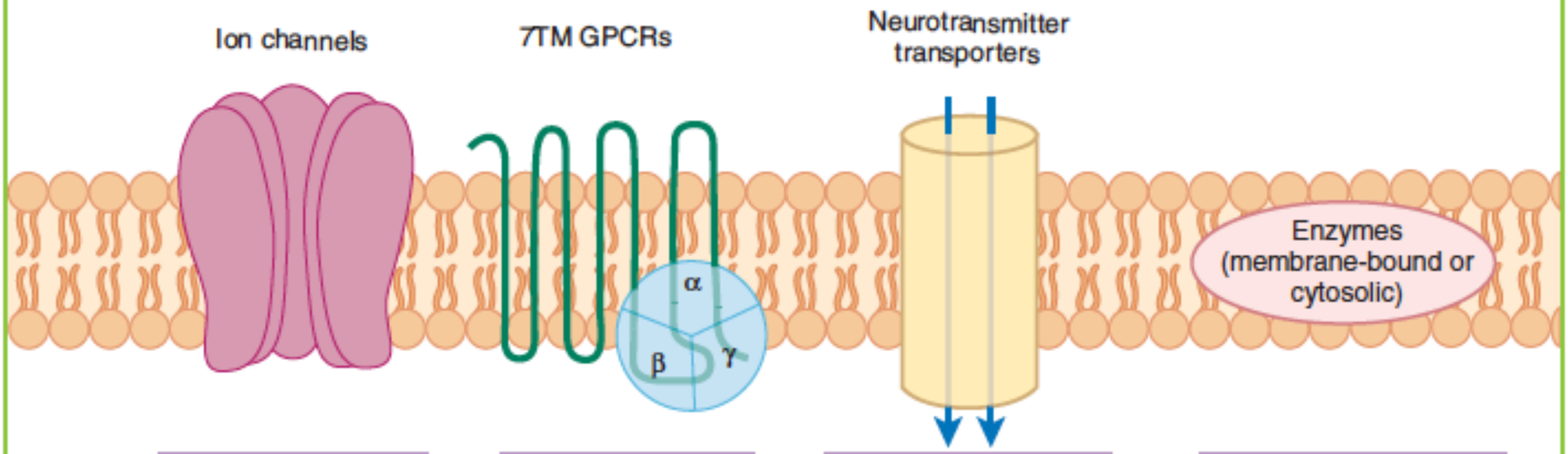
Molecular target:	Nicotinic R GABA R Glutamate R Serotonin R ($5HT_3$)	Adrenergic R Dopamine R Serotonin R Opioid R Muscarinic R	Serotonin T Norepinephrine T Dopamine T GABA T	Tyrosine hydroxylase Monoamine oxidase Catechol-*O*-methyltransferase Amino acid decarboxylase IP_3 metabolism



Drug class:	Nicotine Benzodiazepines Barbiturates Ethanol Anti-epileptics Anesthetics	Anesthetics Analgesics Opiates Hallucinogens Anti-Parkinson Antipsychotics	Tricyclic antidepressants SSRIs Stimulants (cocaine)	Anti-Parkinson's Antidepressants Lithium Alzheimer

Anxiolytic & Hypnotic Drugs

Asst Prof Dr Inam S Arif

isamalhaj@yahoo.com

BENZODIAZEPINES

Alprazolam XANAX
Chlordiazepoxide LIBRIUM
Clonazepam KLONOPIN
Clorazepate TRANXENE
Diazepam VALIUM, DIASTAT
Estazolam
Flurazepam DALMANE
Lorazepam ATIVAN
Midazolam VERSED
Oxazepam
Quazepam DORAL
Temazepam RESTORIL
Triazolam HALCION

BENZODIAZEPINE ANTAGONIST

Flumazenil ROMAZICON

OTHER ANXIOLYTIC DRUGS

Antidepressants VARIOUS (SEE CHAPTER 10)
Buspirone BUSPAR

BARBITURATES

Amobarbital AMYTAL
Pentobarbital NEMBUTAL
Phenobarbital LUMINAL SODIUM
Secobarbital SECONAL
Thiopental PENTOTHAL

OTHER HYPNOTIC AGENTS

Antihistamines VARIOUS (SEE CHAPTER 30)
Doxepin SILENOR
Eszopiclone LUNESTA
Ramelteon ROZEREM
Zaleplon SONATA
Zolpidem AMBIEN, INTERMEZZO, ZOLPIMIST

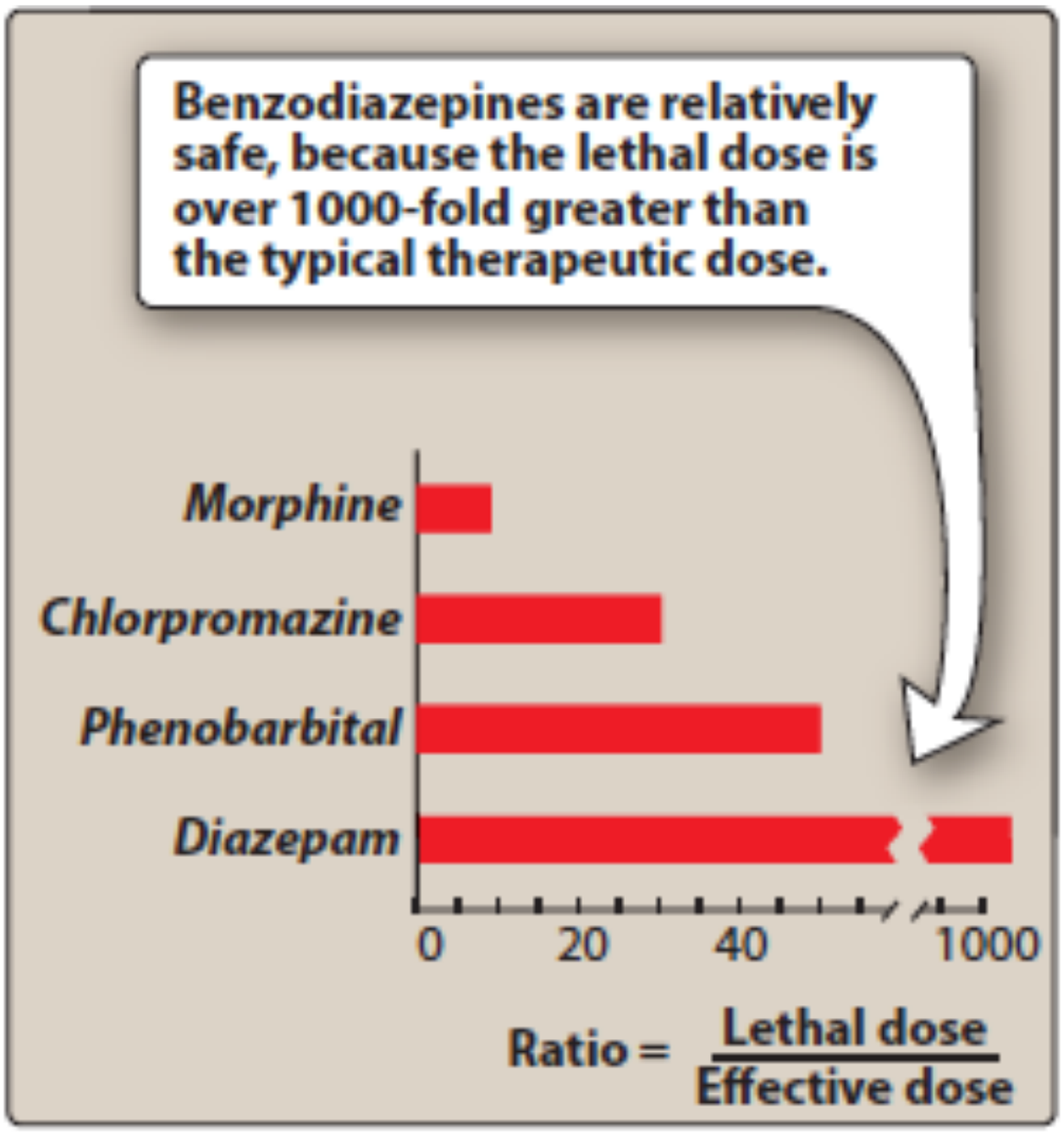
Anxiolytic & Hpnotic Agents

- Anxiety: unpleasant state of tension, apprehension or uneasiness, characterised by, tachycardia, sweating, tumbling & palpitation, in addition to sympath. stimulatio
- Episodes:
  mild, severe, chronic, debilitating anxiety

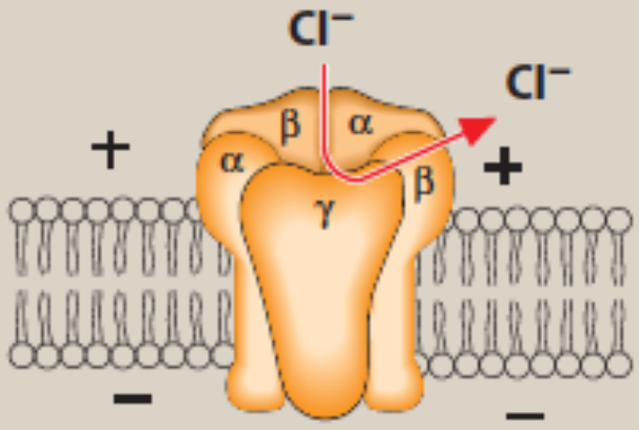
Benzodiazepines

- Safe
- Commonly used for anxiety & insomnia
- Antidepressant with anxiolytic / SSRIs are preferred
- Nonbenzodiazepine hypnotics & antihistamine are used also

Ratio of lethal to effective dose

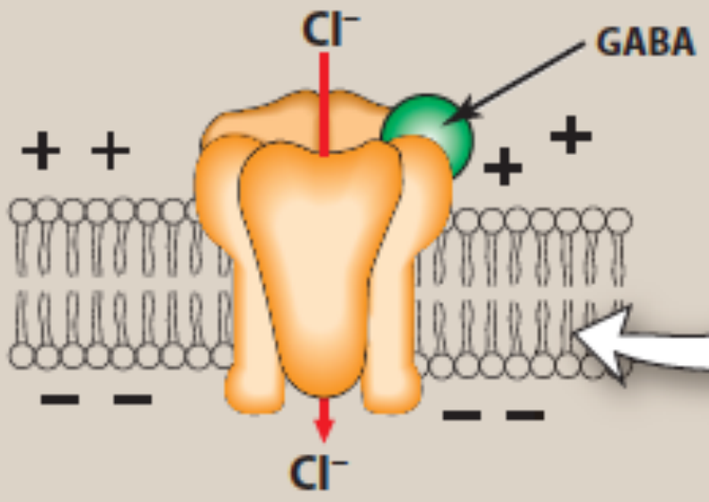


A **Receptor empty (no agonists)**



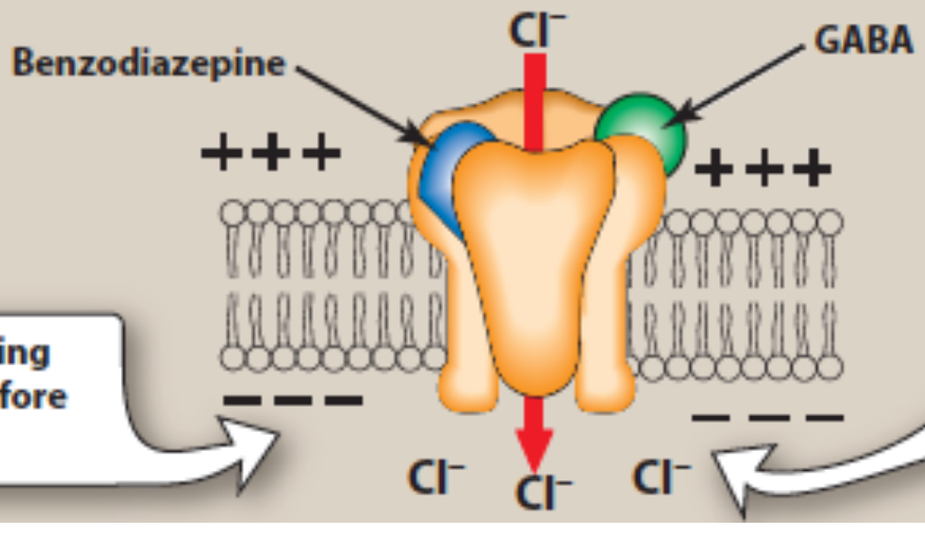
Empty receptor is inactive, and the coupled chloride channel is closed.

B **Receptor binding GABA**



Binding of GABA causes the chloride ion channel to open, leading to hyperpolarization of the cell.

C **Receptor binding GABA and benzodiazepine**



Entry of Cl^- hyperpolarizes the cell, making it more difficult to depolarize, and therefore reduces neural excitability.

Binding of GABA is enhanced by benzodiazepine, resulting in a greater entry of chloride ion.

Long-acting

Clorazepate
Chlordiazepoxide
Diazepam
Flurazepam
Quazepam

Intermediate-acting

10–20 Hours

Alprazolam
Estazolam
Lorazepam
Temazepam

Short-acting

3–8 Hours

Oxazepam
Triazolam

Actions of BZDs

1- Reduction of anxiety, at low doses /anxiolytic / inhibit circuits in limbic system
2- Sedative / hypnotic ($\alpha 1$-$GABA_A$)
3- Anterograde amnesia ($\alpha 1$-$GABA_A$)
4- Anticonvulsant ($\alpha 1$-$GABA_A$)
5- Muscle relaxant (presynaptic inhibition in spinal cord). (Baclofen / SkM relaxant)

Therapeutic Uses

1- Anxiety disorders

- Anxiety secondary to Panic disorder
- Generalised anxiety disorder (GAD)
- Social anxiety
- Post traumatic stress
- Obsessive compulsive disorder
- Extreme anxiety with phobia
- Anxiety related to depression & schizophrenia

- Long acting/ clonazepam, lorazepam, diazepam/ ???
- Antianxiety effect & tolerance (tolerance???)
- Cross tolerance with ethanol
- Alprazolam / short & long term treatment of panic disorder (withdrawal reactions???)

Therapeutic Uses, cont.

2- Sleep disorders

- Hypnotic effect :
  - decrease latency to sleep
  - increase (REM) sleep
- Insomnia treatment (hangover)
- Intermed. acting(temazepam, estazolam)
- Short acting (triazolam,)
- Long acting (flurazepam, quazepam)
- Temazepam / frequent wakening (1-3hrs)
- Triazolam :
  - Difficulty in going to sleep
  - Tolerance
  - Withdrawal symptoms

Therapeutic Uses, cont.

3- Amnesia

premedication for anxiety-provoking & unpleasant procedures / Midazolam

4- Seizures

Clonazepam / adjunctive therapy

Lorazepam & Diazepam / status epilepticus

Clorazepate, Chlordiazepoxide, Lorazepam, Diazepam, Oxazepam / cross tolerance with alcohol

5- Muscular disorders

Diazepam / muscle strain, spasticity

Pharmacokinetics

1- Absorption & distribution:

2- Duration of action:

3- Fate:

metabolised by hep. microsomal sys. to active metabolite
plasma $t_{1/2}$
excreted in urine as glucor. or oxidised metabolites
cross placenta
CI: in pregnancy

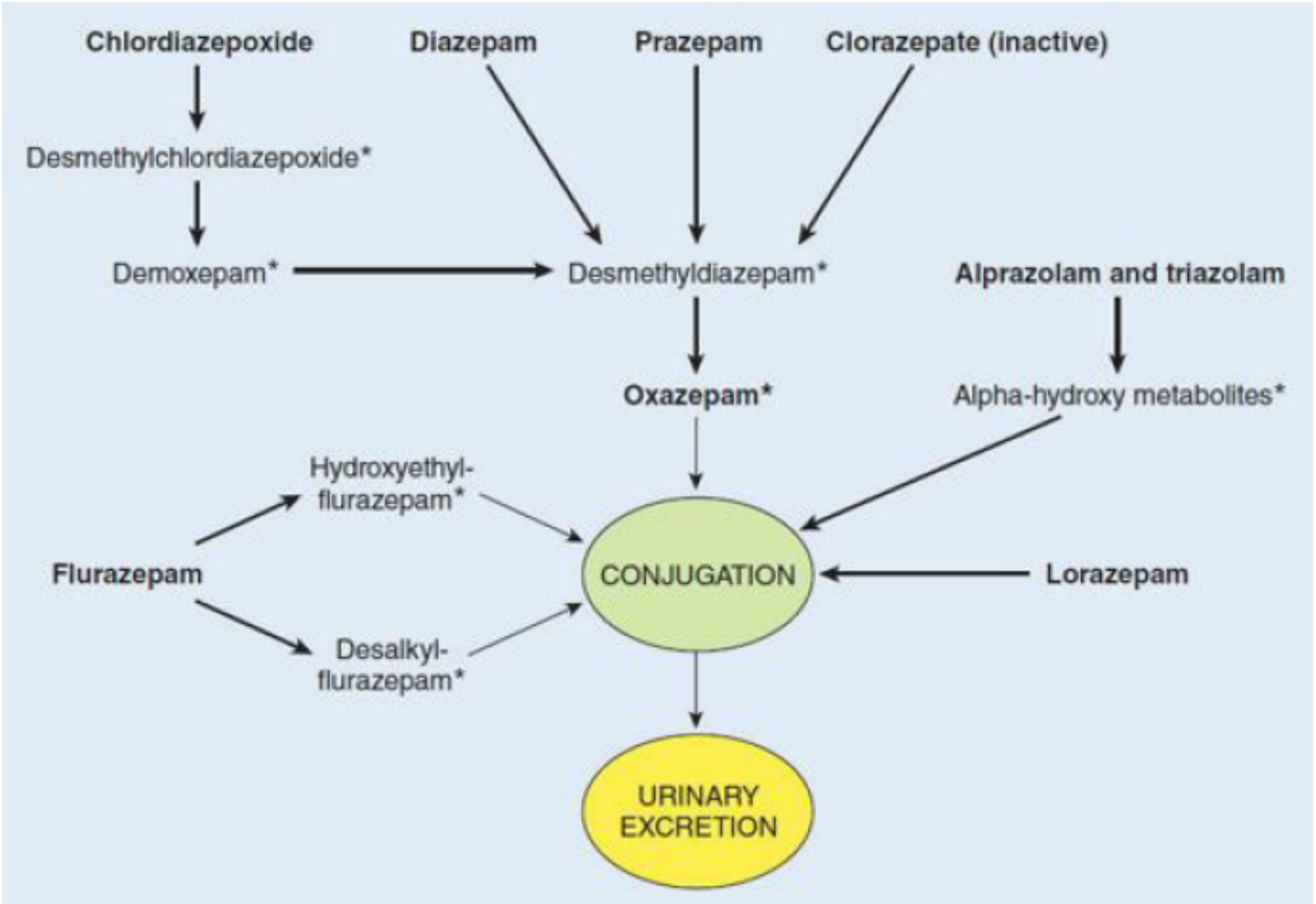
Pharmacokinetics

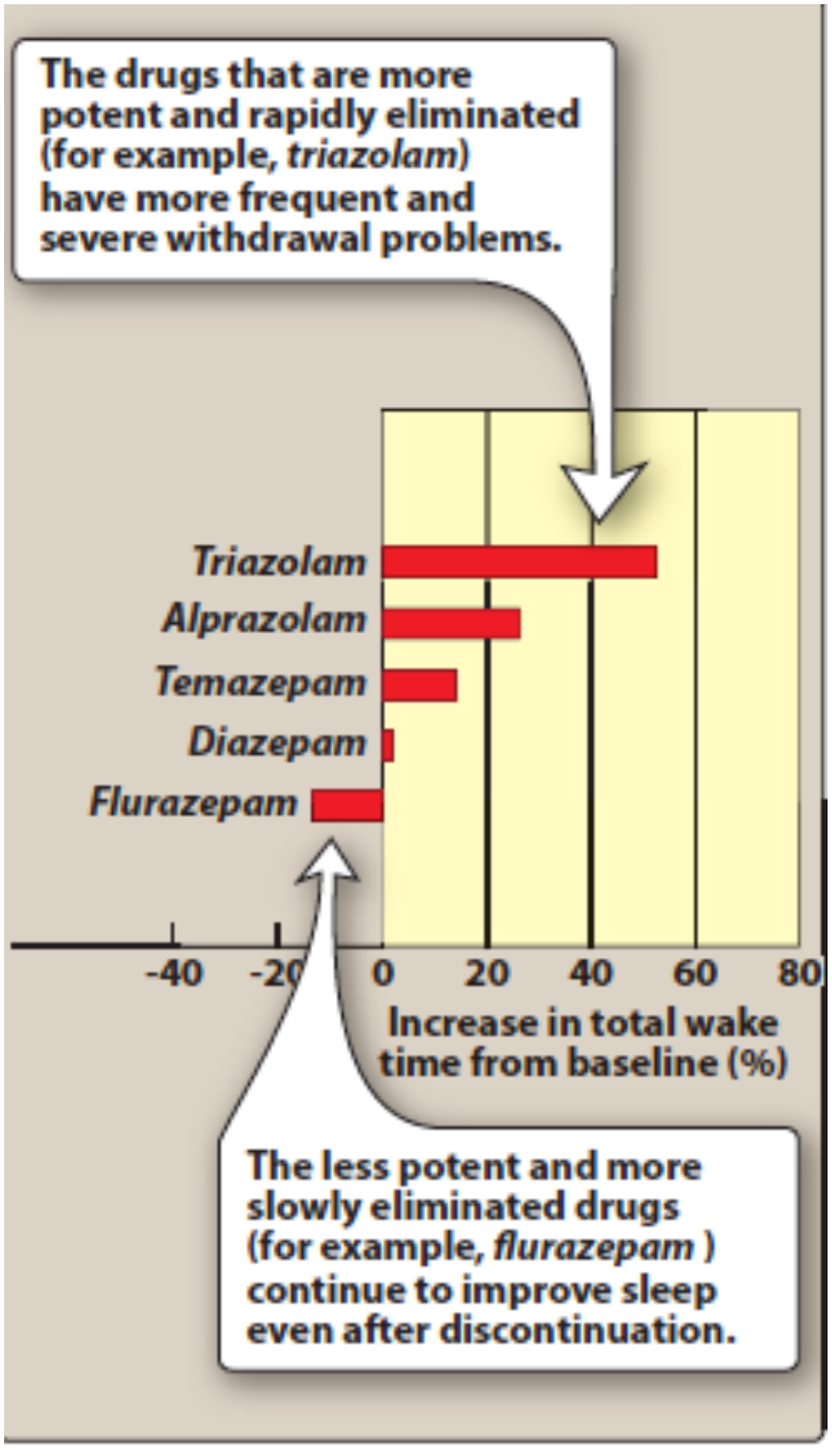
4- Dependence:

- Psychological & physical
- Withdrawal symptoms: confusion, anxiety, agitation, restlessness, insomnia, tension & rarely, seizures
- BZDs with short $t_{1/2}$ (triazolam), induce more abrupt symptoms

5- Adverse effects

- Drowsiness, confusion, ataxia, cognitive impairment
- Triazolam / tolerance, daytime anxiety, amnesia & confusion
- Caution with liver disease, acute angle-closure glaucoma
- Alcohol & other CNS depressant???
- Relatively safe, overdose ???


Chlordiazepoxide
Diazepam
Prazepam
Clorazepate (inactive)
Desmethylchlordiazepoxide*
Demoxepam*
Desmethyldiazepam*
Alprazolam and triazolam
Oxazepam*
Alpha-hydroxy metabolites*
Hydroxyethyl-
flurazepam*
Flurazepam
CONJUGATION
Lorazepam
Desalkyl-
flurazepam*
URINARY
EXCRETION


The drugs that are more potent and rapidly eliminated (for example, *triazolam*) have more frequent and severe withdrawal problems.
Triazolam
Alprazolam
Temazepam
Diazepam
Flurazepam
-40
-20
0
20
40
60
80
Increase in total wake time from baseline (%)
The less potent and more slowly eliminated drugs (for example, *flurazepam*) continue to improve sleep even after discontinuation.

Benzodiazepine Antagonists

- Flumazenil / GABA R antag.
- IV only, rapid onset, short duration, t1/2 1hr
- Frequent admin. is required
- May precipitate withdrawal in dependent patients
- Seizure may occur/ mixed ingestion with TCA
- SE: dizziness, NV & agitation

Other Anxiolytic Agents

- Antidepressants
  - *1st* line / avoiding dependence
  - SSRIs (escitalopram or paroxetine)
  - SNRIs (venlafaxine, duloxetine)
  - SSRIs & SNRIs have lower potential for dependence
- Buspirone
  - Chronic GAD
  - Slow onset
  - 5-HT1A, 5-HT2A, D2
  - No anticonvulsant, M relaxant
  - Few SE
  - Doesn’t potentiateCNS depressants

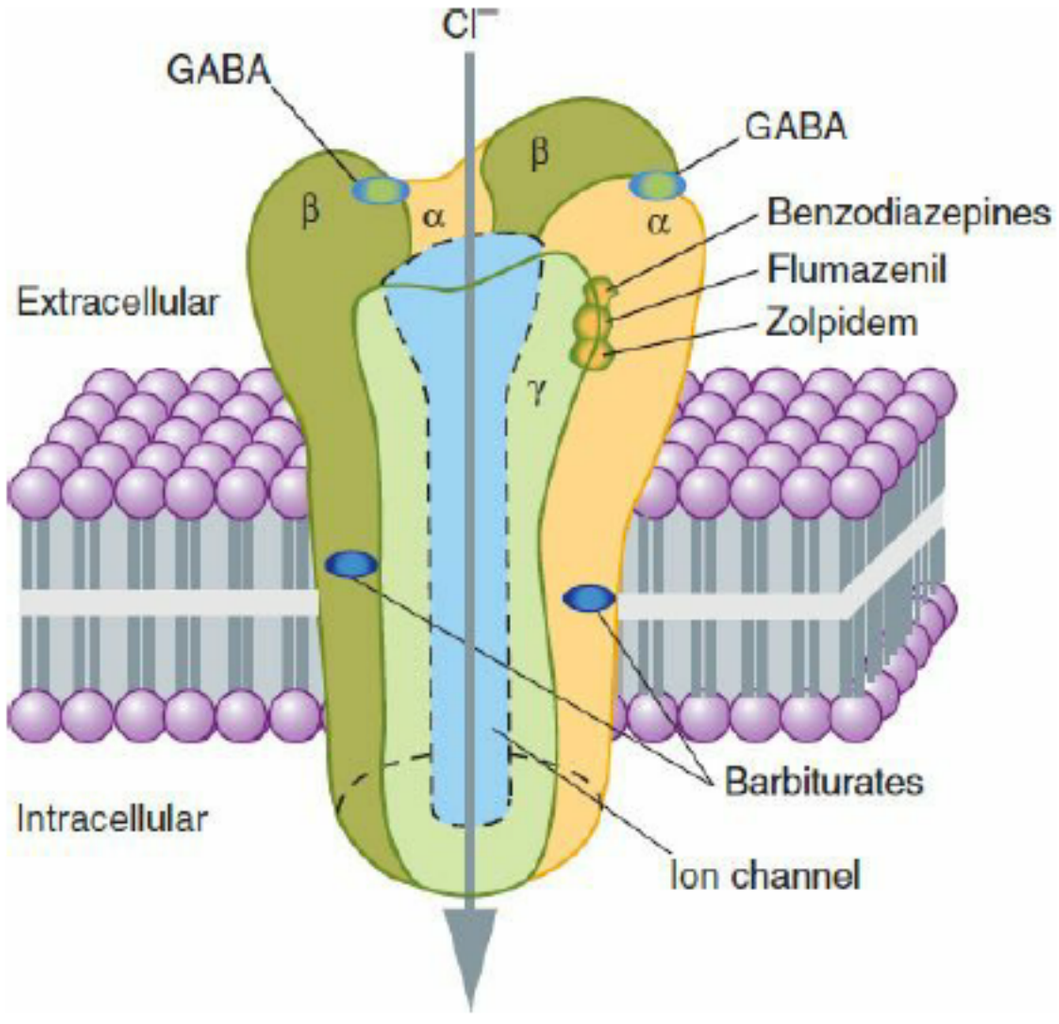
NEUROSCIENCE

Differentiating Tolerance, Dependence, and Addiction

Tolerance occurs when larger doses of drug are required to produce the same effect. Tolerance can occur for numerous reasons: innate tolerance is genetically determined, pharmacokinetic tolerance results from changes in drug metabolism, and pharmacodynamic tolerance is caused by adaptive changes in receptor density or second messenger characteristics. Cross-tolerance is sometimes used pharmacologically during detoxification to allow one drug to substitute for another.

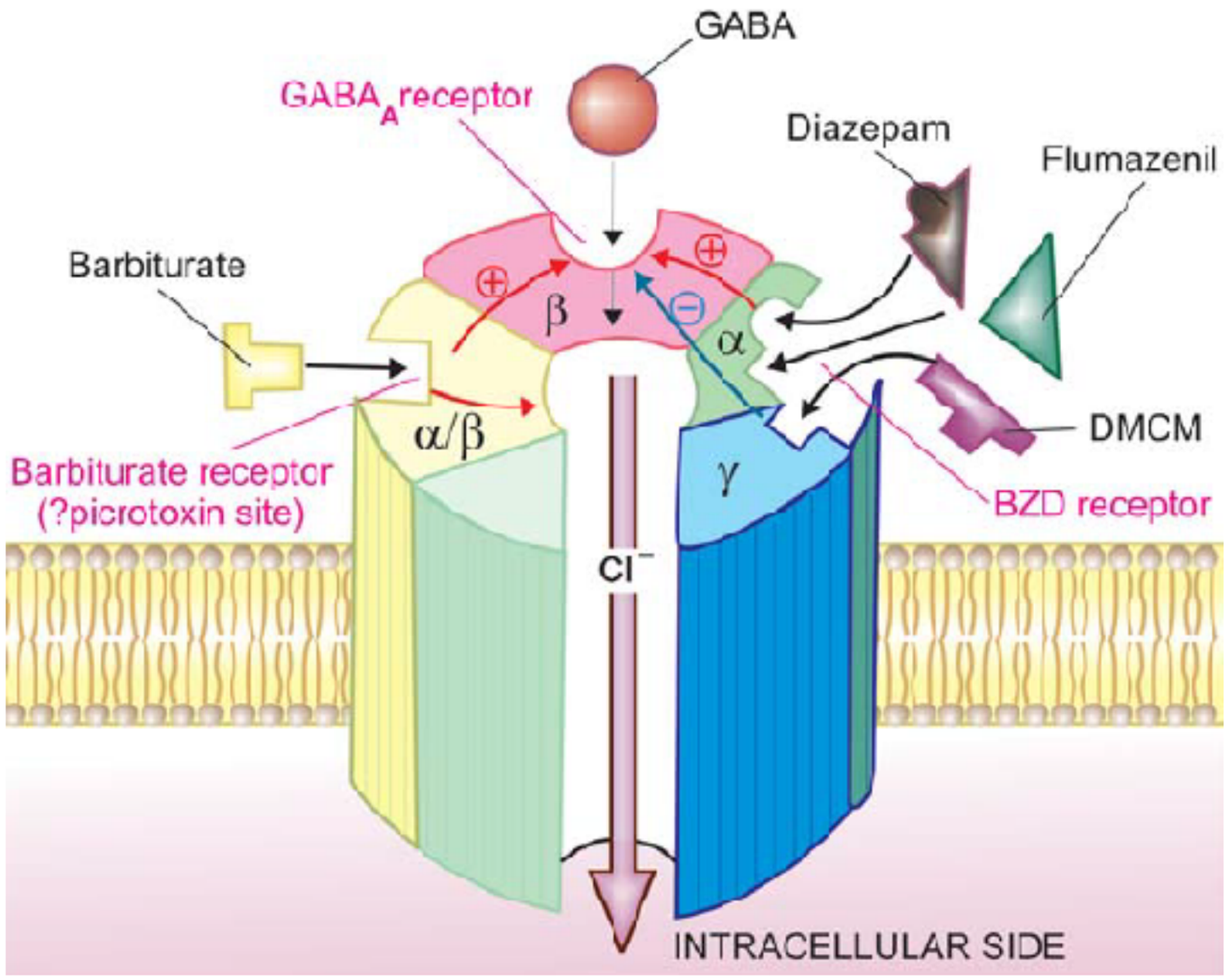
Dependence can be either *physical* or *psychologic*. Psychologic dependence is manifested by cravings for a drug—probably the major cause of relapse. Physical dependence is virtually synonymous with *withdrawal*. Cessation of use of drugs that cause physical dependence will result in withdrawal symptoms. Importantly, tolerance and dependence are biologic phenomena and *do not imply drug abuse*.

Abuse or *addiction* denotes an overwhelming compulsion and preoccupation with obtaining and using a drug. Not all drugs of abuse are associated with the same propensity to cause tolerance or dependence.


Cl⁻
GABA
GABA
β
β
α
α
Benzodiazepines
Flumazenil
Zolpidem
Extracellular
γ
Barbiturates
Intracellular
Ion channel

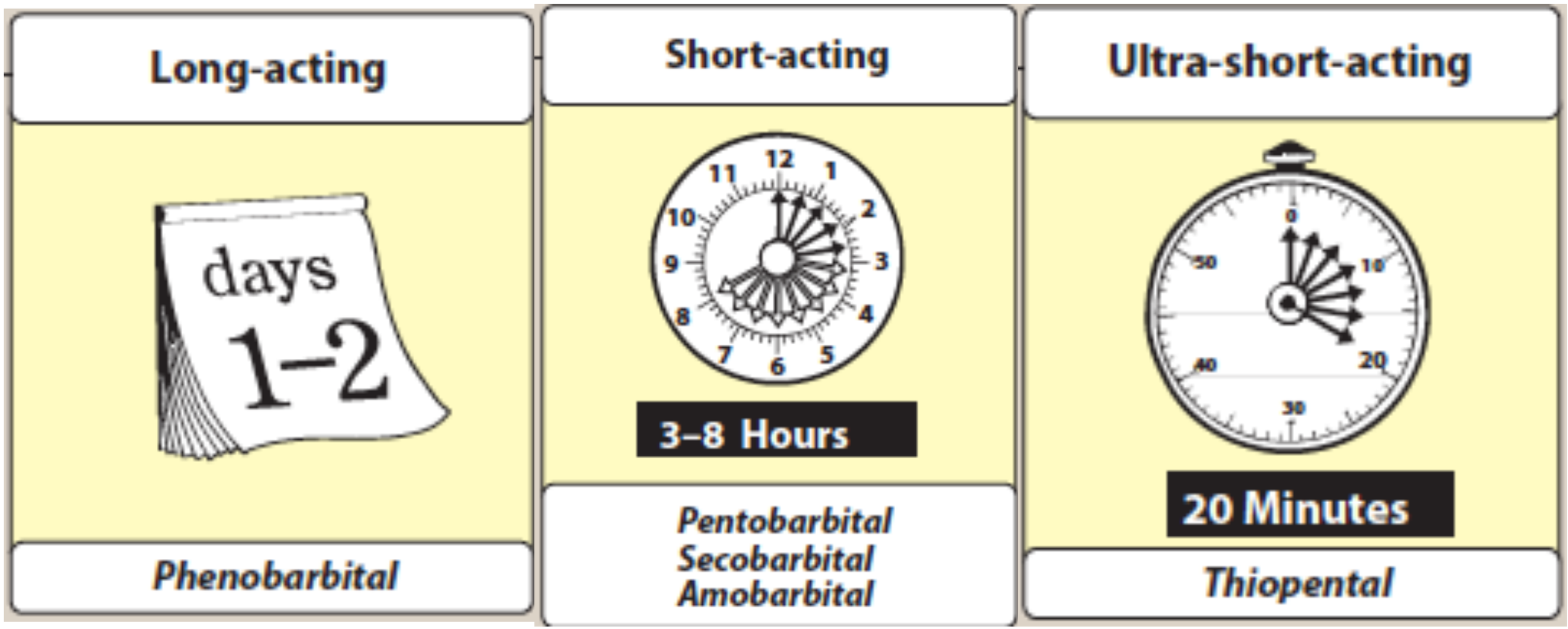
Barbiturates

- ★ Used to induce & maintain sleep
- ★ Replaced by BZDs because they induce tolerance & physical dependence & associated with very severe withdrawal symptoms
- ★ All are controlled sub.
- ★ Thiopental (very short-acting)used to induce anaesthesia



- Prolong duration of Cl^- channel opening
- Block excitatory glutamate receptors
- Anesthetic conc. of pent. block high-frequency Na^+ channel

Classification of Barbiturates



Actions of Barbiturates

- *CNS depression*
  - *low doses (sedation)*
  - *higher doses (hypnosis, anaesthesia???, coma & death)*
    - *Don't raise pain threshold*
    - *chronic use lead to tolerance*
- *Respiratory depression*
  - *Suppress hypoxic & chemoreceptor response to CO2*

Therapeutic uses of Barbiturates

- Anaesthesia, thiopental
- Anticonvulsant, phenobarbital (tonic-clonic seizure)
- Sedative / hypnotic (Butalbital, acetaminophen &caffeine or aspirin & caffeine)

Potential for addiction

Vertigo

Drowsiness

Tremors

Nausea

Enzyme induction

Zolpidem

- Non-BZD compound, bind BZD-R subtype selectively
- No anticonvulsant or muscle-relaxant effect
- Few withdrawal, minimal rebound insomnia, little tolerance
- Rapidly abs., rapid onset, short $t_{1/2}$

Zalpelon

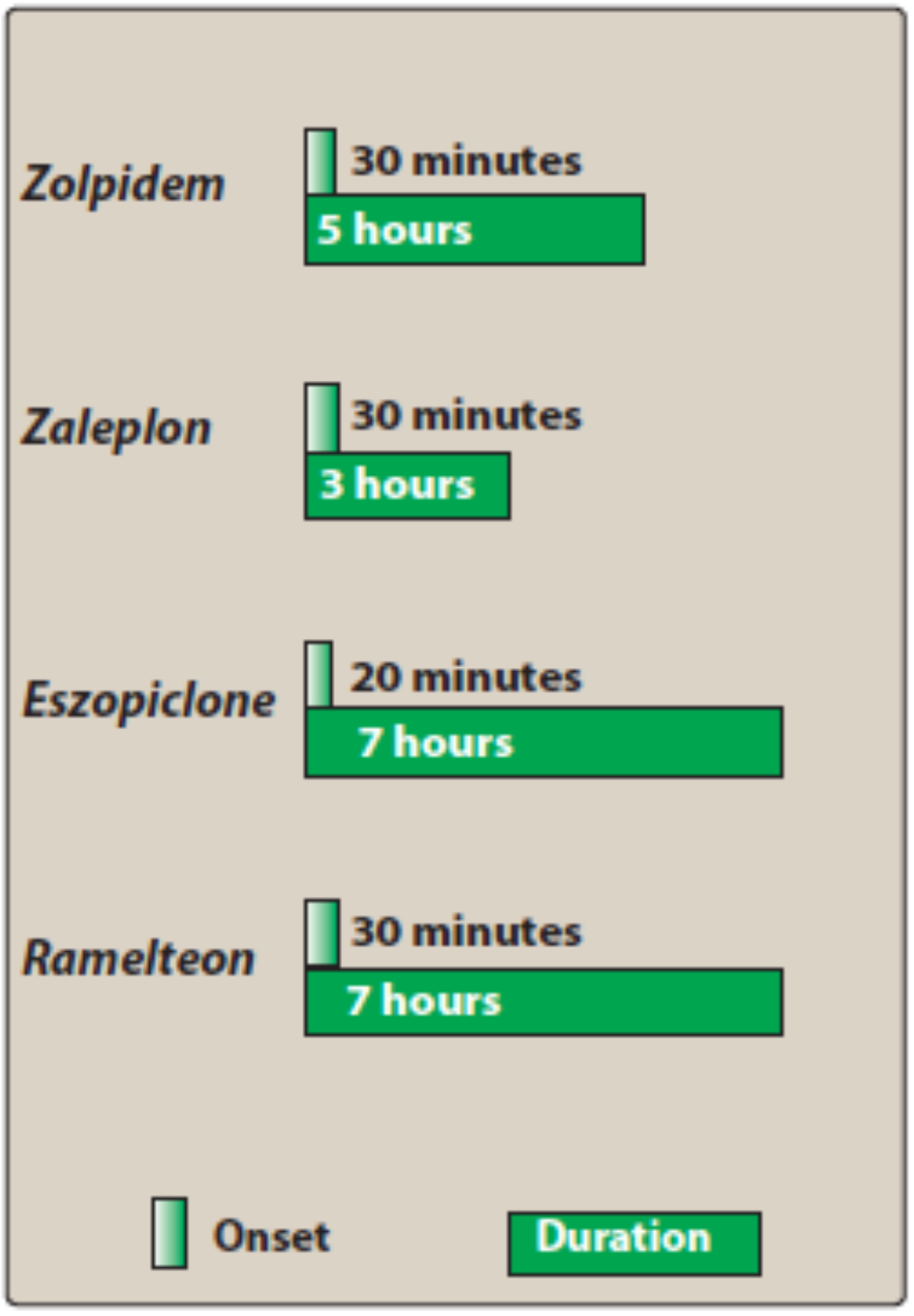
Non BZDs, few residual effects, rapid elimination

Eszopicone

Non BZD, effective in insomnia, rapid abs., & metabolism

Ramelton

Selective MT1 & MT2, used for insomnia, No dependence,
SE: ———, prolactin ???


Zolpidem
30 minutes
5 hours
Zaleplon
30 minutes
3 hours
Eszopiclone
20 minutes
7 hours
Ramelteon
30 minutes
7 hours
Onset
Duration

Therapeutic Disadvantages

Therapeutic Advantages

Benzodiazepines

- *Clonazepam*
- *Clorazepate*
- *Chlordiazepoxide*
- *Diazepam*
- *Flurazepam*
- *Quazepam*
- *Alprazolam*
- *Lorazepam*
- *Temazepam*
- *Triazolam*

- The benzodiazepines may disturb intellectual functioning and motor dexterity.
- The benzodiazepines have the potential for dependence, and withdrawal seizures may occur.

- Withdrawal of drug often results in re-bound insomnia.

- Potential use in chronic therapy for seizures.

- These less potent and more slowly eliminated drugs show no rebound insomnia on discontinuation of treatment.

- Agent of choice in treating panic disorders.

- Do not require Phase I metabolism and, therefore, show fewer drug interactions and are safer in patients with hepatic impairment.

- Useful in long-term therapy for chronic anxiety with symptoms of irritability and hostility.
- Does not potentiate the CNS depression of alcohol.
- Low potential for addiction.

Other agents

- *Buspirone*
- *Eszopiclone*
- *Hydroxyzine*
- *Zaleplon*
- *Zolpidem*
- *Ramelteon*

- Slower onset of action than benzo-diazepines.
- No muscle relaxation nor anticonvulsant activity.

- Have no anticonvulsant or muscle-relaxing properties.

- Has only marginal effects on objective measures of sleep efficacy.

- Effective for up to 6 months.

- Show minimal withdrawal effects.
- Exhibit minimal rebound insomnia.
- Little or no tolerance occurs with pronged use.

- The potential for abuse is minimal with minimal dependence or withdrawal effects.
- The drug can be administered long-term.

Barbiturates

- *Phenobarbital*
- *Pentobarbital*
- *Secobarbital*
- *Amobarbital*
- *Thiopental*

- The barbiturates induce tolerance, drug-metabolizing enzymes, and physical dependence, and they show severe withdrawal symptoms.

- Rapid onset of action.