# New Benzodiazepine Receptor Agonists

- **An hypnotic agent that act on the same receptors as benzodiazepines. Nonetheless, it has no anticonvulsant effect nor muscle relaxation.**

- **It shows minimal withdrawal effects and little or no tolerance effect occur with prolonged use.**

- **Currently it is the most frequently prescribed hypnotic drug in the United States.**

- **Although zolpidem potentially has advantages over the benzodiazepines, clinical experience with the drug is still limited.**

- **Adverse effects includes nightmares, agitation, headache, daytime drowsiness.**

## ZALEPLON

- Its plasma **$t_{1/2}$ is ~1 hours**

- **approved for use immediately at bedtime or when the patient has difficulty falling asleep after bedtime.**

## ZOLPIDEM

- Its plasma **$t_{1/2}$ is ~2 hours**

- **Cover most of a typical 8-hour sleep period, and is presently approved for bedtime use only.**

# Novel Benzodiazepine Receptor Agonists

- Zaleplon and zolpidem are **effective in relieving sleep-onset insomnia**. Both drugs have been approved by the FDA for use for up to **7-10 days** at a time.

- Zaleplon and zolpidem **have sustained hypnotic efficacy** without occurrence of rebound insomnia on abrupt discontinuation.

# MELATONIN CONGENERS

## Mechanism of Action

- Two **GPCRs** for melatonin, **$MT_1$** and **$MT_2$,** are found in the suprachiasmatic nucleus, each playing a different role in sleep.
- **RAMELTEON** binds to both **$MT_1$** and **$MT_2$** receptors with high affinity.
- Binding of **Melatonin** to **$MT_1$** receptors **promotes the onset of sleep**.
- Binding of **Melatonin** to **$MT_2$** receptors shifts the timing of the circadian system.
- **RAMELTEON** is efficacious in combating both transient and chronic insomnia

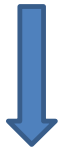
# MELATONIN CONGENERS

## RAMELTEON

- Synthetic tricyclic analog of **MELATONIN**.
- It was approved for the treatment of insomnia, specifically sleep onset difficulties.

## MECHANISM OF ACTION

- Melatonin levels in the suprachiastmatic nucleus rise and fall in a circadian fashion



concentrations increasing in the evening as an individual prepares for sleep, and then reaching a plateau and ultimately decreasing as the night progresses.

# Orexin antagonist
# Suvorexant

- inhibits the effect of orexin by acting as a receptor antagonist of one or both of the orexin receptors, $OX_1$ and $OX_2$.

- These receptors are the biological targets of the endogenous wakefulness-promoting orexin neuropeptides orexin-A and orexin-B

- Medical applications include treatment of sleep disorders such as insomnia.

- Side effects of orexin receptor antagonists include somnolence, daytime sleepiness and sedation, headache, abnormal dreams, fatigue, and dry mouth