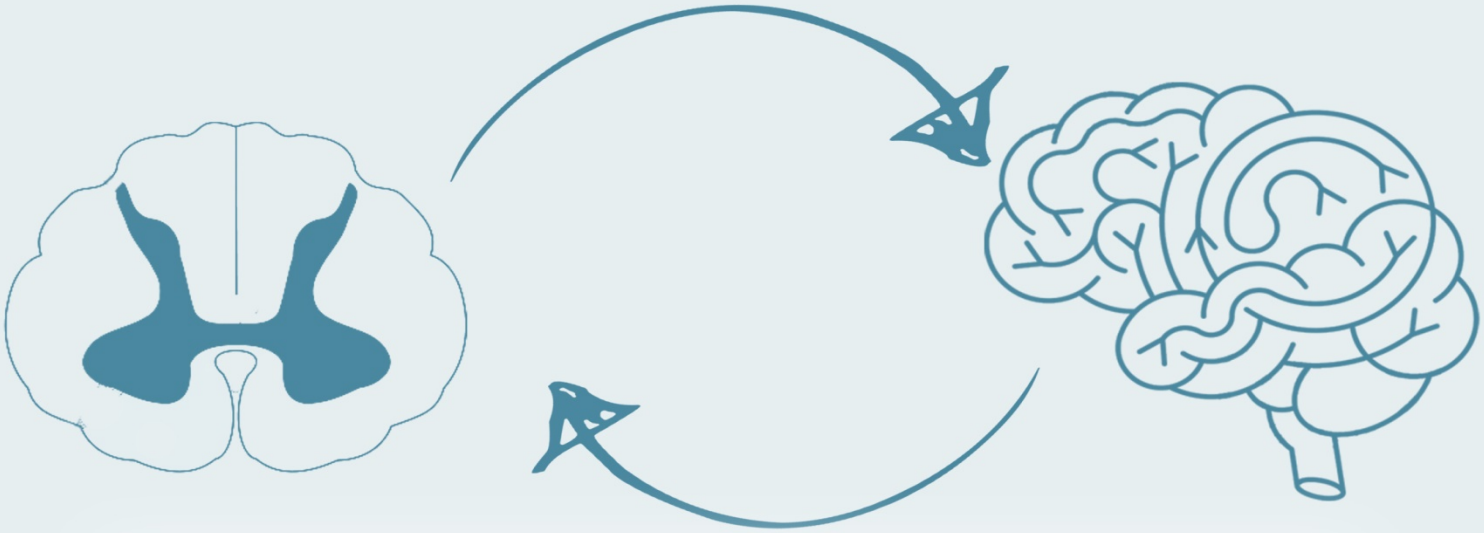

CNS

pharmacology

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number	8
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Opioid Analgesics

Tolerance to opioids

Opioid tolerance develops to high grade to some of the actions, moderate grade for others, but practically, **no tolerance develops to miosis, constipation and convulsions**. For this reason, miosis could be used as a diagnostic sign of opioid abuse (addiction) or poisoning (opioid overdose).

TABLE 31–3 Degrees of tolerance that may develop to some of the effects of the opioids.

High	Moderate	Minimal or None
Analgesia	Bradycardia	Miosis
Euphoria, dysphoria		Constipation
Mental clouding		Convulsions
Sedation		
Respiratory depression		
Antidiuresis		
Nausea and vomiting		
Cough suppression		

The exact **mechanism of tolerance** to opioids is unknown, but it is not metabolic or immunologic, it is **homeostatic or adaptive**; i.e. it is associated with increased efforts from the body to counteract the actions of opioids. Upon the withdrawal of opioids, the patient will have symptoms which are the opposite of the actions of opioids (withdrawal symptoms). This is true with any drug withdrawal; any drug withdrawal is characterized by the appearance of signs and symptoms which are the opposite of the actions of the drug. With β-blockers for example, the patient will have increased heart rate, blood pressure and myocardial oxygen consumption.

Withdrawal reactions of opioids:

These can be categorized according to the time sequence at which they appear:

- **In the first 6-12 hours:**
  - Drug seeking (purposive) behavior: the patient will start looking for the drug even before the appearance of real withdrawal. It is something psychological.
  - Non-purposive signs: Symptoms of over activity of the sympathetic nervous system; restlessness, lacrimation, rhinorrhea, sweating and yawning. It is a form of anxiety.

- **12-24 hours:**
  - Restless sleep for several hours (yen); sleeps a lot but with no benefit. He feels more miserable than before after waking up.
  - Irritability, tremor, dilated pupils, anorexia and gooseflesh skin.

- **24-72 hours: This is the most critical period**
  - Increased intensity of the previous signs, weakness, depression, nausea, vomiting, intestinal cramps, diarrhea, alternate chills and flushes, various aches and pains, increased HR and BP, involuntary movements of arms and legs, dehydration and possible electrolyte imbalances because of the severe diarrhea. These are actions which are opposite to the actions of morphine.

- **Later:**
  - Later, there will be symptoms of autonomic hyperactivity which alternate with brief periods of restless sleep. They gradually decrease in intensity until the addict feels better in 7-10 days but may still exhibit strong craving for the drug.
  - If he survived the first 10 days (he beat the craving, survived dehydration and restlessness and didn't hurt himself during this period), some mild signs may still be detectable for up to 6 months.
  - Delayed growth and development of infants born to addicted mothers may be detected for up to one year. Even though these babies didn't receive any morphine after birth, but they will develop signs and symptoms of delayed growth.

00:00-11:15

Treatment of opioid dependence

1. **Suppression of the withdrawal syndrome**:
   In acute (early) phases, we give morphine to overcome the symptoms of withdrawal. We can give heroine if the patient is severely disturbed by these symptoms because it is more potent and more rapidly acting.
   We can use methadone and clonidine. Clonidine is an α2 central agonist, it was found to reduce the sympathetic activity associated with opioid withdrawal which may be useful.

2. **Opioid substitution**:
   We replace morphine or heroine with less addicting drugs like methadone or LAAM (L-α-Acetyl Methadone, a long acting methadone). Methadone should be given more than once daily. Methadone can substitute for morphine but it is less addictive, so it is used for a period of time to reverse the process of addiction.

3. **Detoxification:**
   By gradually decreasing the dose of methadone or using Naloxone. It can be done with morphine, but it is much easier with methadone because it is longer acting when compared with morphine or heroine. Theoretically, at the end of this stage the patient will no longer be addicted.
   Naloxone is an opioid antagonist. You can keep methadone at the same dose but give naloxone so methadone will not have an effect (i.e. will not work on morphine receptors) because naloxone is an inhibitor of morphine receptor.

4. **Narcotic Antagonists:**
   After stopping methadone, it is supposed that the patient is free of the drug and of the addiction problem. We give Naltrexone for 2-6 months following detoxification to prevent him from taking morphine again. If he took the agonist (morphine) while he is taking the antagonist (naltrexone), he won't feel the euphoric action of morphine.
   Naltrexone is a long-acting antagonist while naloxone is short-acting.

Opioid Agonists

- **Morphine**
- **Codeine**
  - Morphine and codeine are the natural products (obtained from the opium plant)
- **Oxycodone**
- **Hydrocodone**
- **Heroin**
  - Oxycodone and Hydrocodone are semisynthetic drugs from codeine.
  - Heroin is a semisynthetic drug from morphine.
- **Meperidine** (the trade name: Pethidine)
  - It is the most common cause of addiction among health workers.
- **Methadone & L-α-Acetyl Methadone (LAAM)**
- **d-Propoxyphene**
  - It is a very weak addictive and it is sometimes combined with paracetamol. The same goes for tramadol.
- **Tramadol**
  - Tramadol is a morphine derivative. It was initially claimed to have no addictive activity but it was discovered that it is addictive. It is a very good analgesic.

Comparison of Opioid Agonists

Note: We don't have to memorize the entire table, but we should know some of the differences between them:

	Analgesia	Antitussive	Constipation	Respiratory Depression	Abuse Liability
Morphine	+++	++	+++	+++	+++
Heroine	+++	++	+++	+++	++++
Codeine	+	++	++	+	+,--
Oxycodone	++	++	++	++	+++
Meperidine	++	--	+,-	+++	++
Methadone	+++	++	++	+++	++
d-propoxyphene	+	--	+,-	+	+

- ✓ **For analgesic activity:** Morphine, heroine and methadone are good analgesics (+++). Codeine and d-Propoxyphene on the other hand are weak analgesics. Oxycodone is better. However, they still all remain better analgesics than NSAIDs.
- ✓ **For antitussive activity**: Both morphine and codeine are good as antitussive drugs, so you don't have to use morphine for the suppression of cough.
  Before 2 or 3 centuries, pharmacology was based on 2 bottles; one has opium and the other has atropine. Atropine has an anticholinergic activity so it was useful for abdominal and renal pain. Opium was used as an analgesic, antitussive, hypnotic and for diarrhea.
- ✓ **Respiratory depression** is a side effect of these drugs. Respiratory depression is very marked with morphine, heroine, meperidine and methadone. It occurs to a much lesser degree with codeine and d-propoxyphene. That's why codeine and d-propoxyphene are usually combined with paracetamol for stronger analgesia.
- ✓ **Abuse Liability:** Heroine has a higher potential than morphine, oxycodone or others for abuse.

Partial Agonists-Antagonists	**Antagonists**
Pentazocine	Nalorphine
Buprenorphine	Naloxone
Nalorphine	Naltrexone
Nalbuphine	

Naloxone is short acting, so it can be given to neonates of mothers who have been using opioids or for newborns whose mothers used meperidine or morphine anesthesia during delivery. Nowadays, labor anesthesia is mainly achieved by the use of IV anesthesia like meperidine, N_2O, or epidural anesthesia. When opioids were used, the baby might have some morphine in his body and might not breathe. In this case, respiratory depression can be reversed by using an injection of naloxone and repeated 2 or 3 times every 8 or 12 hours.

Naltrexone is longer acting than naloxone.

11:15-24:00

Slides covered: 23-34

Antipsychotic Drugs

These are the drugs used in the treatment of psychotic diseases (e.g. schizophrenia).

Psychological diseases were classified into psychosis (أمراض الذُهان) and neurosis (أمراض العُصاب). Psychotic diseases are more complicated than neurosis. One example of neurosis is anxiety. In neurosis, the problem is usually nervousness. Anxiety for example is associated with sympathetic over activity. But psychotic diseases like schizophrenia are more complicated and involve more difficult manifestations, are usually of unknown etiology.

Tranquilizers (المهدئات) are divided into major and minor tranquilizers. Minor tranquilizers are used in neurosis like those used for anxiety and to induce sleep (hypnotics).

Antipsychotic drugs are sometimes called ***major tranquilizers*** or ***neuroleptics***.

A mnemonic for the actions and side effects of antipsychotic drugs:

Chlorpromazine is the prototype ANTIPSYCHOTIC. Its actions are:

A	Antipsychotic effect in psychotic patients (therapeutic effect)
N	Neuroleptic syndrome in normal persons (unpleasant effect)
T	Temperature control is disturbed
I	Increased chances of epileptic fits due to decreased seizure threshold
P	Prolactin release increases – galactorrhoea & gynaecomastia
S	Side effects – Extrapyramidal e.g. Parkinsonism, dystonias, akathisia, dyskinesia
Y	Yellowness i.e. cholestatic jaundice
C	Cholinergic antagonism leading to dry mouth,etc ← Atropine-like actions
H	Hypotension
O	Obesity
T	Tolerance to some effects like sedation
I	Inhibition of gonadotropin secretion
C	Certain spasticity conditions are relieved

Psychosis: A variety of mental disorders of abnormal perceptions (hallucinations), thoughts (delusions) and behaviors and aggressiveness.
The patient sees and hears things that are not there, he has delusions; for example, he thinks that he is an important person and there are some people spying on him. He might think that his family is planning to kill him, so he might kill them.

One example of psychosis is **schizophrenia**. Schizophrenia has some genetic predisposition:

- A gene encoding neuregulin 1 is associated with schizophrenia in Icelandic and northern European populations. Some cases of schizophrenia run in families.
- Abnormalities of amine neurotransmitter functions, especially dopamine.
- Glutamate, GABA and Acetylcholine receptors, were also proposed to participate.

Schizophrenia can be considered as a "malignancy" of the soul; it is irreversible, hopeless and occasionally ends with death. The patient might commit suicide or crosses the road and a car hits him because he thought that he cannot be harmed.
It is not a disease of modern life (like IHD).

Schizophrenia is common in the young age group (between college students).

History of Antipsychotic Treatment

- Incarceration: In Europe, people used to burn psychotic patients. These patients were treated badly and were imprisoned.
- Herbal
- Psychosurgery
- Electroconvulsive Therapy (ECT): It is still used in severe cases.
- Electrode Implantation

24:00-35:00

- Antipsychotic Drugs: The first effective antipsychotic drug appeared in 1952 which is chlorpromazine.
  After its discovery, the number of hospitalized psychiatric patients decreased significantly. Psychotic patients were not cured, but their symptoms improved, so they were not imprisoned anymore and are more accommodated within the community.

Weston State Hospital

This hospital is in the United States. It was the largest hospital and it was built in 1864. The hospital; 307-acre complex; is the second of the world's largest hand-cut sandstone structures, a National Historic Landmark, that once housed more than 2,500 patients but has stood largely silent since 1994.

After struggling to find a suitable, sustainable use, the state sold it at auction for $1.5 million to an asbestos demolition contractor.

Now, the hospital is a museum and it is open for tourists. The daily tours — which cost $10 to $30, depending on duration — focus on issues such as the evolution of mental health care, the Civil War, the Great Depression, even architecture.

Mechanism of Action

A common mechanism to all antipsychotic drugs is **dopamine receptor antagonism.** There are 5 types of dopamine receptors: D1, D2, D3, D4 and D5. The therapeutic effects are **mainly due to D2 antagonism** (70-80% of the action).

Many of them also work to **antagonize other receptors** like $5HT_{2A}$, α, H1, and M (muscarinic) receptors, most importantly $5HT_{2A}$. This will lead to different mechanisms, different efficacy, potency and toxicity. For example, those which work on M receptors will have anti-muscarinic effects or atropine-like side effects.

Dopamine Pathways

- **Nigrostriatal (Basal ganglia):**
  Coordination of posture and voluntary movement
- **Mesolimbic-mesocortical:**
  Behavioral, mental and emotional
- **Tuberoinfundibular**:
  Inhibits prolactin secretion
- **Medullary-periventricular:**
  Eating behavior
- **Incertohypothalamic**:
  Anticipatory motivational phase of copulatory behavior in rats (sexual activity)

Dopamine receptors

- **Dopamine1-Like Receptors**
  - **D1 Receptor:**
    It is coded by a gene on chromosome 5. It increases cAMP.
    Located mainly in the putamen, nucleus accumbens, and olfactory tubercle
  - **D5 Receptor:**
    It is coded by a gene on chromosome 4. It increases cAMP.
    Located mainly in the hippocampus and hypothalamus

Binding affinity of antipsychotic drugs to these receptors does not correlate with therapeutic potency. Therapeutic potency is related to D2, D3 and D4 receptors.

- **Dopamine2-Like Receptors**
  - **D2 Receptor:**
    Coded on chromosome 11
    Decreases cAMP, opens K+ channels and inhibits Ca++ channels.
    Found in the caudate- putamen, nucleus accumbens and olfactory tubercle

Binding affinity of drugs to D2-like receptors strongly correlates with antipsychotic (therapeutic effect) and extrapyramidal (side effect) potency. Both effects are related to each other; to obtain the therapeutic effect you must have extrapyramidal side effects.

  - **D3 Receptor:**
    Also coded on chromosome 11. It decreases cAMP.
    Located in the frontal cortex, medulla and midbrain
  - **D4 Receptor:**
    Also decreases cAMP

General Features of Antipsychotic Drugs

- Different Affinities for the receptors
- Different Potencies
- Different Activities & Toxicities

- Different Responses of Patients because the nature of the disease is different among them.
- Each may have special benefits for selected patients.
- Older drugs have lower cost and can be given by depot IM injections.

35:00-44:20

Slides covered: 1-16

The End
Good Luck