OPIOID ANALGESICS: withdrawal reaction→ actions get reversed.

•mimic endogenous opioid peptides or endorphins→ hyperpolarization of nerve cells/ presynaptic inhibition→ inhibits the release of neurotransmitters such as substance P and glutamate.

Effects: **1- Dampening effects:**

A- Pain sensation / B- Mood alertness(inhibit norepinephrine) except Methadone/ C- cough center (antitussive effect), such as codeine

2- Stimulant effects:

A- Antinociceptive system / B- antidiarrheal effect(Loperamide)/ C- urinary retention/D- Vagal Centers (respiratory center)

S.E: Euphoria (↑ dopamine dur to ↓ GAB release) heroin/ CNS depression (inhibit NE release)/ N&V/ Diaphoresis and flushing/ Itching (release of histamine/ Pupil constriction (pinpoint pupil)/ Constipation/Respiratory depression/ Bradycardia.

1-Tolerance: decline in the potency of an opioid with continued use/ Increase the dose (gradually)

2-Dependence (physical dependence): withdrawal symptoms upon abrupt discontinuation/ reduction of narcotic therapy/tapering

3-Addiction (Psychological Dependance): Psychological & behavioral syndrome manifested by drug-seeking behavior.

•**Pregnancy:** chronic opioid →fetal dependence, premature delivery, and growth retardation.

•Opioids:

•strong opioid agonists:

a- morphine: severe pain/ leads to hypotension→ used in pulmonary edema/ oral, injection, pump.

• don't use→ bradycardia →vagal stimulation

• don't use→ in labor (use Meperidine)

Morphine-6-glucuronide → contributes to the effects of the parent compound.

Morphine-3-glucuronide → contributes in adverse effects.

renal insufficiency→ buildup of morphine →toxicity in the brain.

b- Hydromorphone: ✓ in renal insufficiency patients

c- Fentanyl: 100 times more potent than morphine/ very high first pass metabolism→ injectable & transdermal patch

In anesthesia: when HR of the patient increased and becomes stressed →pain → fentanyl(IV)

(not reach kidney→ used with patients have kidney problems)

d- Heroin: Similar potency to fentanyl.

e- Mepiridine (pethidine): ✓ in labor & shivering

In kidney disease is not recommended

Repetitive dosing →accumulation of the toxic metabolite normeperidine→ severe Seizures

↑ excretion of serotonin→ contraindicated on patients taking antidepressants 'SSRI.'

f- Methadone: treat all above opioid abuse+ addiction.

Long half-life → ↓ euphoria (methadone rehabilitation or rehabilitation)

- causes long QT interval (torsade de points)

Opioid is contradicted in patients with:

1- prostate hyperplasia

2- asthma

3- cardiac problems

g- oxycodone

•weak opioids:

a- Codeine: dental pain, antitussive/ contradicted in children (in Jordan CYP2D6 convert codeine→ morphine)

b- Tramadol: partial agonist/Inhibition of norepinephrine reuptake/ Moderate pain treatment / contradicted with SSRI.

Antidot→ **naloxone** (only with naïve patient)

ANXIOLYTIC AND HYPNOTIC DRUGS: gender-based

drugs will affect the level of GABA or Serotonin.

Low dose → anti-anxiety

high dose → hypnotic

1- BARBITURATES: **Thiopental** and **pentobarbital**

•severe withdrawal symptoms/ ability to cause coma in toxic doses

•Their toxicity → ↑ doses expelling GABA from its receptor, enhancing Cl- inhibition, fatal outcomes.

MOA: enhance **GABA** receptor affinity→promoting **chloride channel** opening→ **hyperpolarization**→inhibition of action potentials in the CNS

actions

- **A. depress the CNS:** Thiopental (anesthesia for short time)
- **B. Anticonvulsant: in children (Grand MAL syndrome)/ status epileptics: Phen**obarbital (a long-acting)
- **C. Anxiety** **D. muscle relaxant** **E. anterograde amnesia** **F. hypnotic drugs**

2- BENZODIAZEPINES:

Long-acting: diazepam, flurazepam

Intermediate-acting: bromazepam, lorazepam, alprazolam

Short-acting: triazolam **Ultra-short-acting: remimazolam**

BARBITURATES E_{max}→ death, focusing on **duration** of opening.

BENZODIAZEPINES E_{max}→ sedation, affect **frequency** of GABA receptor opening.

- **distribute** (main effect) to the brain/ **redistribute** to lipophilic areas→ Blood concentration **doesn't** reflect drug distribution

A. Reduction of anxiety (anxiolytic): low doses, short periods (long-acting are preferred) → **benzodiazepine dependance syndrome** (desensitization of GABA receptors→ rebound anxiety)

Bridging therapy: benzodiazepines and buspirone for 2 weeks→ buspirone for the next 4 weeks→ SSRI

B. Muscular relaxant: Diazepam, Dantrolene (more common)

C. Sedative and hypnotic: Flurazepam (Hangover effect)/ **bromazepam, lorazepam** (keeps waking up)/ **triazolam** (no induction of sleep)

•reverse the hypnotic effect, we use: **histamine** or **oroxine**.

D. Anticonvulsant: Clonazepam → *chronic epilepsy* treatment, **diazepam** → *grand-mal seizures* (status epilepticus) / in emergency cases for infants with *febrile seizures*

a2: anti-stress/ α1: for sleep.

A.E: Drowsiness, Ataxia, Cognitive Impairment, Tolerance Development

-Caution: **Liver Diseases**, avoid: **Acute Narrow Angle Glaucoma**, Enhanced with **Alcohol**

Flumazenil is the antidote.

3- BUSPIRONE: agonizing activity → inhibitory receptors "5HT1A & 5HT5"/ more than a week to become established

•S.E: headaches, dizziness, nervousness.

•When the patient experiences sexual dysfunction due to SSRIs use/ in **bridging therapy**

ANTIDEPRESSANTS

✴Balancing (*Norepinephrine (NE), Dopamine (DA), and Serotonin)* →treating depression, as they interact with each other and with other chemicals like *glutamate and glycine*.

Antidepressants show similar effects to placebos initially, but real medication tends to result in fewer relapses over time.

- therapeutic effects take 6-8 weeks, causing initial side effects like overexcitement.

1.SSRIs (Selective Serotonin Reuptake Inhibitors):

S.E: GI upset, **s**exual dysfunction (dose dependent), anxiety, insomnia.

Paroxetine: sedating properties/ CYP2D6 inhibition/at night.

Sertraline (Zoloft): more GI adverse drug reactions.

Fluoxetine (Prozac): less discontinuation syndrome/ P450 interactions

- **Serotonin receptors:** Inhibitory: 5-HT1a, 5-HT5. /Excitatory: 5-HT2, 5-HT3, 5-HT4, 5-HT6, 5-HT7.

- **antidepressant** 5-HT1a/ Excitement **side effects** 5-HT1b, 5-HT1c.

2.SNRIs (Serotonin and Norepinephrine Reuptake Inhibitors): Venlafaxine, Duloxetine

S.E: ↑ in diastolic (dose dependent), nausea

Slightly fewer adverse effects than SSRIs

•*Withdrawal symptoms are more severe in SNRI than SSRI.*

SSRI/SNRI Discontinuation Syndrome: symptoms (FINISH) include flu-like symptoms, insomnia, nausea, imbalance, sensory disturbances, and hyperarousal.

3.NDRIs (Norepinephrine-Dopamine Reuptake Inhibitors)

4.TCAs (Tricyclic Antidepressants) (Amitriptyline): inhibit serotonin, norepinephrine, and dopamine transporters, slowing reuptake.

Non-selective

●block certain receptors like muscarinic acetylcholine, alpha-adrenoceptors, and histamine (H1) receptors.

●can cause sedation, orthostatic hypotension, cardiac effects, and anticholinergic effects

5. 5-HT$_2$ antagonists: Nefazodone (SERT, NET), **Trazodone** (SERT/for insomnia), and **Mirtazapine** (for sleep difficulties)

Re-uptake inhibition of serotonin and inhibit 5-HT2A receptors.

●*antianxiety, antipsychotic, and antidepressant effect*

A.E: Sedation (dosed at bedtime)/ dose-related GI side effects/ weight gain (**Mirtazapine**)

★ **The monoamine hypothesis**: low levels of mentioned neurotransmitters, inhibiting the enzyme monoamine oxidase (MAOIs) → increase these chemicals.

★**The Neurotrophic Hypothesis:** decrease in (BDNF) → structural changes in brain → depression. (Antidepressants → BDNF levels, enhancing brain connectivity and plasticity.)

6.MOA-inhibitors: are only used when: resistant to SSRIs and SNRIs/wear off drug effect/ Atypical depression.

- **Phenelzine** →nonselective
- **Moclobemide** →MAO-A (target serotonin)
- **Selegiline** →MAO-B (increase dopamine / in Parkinson's patients).

should avoid tyramine-rich foods like aged cheese.

Serotonin syndrome: combining medications like MAO inhibitors, tricyclic antidepressants, and SSRIs →symptoms like hyperthermia, seizures, and even death.

but **5-HT2** inhibitors are safer and can be used with SSRIs to treat **insomnia.**

7. Buproprion:

never used alone.

- augmenting agent of serotonin (SSRI)
- MOA: reuptake inhibition of dopamine and norepinephrine

unsuitable for bipolar

- No weight gain, sexual s.e, sedation, and cardiac interactions but may induce mania, anxiety, agitation, and insomnia.

HYPNOTICS

- **New Benzodiazepine Receptor Agonists(Z-drugs):** bind to the a1-subunit /only hypnotic activity.

A.E: nightmares, agitation, headache, daytime drowsiness, and sleepwalking (reduction in dosage)

ZALEPLON+ zopiclone: induction of sleep **ZOLPIDEM:** sleep-maintenance

- **MELATONIN CONGENERS:** does NOT always produce effects

RAMELTEON: Binds strongly to MT1 and MT2 receptors.

Melatonin: either MT1 Receptor (sleep onset) or MT2 Receptor (circadian rhythm timing)

- **Orexin antagonist: Suvorexant** modest activity.

Inhibits the effect of orexin(A/B) by blocking orexin receptors (OX1 and/or OX2) to induce sleep by countering wakefulness.

S.E: somnolence, daytime sleepiness, headache, abnormal dreams, fatigue, and dry mouth (dose dependent)

SCHIZOPHRENIA: genetic and environmental factors

- Continuous **(+) symptoms** (hallucination) and **(−) symptoms** (depression)

- treated with medications indefinitely.
- Withdrawal-like syndrome: (sedation)

S.E of antipsychotics:

a. **Acute dystonia**: 1- 5 d /**Antiparkinsonian agents are diagnostic and curative. (**anticholinergic agents)
b. **Akathisia:** Reduce dose or change drug: **antiparkinsonian agents, benzodiazepines, or propranolol**
c. **Parkinsonism: Antiparkinsonian agents**
d. **Tardive dyskinesia:** months or years (worse on withdrawal)/ **initially increasing the dose then gradual reduction**

- Main categories are:

1- Typical antipsychotics: dopaminergic receptor mainly D2 → treat (+) symptoms only

Haloperidol, chlorpromazine and **Fluphenazine**

2- Atypical antipsychotics: 5-HT2/D2 (both +/− symptoms)

a- Risperidone: D2: treat positive symptoms/ alpha: cause orthostatic hypotension/ 5HT2: inhibiting negative symptoms/ histamine: produce sedation. (Low dose → Parkinson-like symptoms, high dose → acute dystonia and akathisia)

•Endocrine effects are different between men and women (d-receptor inhibition)

b- Clozapine: Best drug but Agranulocytosis is a fatal S.E

c- Olanzapine: Low affinity fewer side effects

high efficacy but are associated with significant weight gain and diabetes→ from blocking the **5HT2C** receptor.

d- Quetiapine: Shares sedation, orthostatic hypotension, weight gain

e- Ziprasidone

f- Aripiprazole: partial agonist at D2 receptors/ avoiding common side effects.

• affinity for muscarinic, α1-adrenergic, serotonin, and histamine receptors.

•S.E: dizziness/ weight gain.

BIPOLAR DISORDER

1- Lithium: very narrow therapeutic index lacks psychotropic effects.

MOA: affecting nerve membranes/stabilizes the firing condition of manic patients by regulating the electricity of nerve membranes/interacts with serotonin/ regulate CNS gene expression

S.E: constant monitoring is key.

a- ***Leukocytosis:*** benign + reversed.

b- ***Tremor:*** hyper-sympathetic/ during therapeutic doses/ deal with it by **propranolol.**

c- ***Hypothyroidism:*** benign/ levothyroxine as a drug for bipolar patients to keep the thyroids hormones in the upper limits.

d- ***ADH inhibition*** (Polydipsia and polyuria): sodium loss exceeds lithium loss, leading to toxic effects of lithium.

nephrogenic diabetes insipidus/**amiloride** to stop it.

Recommendations: Drinking 1.5-3 liters of water /Monitoring sodium

e- Not advised to take ***during pregnancy***, affects fetal heart development.

lithium has no antidote; in toxic dose we do **hemodialysis**.

If Lithium Doesn't Work: **2-Valproic Acid:**

MOA: Augments the post-synaptic action of GABA at its receptors.

• Best for **rapid-cycling** and acute-mania- S.E: sedation, tremor, and possible loss of hair

3-Carbamazepine: **rapid-cycling**/sedation, ataxia **4-Lamotrigine**

5-Atypical Anti-psychotics: Clozapine, Risperidone, and Olanzapine, Aripiprazole

V2: highlighted

Buspirone is ANXIOLYTIC

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