PHARMACOLOGY

LECTURE NO. 5

WRITER : Waad almanaseer

CORRECTOR:

DOCTOR: Yacoub Irshaid

Sedative-Hypnotic Drugs

Yacoub M. Irshaid, MD, PhD, ABCP

Department of Pharmacology

Sedative-Hypnotic Drugs

- **The perceived relief of anxiety, euphoria, disinhibition فقدان الرادع and promotion of sleep is the cause of the compulsive use(addiction) of virtually all sedative-hypnotics.**
- **The consequences of abuse can be both psychologic and physiologic.**

compulsive use → tolerance → psychological and physiological dependence characterized by withdrawal syndrome

Sedative-Hypnotic Drugs

- **The psychologic component may initially parallel simple neurotic behavior pattern similar to that in coffee drinker and cigarette smoker. This isn't a physiologic dependence**

  هاد زي لما يكون الواحد بشتغل و ملهي وفجأة يحكي بدي أشرب اشي

***One of the most addictive drugs is nicotine**

- **When the pattern of sedative-hypnotic use becomes compulsive, more serious complications develop, including tolerance and physiologic dependence which is a discontinuation of the drug leading to withdrawal syndrome.**

Sedative-Hypnotic Drugs

- **Physiologic dependence is an altered physiologic state that requires continuous drug administration to prevent an abstinence or withdrawal syndrome.**
- **This syndrome consists of increased anxiety (we called them anxiolytics so if you stop taking them you will have anxiety), restlessness, insomnia, CNS excitability(they are CNS depressant and the worst effects are the respiratory depression and coma) that may progress to convulsions(the worst), weakness and orthostatic hypotension.**

Sedative-Hypnotic Drugs

- **Drugs with long half-life are eliminated slowly enough to accomplish gradual withdrawal with few physical symptoms.**
- **Drugs with short half-lives may show signs of withdrawal even between doses (triazolam).**

Sedative-Hypnotic Drugs

- **Withdrawal symptoms of zolpidem, zaleplon, or eszopiclone(**Hypnotics) **are less intense than that with BDZs.**
- **The degree of tolerance achieved is not identical for all pharmacologic effects.**
- **Lethal dose range is <u>not</u> altered significantly by long-term use. If there is a tolerance for a specific pharmacological effect and the patient increases the dose to get the effect there will be a risk of death .**

Sedative-Hypnotic Drugs

- **Cross-tolerance between different sedative-hypnotics, including ethanol, can lead to unsatisfactory therapeutic response when standard doses of a drug are used in a patient with a recent history of excessive use of another agent.** so before you give your patient Sedative-Hypnotic Drugs you have to ask about taking alcohol because if the patient has a tolerance of alcohol and you give him /her for example benzodiazepine it wont work well
- *they have the same tolerance mechanism

Benzodiazepine Antagonists

Flumazenil: **it reverses the excessive pharmacological effect or adverse reaction of benzodiazepine but if it taken by an addict it will precipitate withdrawal syndrome**

A benzodiazepine derivative with high affinity for BDZ binding sites on $GABA_A$ receptor. It is a competitive antagonist .so , Flumazenil reverses the action of benzodiazepine and zolpidem&its family but not any other CNS depressor

It blocks many of the actions of BDZs, zolpidem, zaleplon, and eszopiclone.

- **It does not antagonize the CNS effects of other sedative-hypnotics, ethanol, opioids or general anesthetics.**

Benzodiazepine Antagonists

- **Flumazenil is used for reversing the CNS effects of BDZ overdose and to hasten recovery following use of these drugs in anesthesia and diagnostic procedures.**
- **Antagonism of BDZ-induced respiratory depression is less predictable. The patient may need assisted ventilation**
- **It has a short half-life due to rapid hepatic clearance (0.7-1.3 hours)+ produces an active metabolites**

Benzodiazepine Antagonists

Adverse effects:

- **Agitation, confusion, dizziness, and nausea.**
- **Severe abstinence syndrome in patients with physiologic dependence**
- **May cause seizures and cardiac arrhythmias in patients who have ingested benzodiazepines with tricyclic antidepressants.**

Sedative-Hypnotic Drugs

Therapeutic Uses:

1. **Relief of anxiety states: The cause also needs treatment. Alprazolam has been found (by comparative studies)to be particularly effective in panic (هلع) disorders and agoraphobia (رهاب الخلاء).**
2. **Treatment of insomnia:**

- **Insomnia usually has underlying medical condition or psychiatric illness. True primary insomnia is rare. you have to treat the cause .**

- **Benzodiazepine and the newer agents are preferred over barbiturates.**

3. **For sedation and anti grade amnesia which means that you forget the events after taking the drug before and during medical and surgical procedures like endoscopic operations (Midazolam).**
4. **Epilepsy and seizures (termination of an attack).**
5. **As a component of balanced anesthesia (IV).**
6. **Note: the barbiturates have a very limited uses ,they have 2 valid uses: (IV) anesthesia and febrile convulsion in children**

***retrograde means you forget the events before taking the drug**

***Midazolam يُعطى للسيدات المتألمات من عملية الولادة في المرحلة الاخيرة بناموا فترة و لما يصحوا بكونوا ناسيين انه صار ولادة يعني نسيوا ما حدث بعد تناول الدواء**

Sedative-Hypnotic Drugs

6. For control of ethanol or other sedative-hypnotic withdrawal states using long action Benzodiazepine
7. For muscle relaxation in specific neuromuscular disorders.
8. Parenteral lorazepam for suppression of delirium tremens(confusion with hallucination) (alcohol withdrawal).
9. Drug-induced hyperexcitability states.

Sedative-Hypnotic Drugs

Adverse Effects:

Many result from CNS depression.

1. **Relatively low doses may lead to drowsiness, impaired judgment, and diminished motor skills; With impact on driving ability, job performance, and personal relationship.**

Sedative-Hypnotic Drugs

2. **Benzodiazepines may cause a significant dose-related anterograde amnesia, impaired ability to learn new information, while leaving the retrieval of previously learned information intact.**
3. **Confusional states especially in the elderly are most commonly caused by overuse of sedative-hypnotics.**

Sedative-Hypnotic Drugs

4. Hangover effects:

- **Include effects such as drowsiness, dysphoria, and mental or motor depression the following day.**
- **Not uncommon with agents with long half-life.**
- **Elderly patients are more sensitive.**

It is specially important in elderly and important in young.

Sedative-Hypnotic Drugs

5. At higher doses, may produce lethargy or a state of exhaustionانهيار, or symptoms equivalent to ethanol intoxication.
6. Exacerbation of breathing problems in patients with chronic pulmonary disease and those with symptomatic sleep apnea.
7. Cardiovascular collapse.

Sedative-Hypnotic Drugs

8. Extensive clinical use (triazolam) has caused behavioral disinhibition, delirium, aggressionعدائي, and violenceمجرم.addicts and long term users.
9. Hypersensitivity reactions.
10. Teratogenicity.it crosses the placenta
11. Barbiturates are contraindicated in patients with a history of acute intermittent porphyria(heme metabolism).

Sedative-Hypnotic Drugs

Drug Interactions:

1. **Additive effect with CNS depressants, alcohol, opioids, anticonvulsants, phenothiazines, antihistamines and antidepressant drugs.**
2. **Interactions at the level of drug metabolizing enzymes. Barbiturates induce drug metabolism.**

Hypnotics

Ramelteon:

- **Is an agonist at melatonin receptors, MT_1 and MT_2, located in the suprachiasmatic nuclei of the brain. The pineal gland that secretes melatonin calcified early during life so when you give a stimulation for the receptors you induce sleep**

***it's a benefit for the patients who unable to sleep**

- **Melatonin receptors are thought to be involved in maintaining the <u>circadian rhythms underlying the sleep-wake cycle.</u>**
- **Prescribed for patients who have difficulty in falling asleep.**
- **Insomnia الها اشكال مختلفة ممكن المريض صعب يروح ينام بس اذا نام خلص بضل نايم و ممكن بنام بسهولة بس بصحى أكتر من مرة باليل فلازم ندور على السبب لانه الدوا رح يختلف**

Ramelteon

- It has NO effect on GABAergic neurotransmission in the CNS.
- No rebound insomnia or withdrawal symptoms.
- Rapidly absorbed after oral administration and undergoes extensive first-pass metabolism (CYP1A2) , forming an active metabolite with a longer half-life (2-5 hours). CYP2C9 contributes.
- Metabolism induced by rifampin.

- **Ramelteon should not be used in combination with inhibitors of CYP1A2 (ciprofloxacin, fluvoxamine, tacrine, zileuton) or CYP2C9 (fluconazole).**

Adverse effects:

1. **Dizziness, somnolence, fatigue.**
2. **Endocrine changes (decreases testosterone levels in males hypogonadism , and increases prolactin levels in both females and males leading to infertility).**

- **Use with caution in patients with liver dysfunction.**

Orexin Receptor Antagonists

Almorexant, Suvorexant

- **Sleep-Enabling Drugs**
- **Orexin A and B are peptides found in specific hypothalamic neurons.**
- **They are involved in the control of wakefulness and they are silent during sleep. Remember melatonin is responsible for sleeping.**
- **Orexin levels increase in the day and decrease at night in the hypothalamus .**

Orexin Receptor Antagonists

- **Loss of orexin neurons is associated with narcolepsy (a disorder characterized by daytime sleepiness) and cataplexy (sudden loss of muscle tone while a person is awake because of reduction of neurons that contain orexin).**
- **Suvorexant is a substrate of CYP3A4, and its half-life is prolonged by inhibitors of the enzyme including azole antifungal drugs, clarithromycin, and verapamil.**

Anxiolytics

Buspirone: it is an anxiolytic only

- **Has a selective anxiolytic effect.**
- **It relieves anxiety without causing marked sedation, hypnosis, or euphoria.no euphoria no addiction**
- **Has NO anticonvulsant or muscle relaxant effects.**
- **Does not interact with GABAergic systems.**

Buspirone

- **Anxiolytic effect may be due partial agonist activity at brain 5-HT_{1A} receptors.**
- **It has affinity for brain dopamine D_2 receptors.**
- **No rebound anxiety or withdrawal signs on abrupt discontinuance.**
- **Not useful for withdrawal syndrome from benzodiazepines or other sedative-hypnotics.**
- **Has minimal abuse liability.**

Buspirone

- **Anxiolytic effect takes 3-4 weeks to be established → unsuitable for acute anxiety states .you have to explain for patients and their families that it needs a long time to start working.**
- **Used for generalized anxiety states but is less effective in panic disorders.**
- **Rapidly absorbed orally but undergoes extensive first-pass metabolism by CYP enzymes to form several active metabolites .this means there is a lot of drug- drug interactions**
- **One of the metabolites has an α_2-adrenoceptor blocking action.**
  Pre synaptic adrenergic receptors mediate negative feedback
- inhibition of catecholamines

Buspirone

- **Its elimination half-life is 2 - 4 hours. It is increased by inhibitors (erythromycin, grapefruit juice and ketoconazole) of CYP3A4 and decreased by its inducers (rifampin).**
- **Liver dysfunction may slow its clearance.**
- **Causes less psychomotor impairment than BDZs.**
- **Does not affect driving skills.**
- CYP3A4 ;metabolise of 50%of therapeutically available drugs that are eliminated by metabolism

Buspirone

- **Does not potentiate effects of conventional sedative-hypnotics, ethanol, tricyclic antidepressants.**
- **Elderly patients are not more sensitive to its actions.**

Adverse effect:

1. **Nonspecific chest pain, tachycardia, palpitations, dizziness, nervousness, headache, tinnitus. Because of release for catecholamine by α2 receptor blocking.**

Buspirone

2. **Gastrointestinal distress.**
3. **Paresthesias.**
4. **Dose-dependent pupillary constriction.**

α receptors do circular muscle contraction but also beta receptors do radial muscle contraction result in dilation of pupil.

2. **Blood pressure may be significantly elevated in patients receiving monoamine oxidase (MAO) inhibitors.**