, buspirone has little or no sedative effect and lacks the muscle relaxant and anticonvulsant properties of the benzodiazepines.

3- Buspirone does not potentiate the central nervous system depression caused by sedative–hypnotic drug or by alcohol

4- Buspirone does not prevent the symptoms associated with benzodiazepine withdrawal.