Drugs Affecting the CNS

I - Axiolytics = Anxiety

Hypnotics = insomnia

II. Analgesics = pain → opiods

NSAI

III. Antiepileptics = Epilepsy

IV. CNS stimulants = depression

V. Antidepressants =

VI. Neuroleptics =

VII. Anaesthetics

VIII. Neurodedenerative diseases

- Anti-parkinson Drugs
- Anti-ALZheimer Drugs

- Sedatives = مهدئات ?
- Hypnotics = منومات Insomnia = ارق
  sleep inducing drugs
- Anxiolytics = القلق مضادات
  = minortranquilizers:

Anxiety = Acute
Chronic

① = Signs & symptoms of some metabolic diseases
e.g.: thyrotoxicosis
= proper diagnosis.
= cause.
② unknown source
③ known cause.
④ Associated with other mental disease = depression

* mental disorder

Signs & symptoms:

- fear
- tachycardia
- sweating
- trembling
- palpitation

} sympathetic activation (Adrenaline, noradrenaline) etc.

= minor = acute = No treatment
minor "

Sever = - good diagnosis.
- psychotherapy =
  - psychiatrist
  - Social assistance.

Drugs:

1-

Benzodiazepines

- Diazepam = Valium
- Alprazolam
- Clonazepam
- Estrazolam
- flurazepam
- Lorazepam
- oxazepam
- Triazolam
- etc.

1970's

Benzodiazepine Antagonists

- flumazenil

According to:

Drug addiction
Drug safety
Drug interaction

1960's

- Benzodiazepines are most widely used as hypontics & anxiolytics

2- Barbiturates

- Amobarbital
- phenobarbital
- pentobarbital
- secobarbital
- thiopental

(barbiturates are rarely used)

1950's

3- Meprobamates

4- other anxiolytic drugs:
- Buspirone
- Hydroxyzine
- antidepressants - particularly associated with depression

5- other hypnotic agents = side effects"
- Antihistaminics
- chloral hydrate
- ethanol
- etc.

Benzodiazepines

Safe drugs: wide therapeutic range

the lethal dose is over 1000-fold greater than the therapeutic dose.

? therapeutic index = $\frac{\text{lethal dose}}{\text{Effective dose}}$?(in animals)

Very safe drug **except** when combined with other CNS depressants e.g: alcohol

Don't mix CNS depressants مع بعض

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Mechanism of action آلية العمل

- GABA Receptors = γ-aminobutyric acid receptors.
  = inhibitory neurotransmetter in the CNS

- Composed of three subunits - α, β, γ subunits
  " postsynaptic membrane"

- pharmacological effects depends on:-
  - binding of benzodiazepine to specific GABA subunits = binding sites to benzodiazepine
  - location = CNS ↑ these receptors.

mechanism of benzodiaz-pine action

1- Empty GABA Receptors = associated with chloride ions channels.

- empty receptors are inactive receptors
- chloride ions channels are closed
- chloride ions are outside membranes

2- Binding of GABA "neurotransmitter" to its receptors

- opening of chloride ion channel
- increase in chloride conduction
- hyperpolarization of the cell membrane (small, minor effect)
- hyperpolarization of membrane of cells → more difficult to depolarize
- more difficult of to excite (↓ neuronal excitabil

3- Binding of benzodiazapine receptor adjacent to GABA receptors enhanced the activity of GABA → increases their effect → greater entery of chloride ions → more hyperpolarization → more reduction of neuronal excitability (benzodiazepine modulate the effect of GABA)

Benzodiazepines actions

1- No analgesic actions: ... : ملاحظات

e.g. Renal colics → الحالة

لا يسبب

2- No antipsychotic action.

3- No effect on ANS.

1- Anxiolytic = limbic system الجهاز الحوفي

α_2- Receptors subunit

2- Sedative → hypnotic

1/3 dose → high dose

α_1 GABA receptors subunit.

3- Anterograde amnesia: α_1-GABA subunit.

- temporary
- impairs ability to learn.
- " " to form New memories.
-

4- Antiepileptic = anticonvulsant = α_1 subunit.

e.g. . status epilepticus

. seizure disorders

5- Muscle Relaxant: skeletal Ms. = α_2 -subunit

= spinal cord = sciatica = عرق النسا .disc -

therapeutic uses : indications

1- Anxiety disorders → All types.
Not every day life stress.

2- Muscular disorders: skeletal Ms.
- Ms. strain
- degenerative disorders (Ms)
- cerebral palsy.

3- Amnesia: unpleasant procedures
receptive to instruction
- endoscope
- bronchoscop.
- dental procedures
- angroplasty
- induction of anaesthesia → IV.

4- Seizures: Clonazepam. diazepam, lorazepam.
- grandmal epilepsy
- Status epilepticus.

5- sleep disorders = Insomnia.
= sleep induction - flurazepam
→ All through
= frequent waking - Temazepam
= triazolam = sleep induction -

side effects

1- dependence = . psychological
. physical
} ? . prolonged use
. withdrwal action

2- Drowsiness and confusion:

- most common
- ataxia = Motor coordination
? driving motomobiles
↓
reaction time.

3- liver disease = dangerous.

4- Don't mix with CNS depressants
e.g. Alcohol

lipophylic = . well absorbed from GIT.
. widely distributed in body
- fat -
- brain
- etc.
• pass placenta → Newborn.
• milk of lactating ladies

Duration of actions : short, intermediate, long-acting.

. determine therapeutic uses.

fate - (1) hepatic Microsomal system. Cyt p450'

(2) × active × non-active metabolites.

(3) Drug interaction

(4) Distribution & redistribution

(5) Newborn - Milk.

Benzodiazepine antagonists = Flumazenil

- GABA - Receptor antagonist
- IV administration only.
- Reverse the effect of benzodiazepines.
- Rapid onset
- short duration = $T_{1/2}$ = 1 hour.
- ppt withdrawal reation in case of dependence → seizures.

side effects:
- Dizziness
- Nausea
- Vomiting
- agitation

Barbiturates

1- Long-acting = 1-2 days
- phenobarbital – anti-convulsants

2- Short-acting = 3-8 hours
- pentobarbital
- secobarbital
- Amobarbital
} – sedative, hypnotics
Not anxiolytics

3- Ultra-short-acting = 20 minutes
- thiopental } intravenous anaesthesia.

Mechanism of action:

All of its action is inhibitory effect.

↓ neuronal activity.

– Sedatives
– hypnotics
} I- GABA Neurotransmitters.
- interaction with GABA-receptors → ↑ GABA inhibitory effect.
- their receptors are different from benzodiazepine receptors
- ↑ GABA effect on chloride ion transport through chloride channels.

II - block excitatory glutamate receptors

III - Anaesthetic effect:-
- block - high frequency sodium channels

pharmacological actions

I Depression of CNS

CNS depression ↓ dose ↑ dependent

- I - low doses → sedation = calming + ↓ excitement
- II - high doses → hypnosis
- III → anaesthesia → loss of feeling → loss of consciousness
- IV → Coma → death.

Note =@ barbiturates are not analgesic drugs
→ may exacerbate pain → ألم

② long use → tolerance.

II - Depression of R.C.

① ↓ Chemoreceptor response to CO_2.

② chynostock breathing (Respiratory depression)

③ death.

III Drug - Drug interaction: → Metabolic tolerance

① induction of Cyt P450 system enzymes in hepatocytes, chromosomal enzymes.

② chronic administration

③ enhance metabolism of its own & to other drugs, auto-induction, hetero-induction
e.g phenytoin, theophylline, warfarin etc.

Thiopental uses:

1- Anaesthesia: - Ultra-short acting = thiopental
- intravenous administration
- distribution & redistribution.
- e.g. induction of anaesthesia.
short-duration procedures.

2- Anti-convulsants: long-acting - phenobarbital =
- tonic-clonic seizures
- status epilepticus
- eclampsia.
- drug of choice = febrile seizures
young children

3- anxiety = mild-sedation = hypnotics } replaced by benzodiazepines.

pharmacokinetics:
- rapidly absorbed
- widely distributed all through the body
- cross placenta
- metabolism: Cyt p450 enzymes
- liver
- enzyme induction
- autoinduction
- heteroinduction.

Side effects

1- CNS = drowsiness, ↓ concentration etc.

Not = synergistic with other CNS depressant,

fatal with alcohol

2- hangover: - وجود بقايا الدواء في الجسم

- ↓ normal life
- after waking in the morning.
- nausea & vomiting
- house-wife syndrome.

3- Drug-Drug interaction: enzyme inducer.

hepatic enzyme.

4- dependence: - tolerance
- physical dependence
- withdrawal reaction → death.
- stress-syndrome: . tremors
  - anxiety
  - weakness
  - restlessness
  - Nausea, vomiting
  - seizures
  - delirium
  - cardiac arrest

5- Poisoning: → death. - drug overdose

- ↓ RC.
- ↓ CVS
- No specific antagonist

Ht = haemodialysis - alkalinization of urine.

other agents

- **Buspirone:**
  - used in long-term ttt of Chronic anxiety + irritability & hostility
  - Doesnot potentiate the CNS depression of ethanol
  - lower potential of addiction.

Notes
- slower onset of action than benzodiazepine
- No skeletal Ms relaxation
- No antiepilentic effect.

- **Eszopiclone**: effective up to six months.
- **Zaleplon** → **Zolpidem**
  - No anticonvulsant effect.
  - No effect of skeletal Ms.
  - minimal withdrwal actin.
  - minimal rebound insomnia.
  - No tolerance with chronic use.
- **Ramelteon** / Rameiteon = No abuse
  - No dependence
  - No withdrwal reaction
  - long use