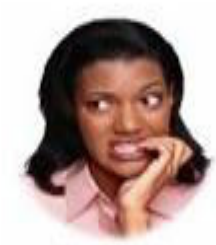
SEDATIVES, HYPNOTICS & ANXIOLYTICS

Anxiety-Most common CNS disorder



Restless

Worry

Frighten

servingnature

Anxiolytics

1. **Benzodiazepines**
2. **5-HT 1A Receptor agonists- Buspirone**
3. **Newer Drugs- zoleplon zolpidem remalteon eszopiclone**
4. **Barbiturates**
5. **Other hypnotic agents- Some antihistamines (promethazine, hydroxyzine, diphenhydramine)**

   Some neuroleptics (Chlorpromezine, Triflupromazine)

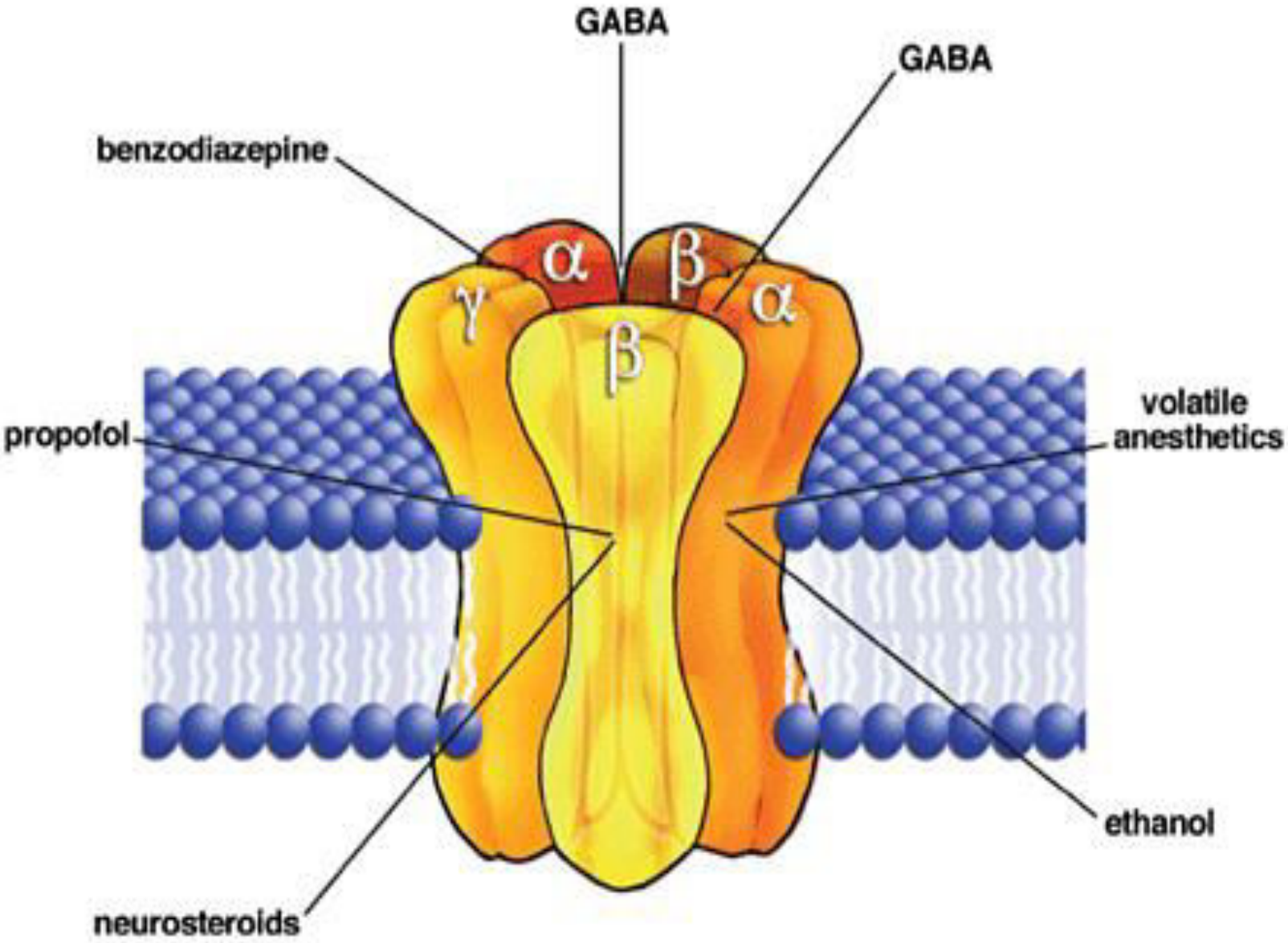
   Opiods; Morphine, Pethidine

   Some Anticholinergics; Hyoscine
6. **Beta receptor antagonists; Propranolol**

Background

- GABA: Main inhibitory neurotransmitter
- GABA receptor- composed of alpha, beta and gamma subunits

  Span the post synaptic membrane
- Depending on types, no. of subunits and brain region localization, activation of receptors results in different pharmacological effects



GABA A Receptor- most versatile receptor complex in body

- This receptor has many other drug receptors; these drugs bind at their specific sites and enhance effects of GABA neurotransmitter

- Benzodiazepine receptors are found ONLY in CNS and their location parallels that of GABA-ergic neurons

Benzodiazepines

- Effects in increasing doses

  Minimum → Maximum

  (tranquilizers) (partial anesthesia)
- BDZ bind to specific high affinity sites that are SEPARATE but adjacent to GABA binding sites
- Binding of BZ enhances the affinity of receptor for GABA binding and INCREASED frequency of Cl channel opening

BDZ Classification Acc To DOA

1. Short Acting (2-6 hrs)

   Trizaolam

2. Intermediate Acting (10-40 Hrs)

   Temazepam, Lorazepam, Oxazepam, Alprazolam

3. Long Acting (20-100 hrs)

   Diazepam, Clorazepate

THERAPEUTIC CLASSIFICATION

- Sedative/ Hypnotics

  Temazepam, Flurazepam, Nitrazepam
- Anxiolytics

  Diazepam, Oxazepam, Lorazepam
- Anticonvulsants

  Diazepam, Nitrazepam, Clonazepam
- Central muscle relaxants

  Diazepam, Flurazepam, Clonazepam

PHARMACOKINETICS

- Generally given ORALLY but at times PARENTERALLY
- ABSORPTION- from gut
- RAPIDITY of onset of action depends upon lipid solubility
- easily cross BBB and Placental barrier
- Once absorbed rate at which a BDZ crosses CSF depends upon protein binding, lipid solubility and ionization constant

METABOLISM

- via Phase I then Phase II reactions
- MOST BDZ are extensively met by ***HEPATIC MICROSOMAL SYSTEM***
- ***t ½ is important-*** because therapeutic use is dependent upon DOA that depends inturn on active metabolite
- ***EXCRETION:*** via urine as glucuronides or oxidized metabolites

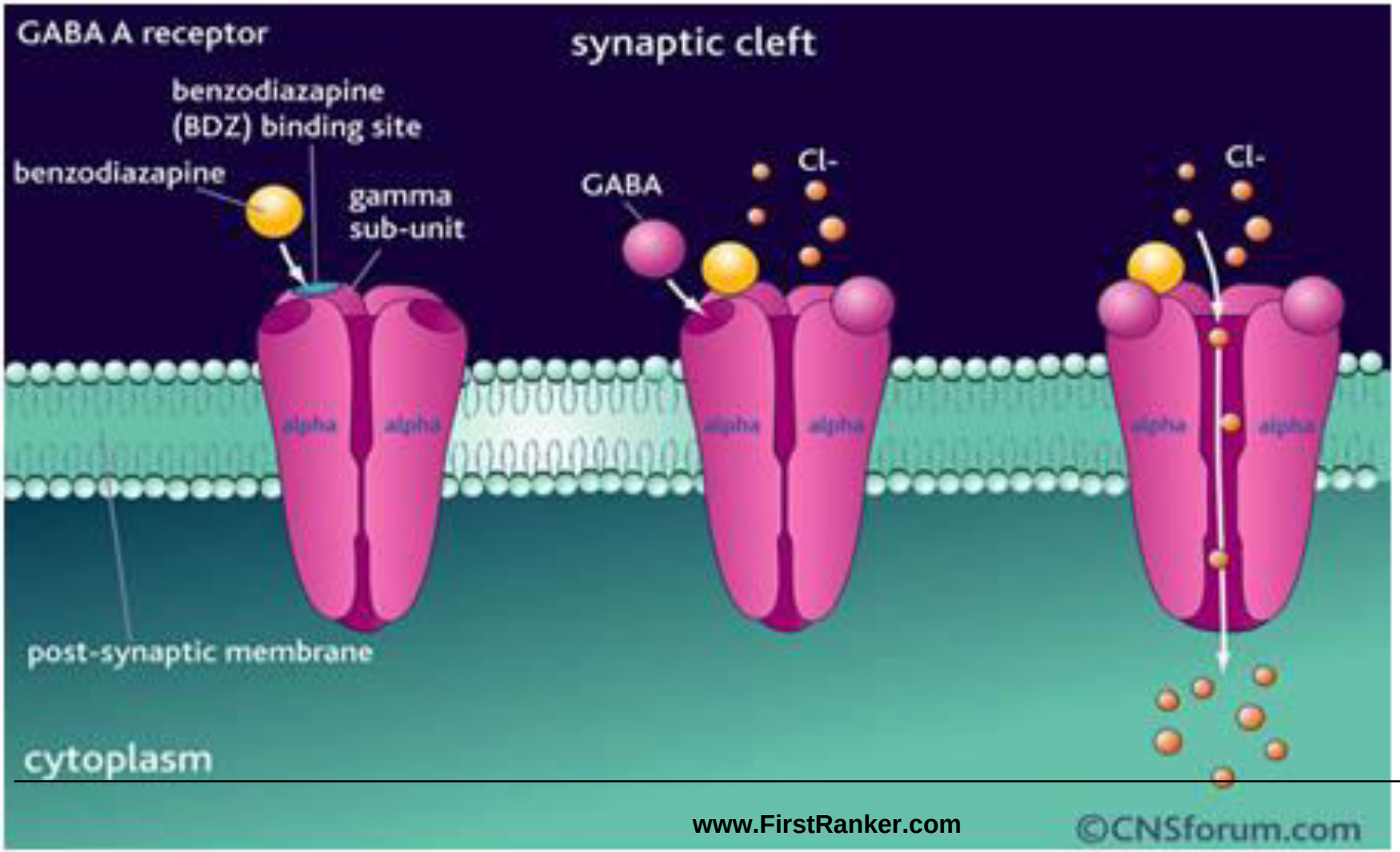
- N-Dealkylation → Hydroxylation
  ↓
  Glucuronide conjugation
- Longer acting agents form metabolites with longer t1/2

BDZ -Mechanism of Action

- GABA-ERGIC not GABA-mimmetic
- Potentiate inhibitory effect of GABA
- without ***GABA they cannot produce effect***
- supramolecular complex having pentameric structure enclosing ***a chloride channel***
- BDZ receptor- b/w alpha and gamma

  GABA receptor- b/w alpha and beta units

BDZs on GABA receptor



GROUP ACTIONS
no effect on ANS, no analgesia

- anti anxiety- at low doses
- sedation- calming effect
- hypnosis- sleep induction
- anterograde amnesia
- anti convulsant action
- central muscle relaxation- increased pre-synaptic inhibition in spinal cord
- IV use in anesthesia- pre anesthetic med

- relieve agarophobia and neophobia
- DIAZEPAM if given IV has analgesic axn
- ALPRAZOLAM- anti depressant axn
- CVS EFFECTS- depression of vasomotor centre in TOXIC DOSES cause myocardial and vascular tone depression
- RESPIRATORY EFFECTS- dose related depression of respiration

THERAPEUTIC USES

Pharmacokinetic properties are important consideration in choosing one BZ over other as their DOA varies widely among group.

- To relieve anxiety
- Treatment of insomnia
- Sedation and amnesia before & during short surgery that does not require much analgesia

  e.g; endoscopy, cardioversion, obs procedures

Consciuos sedation

- Symptomatic treatment of epilepsy /convulsions
- To control ethanol or sedative/ hypnotic withdrawl states; Chlorazepate, diazepam
- Component of balanced anesthesia; for induction and maintenance of GA- ***BDZ are adjunct and do not cause full anesthesia***
- Control of convulsions induced by local anesthetic overdose

- For muscle relaxation in specific NM disorders- multiple sclerosis, cerebral palsy
- diagnostic aid for treatment in psychiatry
- Alprazolam- antidepressant

ADVERSE EFFECTS

- sedation
- hang-over: confusional states in elderly, lethargy , lassitute

  ataxia in increased doses
- loss of memory
- GIT upset/ epigastric distress
- Paradoxical behavioral disturbance
- Floppy baby syndrome in neonates

- dependence
- tolerance- with short t1/2
- cross tolerance between BDZ and other CNS depressants

DRUG INTERACTIONS

- BZ act in additive manner with alcohol, barbiturates and anticonvulsants
- Smoking induces P450 2C enzyme which metabolizes BZ therefore smokers need large doses
- SSRIs increase diazepam levels by altering clearance

PRECAUTIONS

- liver disease
- alcohol and other CNS depressants

BDZ ANTAGONISTS

- FLUMAZINEL

endogenous BDZ like mediator

DBI- diazepam binding inhibitor

ONLY inhibits BDZ action

cause convulsions, insomnia, restlessness & inhibit all effects of BDZ

met by liver- rapidly

- short half life compared to BDZ so repeated doses required
- given to a patient who becomes dependent on BDZ
- ABSTINENCE SYNDROME: if BDZ+ TCA are taken together and flumazinel is given- chances of arrhythmias and convulsions increase

BDZ ANTAGONISTS

- BDZ inverse agonists- β carbolines
- GABA A receptor antagonists BICUCULLINE
- GABA synthesis inhibitor- THIOSEMICARBAZIDE

THANK YOU