Lecture 1 (Analgesics and sedatives)

- Opioids don't have ceiling effect; they can relieve strong pain.
- Activation of mu-opioid receptors by opioids results in:
  1. Inhibition of substance P and glutamate (pain neurotransmitters) release through hyperpolarization of nerve cells
  2. Release of dopamine, inducing euphoria.
- Opioids side effects:
  - **Euphoria (especially heroin)**
  - CNS depression
  - Nausea and vomiting
  - **Respiratory depression** (the most important)
  - **Urinary retention (contraindicated in prostate hyperplasia)**
  - Diaphoresis and flushing
  - **Pupil constriction** (miosis, pinpoint pupil)
  - **Constipation (contraindicated in patients with gallstones)**
  - Itching due to **histamine** (**contraindicated in asthma**)
  - **Bradycardia.**
- **Cancer patients who are on opioids** are recommended to use **laxatives** (to reverse constipation).
- Opioid effects:

  1- Stimulant effects:
  - + Vagus nerve
  - Antinociceptive system (analgesic)
  - Constipation (antidiarrheal)
  - Urinary retention

  2- Dampening effects:
  - Pain
  - Mood & alertness
  - Respiratory and cough centers (antitussive).
- **Constipation and pinpoint pupil persist with opioids, despite tolerance.**
- Repeated use of opioids can lead to:
  - **Tolerance**: **downregulation** of mu-receptors, can be overcome by **increasing the dose gradually.**
  - **Dependance** (abstinence syndrome): withdrawal symptoms appear upon discontinuation of the drug, can be overcome by **tapering** (gradual reduction of the dose instead of sudden abrupt).
  - **Addiction** (drug abuse).

Lecture 2 (Analgesics and sedatives)

- **Withdrawal symptoms; all opioids' actions get reversed**:
  - Pain, hyperventilation, dysphoria, depression, restlessness, insomnia, fearfulness, diarrhea, pupillary dilation, hyperthermia, lacrimation, runny nose & chilliness.
- Opioids:
  - **Strong opioids:**
    1. **Morphine**
       - ✓ The **prototype**

- ✓ Leads to **hypotension** (relaxes precapillary sphincter), so it's used in **treatment of acute pulmonary edema**
- ✓ Excreted by kidneys, so **contraindicated in renal insufficiency**
- ✓ **Hydromorphone** is preferred over morphine in patients with decreased renal clearance
- ✓ If a patient is on a morphine pump and experiencing severe pain, they can only administer 1/5 of the dose before its scheduled time.

2. **Oxycodone** (just like morphine)
3. **Methadone**
   - ✓ **Treatment of addiction** (methadone rehabilitation)
   - ✓ MOA: **NMDA receptors blocking**, which is different from morphine's, so it treats difficult-to-treat pain, especially when morphine fails to, this process is called **opioid rotation.**
   - ✓ **Long half-life**
   - ✓ May **elongate QT interval** which causes death.
4. **Fentanyl**
   - ✓ 100 times **more potent than morphine**
   - ✓ Narrow therapeutic index
   - ✓ Has **high first-pass metabolism**, so it's available in **injectable and transdermal forms**
   - ✓ Rapid onset and short-acting **(used in operations)**
   - ✓ Excreted by the **liver**.
5. **Meperidine (pethidine)**
   - ✓ Activates mu-receptor and **inhibits vagal activity (muscarinic receptors)**
   - ✓ It has **fewer side effects** than morphine (**no constipation, miosis, etc.**) because it inhibits muscarinic receptors, so can be given in patients with asthma and gallstones
   - ✓ **Repetitive dosing** leads to accumulation of the metabolite normeperidine that **causes seizures**
   - ✓ Used in **labor**, **shivering** and **colic pain (diverticulitis)**
   - ✓ Excreted by **kidneys**
   - ✓ **Contraindicated with other drugs that increase serotonin (e.g., SSRIs) (causes serotonin syndrome).**

- **Weak opioids (partial agonists, less side effects,** no respiratory depression**):**

1. **Codeine**
   - ✓ Used for antitussive purposes and **dental pain**
   - ✓ Higher bioavailability than morphine
   - ✓ **CYP2D6 converts codeine to morphine**. In Jordan, individuals are **ultra-rapid metabolizers** for this enzyme, increasing the risk of toxicity compared to poor metabolizers.
2. **Tramadol**
   - ✓ Rapid
   - ✓ Works on NMDA receptors
   - ✓ Treats moderate pain
   - ✓ **Increases norepinephrine** levels that causes α2 receptor activation and thus inhibits NE release, and it's **contraindicated with SSRIs and MAOIs** (serotonin syndrome).

- Heroin was used as a drug, but its euphoric effects led to its discontinuation.
- **Naloxone** is an **opioid antagonist** used to rapidly reverse opioid overdose (**antidote**).
- A patient without tolerance, dependence, or addiction is termed **naive**. To ensure optimal half-life, **naloxone might require repeated administration** for parallel effects with the opioid's half-life. However, fentanyl half-life is short so we aren't required to repeat the dose.

- Peripherally acting opioids (e.g., loperamide) are used to treat diarrhea and don't cross BBB.

Lecture 3 (Analgesics and sedative)

- **Anxiolytic** (antianxiety) and **hypnotic** (sleep-inducing) drugs may require **gender-based dosages** due to potential differences in stress levels between men and women.
- When mentioning stress here, **we refer to chronic stress not everyday stress (e.g., exams).**
- Stress is regulated by two factors:
  - GABA (by Benzodiazepines)
  - Serotonin (by SSRIs)
- Scientists used to believe that all anxiolytic drugs are also hypnotics, **but this isn't true**. Hypnotic drugs work almost the same as anxiolytic; they both release GABA but from different areas.
- **Anxiolytic and hypnotic drugs:**
  - **At low doses, they relieve stress. At high doses, they induce sleep**.

1. **Barbiturates** (old drugs)
   - GABA receptor complex = GABA receptor + Cl^- channel
   - Barbiturates bind to GABA receptor and increase the **duration** of Cl^- channel opening
   - **Higher toxicity**, can lead to paralysis and death
   - E.g., **phenobarbital, thiopental**
   - **Phenobarbital** is used in **grand-mal epilepsy**
   - **Thiopental** is rapid and short acting and thus used in operations to **induce anesthesia**.
2. **Benzodiazepines** (new drugs)
   - Bind to GABA receptor (**different site than Barbiturates**) and increase the **frequency** of Cl^- channel opening
   - **Lower toxicity**
   - **They don't induce anesthesia**, unlike barbiturates.

- **Duration** has a **higher effect** of inhibition than frequency of channel's opening.
- If a patient **abruptly** discontinues the drug, GABA receptors may have undergone **downregulation** due to chronic exposure, leading to **rebound anxiety**.

Lecture 4.1 (Analgesics and sedatives)

- **Benzodiazepines** are used as **anxiolytics**, **hypnotics**, **muscle relaxants**, **antiepileptics** (anticonvulsants) and to **induce anterograde amnesia**.
  - Long-acting: **Diazepam** and **Flurazepam**, used for **chronic stress**
  - Intermediate-acting: **Alprazolam** and **Lorazepam**
  - Short-acting: **Triazolam**
  - Ultra short-acting: Remimazolam?
- SSRIs take 6 weeks to show noticeable effects, making diazepam the only option to treat stress.
- The "**Bridging therapy**" regimen: **Benzodiazepines** and Risperidone for 2 weeks, then continue Risperidone for 4 weeks, **followed by SSRIs**.
- Cross tolerance exists among this group of agents and has been associated with a decrease in GABA receptors density.
- The Cl^- channel comprises 5 subunits. GABA binding to different subunits alters its effects. **The α2 subunit affects the limbic system (stress), while α1 is involved in the "melatonin pathway" for sleep regulation**. Consequently, not all anti-stress medications induce hypnotic effects.
- To reverse the hypnotic effect, we use histamine or Orexin.

- **Flurazepam, Bromazepam, Lorazepam** and **Triazolam** are the best drugs that produce the **hypnotic effect.**
- **Triazolam** is given if the patient **struggles to fall asleep**, but once asleep, remains asleep.
- **Bromazepam** is given if the patient keeps waking up during sleep (**intermittent sleep**).
- **Flurazepam** is prescribed if the patient has difficulty sleeping for an **extended period**.
- Thus, the choice of medication depends on the duration of sleep; short-acting triazolam for shorter durations and long-acting flurazepam for prolonged sleep.
- **Diazepam** is used in disc herniation (as a **muscle relaxant**) in higher doses than stress treatment. (Not approved by FDA)
- Clonazepam is useful chronic treatment of epilepsy, whereas diazepam is the drug of choice in terminating grand-mal epileptic seizers (status epilepticus).
- They can be given to **infants** in **emergency** cases of **febrile seizures**.
- The short-acting agents are employed in premedication for endoscopic and bronchoscopic procedures such as angioplasty (**anterograde amnesia**)
- Side effects of Benzodiazepines:
  - **Drowsiness** and confusion (**hangover effect)** (most common)
    - **Flurazepam is most commonly associated with it**, leaving patients feeling sleepy and dizzy upon waking, whereas triazolam typically produces less of this effect.
  - **Ataxia**
  - **Cognitive impairment** (given to children with dental phobia)
  - **Triazolam often shows rapid development of tolerance**, early morning insomnia, daytime anxiety.
- Interactions and precautions:
  - Used cautiously in treating patient with **liver diseases.**
  - Should be avoided with **glaucoma**.
  - **Alcohol** and other CNS depressant **enhance the sedative-hypnotic effect**, **and causes euphoria. (Benzodiazepines alone don't cause euphoria)**
- **Flumazenil** is the **antidote** for all Benzodiazepines.

Lecture 4.2 (Anxiolytics and hypnotics)

- **New Benzodiazepine receptor agonists (z-drugs):**
  - They bind only to **α1** subunit of Cl^- channel
  - **They only have hypnotic effect**, rather than anxiolytic, antiepileptic, etc.
  - They show **minimal withdrawal effects and little or no tolerance** effect occur with prolonged use.
  - Side effects: **nightmares**, agitation, headache, daytime drowsiness, and **sleepwalking**.
  - **These side effects are more pronounced in women**, which explains the lower dose prescribed for them.
  - Examples:
    - **Zolpidem**
      - Its plasma t 1/2 is ~2 hours
      - **Covers most of a typical 8-hour sleep period**
      - We dose the patient with more than the eliminating half-life "4 times more"
      - Used for **longtime** sleep
    - **Zaleplon** & Zopiclone
      - Its plasma t 1/2 is ~1 hours

        - Used for **induction** of sleep
    - Both drugs have been approved for use for up to **7-10 days** at a time.
    - Both have sustained hypnotic efficacy **without occurrence of rebound insomnia.**

- **Melatonin congeners**:
    - **Melatonin and Ramelteon** bind to MT1 and MT2 receptors; MT1 promotes the onset of sleep (for insomnia), while MT2 shift the timing of circadian system (for jet-lag).
        - **Ramelteon**:
            - **Synthetic** tricyclic **analog** of Melatonin
            - It was approved for the **treatment of insomnia**, specifically sleep onset difficulties.
            - MOA: Melatonin levels in the suprachiasmatic nucleus rise and fall in a circadian fashion.
- **Orexin antagonists (Suvorexant)**
    - Orexin promotes wakefulness, so its antagonist will indeed be **hypnotic**
    - They have modest activity
    - They have **dose-dependent effect**, so increasing the dose will show stronger side effects
    - Side effects: **somnolence, daytime sleepiness** and sedation, headache, abnormal dreams, fatigue, and dry mouth
- **Buspirone**
    - **5HT agonist**
    - The **anxiolytic effects** of buspirone may **take more than a week to become established**, making the drug unsuitable for management of acute anxiety states (not very effective in panic disorders).
    - Augmenting agent
    - Buspirone **lacks** anticonvulsant and muscle-relaxant properties
    - **The frequency of adverse effects is low**, the most common effects being headaches, dizziness, nervousness.
    - **Serotonin syndrome is not a concern**
    - **Used in bridging therapy and if the patient has sexual dysfunction due to SSRIs use.**

Lecture 5.1 (Antidepressants)

- Clinical trials have shown that antidepressants effect is almost equal to placebo effect.
- **Antidepressants need 8 weeks to reach their maximal efficacy.**
- To increase the efficacy of antidepressants we need to give patients **psychotic therapy**.
- Antidepressants:
    1. **Serotonin-<u>specific</u> reuptake inhibitors (SSRIs)** “the most used drugs”
        - Used for depression, obsessive compulsive disease (الوسواس القهري) & anxiety
        - Side effects:
            - GI upset
            - **Sexual dysfunction**
            - **Anxiety, restlessness & insomnia**
            - **Dizziness**
        - Can develop **discontinuation syndrome**, which causes flu-like symptoms, insomnia, nausea, imbalance, sensory disturbances, hyperarousal **(F.I.N.I.S.H)**
        - Examples:
            A. **Paroxetine**:
                - **Sedating properties** (dose at night), because it antagonizes 5-HT1 C,B

        - Significant **CYP2D6 inhibition**
    B. **Sertraline**:
        - Increased number of **GI adverse drug reactions**
    C. **Fluoxetine**
        - **Less discontinuation syndrome**
        - Significant P450 interactions so this may **not** be a good choice in pts already on **several medications**
        - Initial activation can induce anxiety and insomnia
- You need to pay attention, if the patient has GI problems, don't give him sertraline and so on...

2. Serotonin/Norepinephrine reuptake inhibitors (SNRIs)

- **If the patient doesn't respond to SSRIs, we use these drugs**
- Slightly greater efficacy than SSRIs
- **Slightly fewer adverse effects than SSRIs**
- E.g., **Venlafaxine** & **Duloxetine**
- Side effects:
    - **Significant nausea and vomiting**
    - **Increase in blood pressure**
    - **Bad discontinuation syndrome**

3. 5-HT antagonists

- E.g., **Nefazodone, Trazodone, Mirtazapine**
- Inhibition of 5-HT2A receptors in both animal and human studies is associated with substantial antianxiety, antipsychotic, and antidepressant effects
- Nefazodone is a **weak inhibitor** of both SERT and NET, whereas trazodone is also a **weak** but selective inhibitor of SERT
- **Mirtazapine** can be advantageous **in patients with depression having sleep difficulties**
- Low doses of trazodone have been used widely both **alone and** concurrently **with SSRIs or SNRIs to treat insomnia**
- Side effects:
    - **Sedation**
    - GIT side effects
    - **weight gain (mirtazapine)**

- **5-HT antagonists don't cause serotonin syndrome if given with SSRIs**

Lecture 5.2 (Antidepressants)

4. Monoamine oxidase inhibitors (MAOIs)

- MAO metabolizes monoamines
    - MAO-A oxidizes epinephrine, norepinephrine, serotonin
    - MAO-B oxidizes phenylethylamine
    - Both oxidize dopamine nonpreferentially
    - If serotonin needs to be increased, A is the target. If dopamine needs to be increased, B is the target. Therefore, **MAO-A inhibitors** are the ones used **for depression treatment.**
- **Phenelzine** is a **none selective** one
- **Moclobemide** is a reversible and selective inhibitor of **MAO-A** (antidepressant)
- **Selegiline** is a selective for **MAO-B** (increases dopamine level in Parkinson's disease)
- They aren't used much anymore, they are given for **resistant depression** (if other drugs don't work), and for **atypical depression** (the patient laughs but depressed deep down)

- Side effects: blood pressure problems, **dietary requirements**, weight gain, insomnia & edema.
    - **MAO metabolizes tyramine found in cheese**. MAOIs can cause **tyramine buildup** in the blood. (Extra)
- **MAOIs are contraindicated with SSRIs due to serotonin syndrome.**

5. **Bupropion**
    - **Augmenting agent (not alone)**
    - MOA: reuptake inhibition of **dopamine and norepinephrine (not serotonin).**
    - So, **Serotonin syndrome is not a major concern**.
    - **No** weight gain, sexual side effects, sedation or cardiac interactions **(almost no side effects).**
    - **Low induction of mania**
    - **Does not treat anxiety** unlike many other antidepressants and **can actually cause anxiety, agitation and insomnia**
6. **Tricyclic antidepressants**
    - E.g., **Amitriptyline**
    - **TCAs inhibit serotonin, norepinephrine, and dopamine transporters**.
    - They **block** other receptors like **muscarinic** receptors, **alpha-adrenoceptors**, and histamine (**H1**) receptors.
    - Treat **resistant depression**.
    - Again, don't combine them with SSRIs!
    - Side effects from unselective binding to other receptors:
        - **Sedation**
        - **Orthostatic hypotension**
        - **Cardiac effects (prolong QRS and QT intervals)**
        - **Anticholinergic effects** dry mouth, constipation, blurred vision, urinary retention

Lecture 6 (Schizophrenia 'antipsychotic drugs')

- Schizophrenia symptoms comprise:
    - **Positive symptoms**: **hallucinations**, delusions, disorganized thoughts, perception disturbances & inappropriate emotions.
    - **Negative symptoms**: blunted emotions, anhedonia & lack of **feeling**.
- **Schizophrenia drugs are not a cure; medications must be used lifelong.**
- **Schizophrenia drugs:**
    - **Typical (old) drugs: dopamine (D2) antagonists**
        - **Haloperidol** is the prototype, used to treat the **acute attack** due to its **strong potency.**
        - **Fluphenazine**
        - Relieve **positive** symptoms (hallucinations), cause more depression though.
        - Side effects:
            - **Parkinsonism** (due to antagonism of D2R)
                - **Antiparkinsonian agents (anticholinergics)** could prevent it
            - **Akathisia** (restlessness and agitation)
                - **Benzodiazepines and Propranolol** could prevent it
            - Acute **dystonia** (spasm of neck and upper limb)
                - **Antiparkinsonian agents (anticholinergics)** could prevent it
            - **Tardive dyskinesia** (oral-facial dyskinesia, **occurs after months or years**)
                - Benzodiazepines could prevent it
    - **Atypical (new) drugs: 5-HT_2/D2 antagonists**

        - All of them work well on D2 (positive symptoms), but **they differ in their effect on 5HT (negative symptoms)**
        - **Risperidone**, it blocks:
            - 5HT2A
            - D2
            - α1 (causing orthostatic hypotension)
            - H1 (causing sedation)
        - **Olanzapine and Clozapine**
            - They block:
                - 5HT2A
                - D2
                - **5HT2C** (causing **weight gain** and **DM** on the long run)
                - α1
                - H1
            - Side effect: **Clozapine** (not Olanzapine) can cause **agranulocytosis**, so it's not the first choice even though it's the **most effective.**
        - **Aripiprazole**
            - **Partial agonist at D2 receptor**
            - It needs a **loading dose**
- **Blockage of D2 receptors increases prolactin levels (delayed menstruation and gynecomastia).**

Lecture 7 (Bipolar disorder)

- Bipolar disorder is characterized by mania and depression (ups and downs).
- Increase in catecholamines causes mania, and decrease in catecholamines causes depression.
- To treat it we use **Lithium:**
    - **Narrow therapeutic index**
    - Expected MOA: Affects nerve membranes, multiple receptor systems and intracellular 2nd messenger impulse transduction systems.
    - Relate to plasma concentration levels, so **constant monitoring is key**
    - **Not** advised to take **during pregnancy**, affects fetal heart development
    - Side effects:
        - **Fine tremors, treated by propranolol**
        - Leukocytosis
        - **Hypothyroidism**
        - **Polyuria and polydipsia (diabetes insipidus)** due to its inhibition of ADH. Therefore, patients should prioritize hydration and **maintain stable sodium levels**
- If lithium doesn't work, we may use: (not exam material, as we are supposed to have taken them in the midterm exam)
    - **Valproic acid**
        - Augments the action of GABA at its receptors
        - **Best for rapid-cycling and acute-mania**
    - **Carbamazepine**
        - **Best for rapid-cycling**
    - **Lamotrigine**
    - **Atypical antipsychotic** (Clozapine, Risperidone, etc.)
- **Lithium doesn't have an antidote,** the only way to reverse the toxicity is **hemodialysis**

V2: Page 8, **blockage of D2 receptors increases prolactin levels (delayed menstruation and gynecomastia).**

V3: Page 3, alpha 1 and alpha 2 were flipped, the doctor made a mistake and corrected it

V4: Page 8, Side effect: **Clozapine (not Olanzapine)** can cause **agranulocytosis**, so it's not the first choice even though it's the **most effective.**

Diazepam isn't approved by FDA to be used for disc herniation

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