# All India Institute of Medical Sciences Rajkot

## e – Bulletin

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# Contents

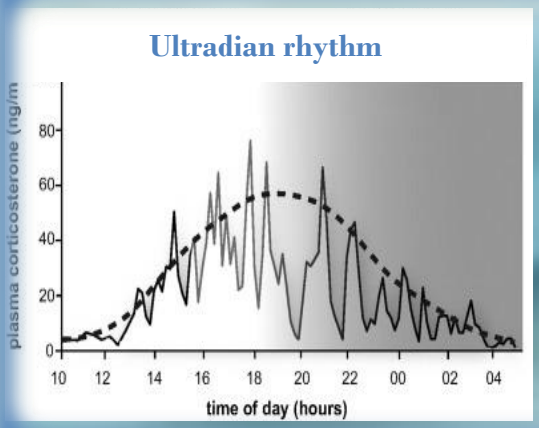
# Chronopharmacology

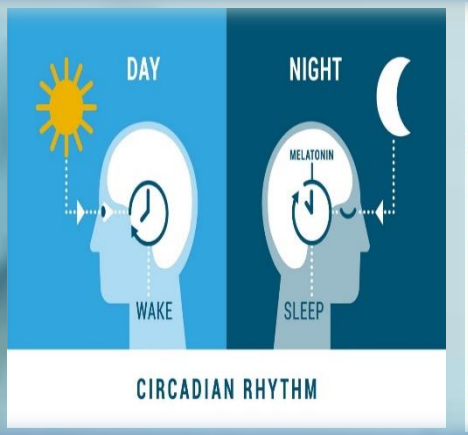
- **Chronopharmacology** studies how biological rhythms impact on drug pharmacokinetic (Chronokinetics), pharmacodynamics (Chronopharmacodynamic).
- It is the study of how the effect of drug varies with timing of biological events, rhythms and endogenous periodicity.[1]
- The 24-hour rhythms of biochemical, physiological, and behavioral processes controlled by the circadian clock influence the effectiveness and toxicity of many drugs based on the time they are administered.[1]
- **There are two main principles of chronopharmacology:**
  - **Chronopharmacokinetic:** How biological rhythms affect what the body does to the drug (Pharmacokinetic).[2]
  - **Chropharmacodynamic**: It deals with the biochemical and physiological effects of drugs on the body, the mechanisms of drug action, the relationship between drug concentration and effect in relation to circadian clock.[3]
- **The goal of chronopharmacology:**
  Improve the understanding of periodic and predictable changes in both desired (therapeutic) effects and tolerance of medications.[2]

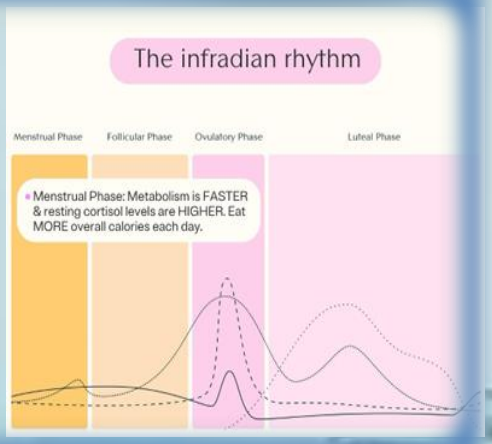
- **Chronesthesy:** It explores the relationship of biological rhythms on the effects of the drugs in the body.[3]
- **Chronotherapy:** Medication with tailored timing of doses to match the body's natural daily rhythms and behaviour pattern in order to increases beneficial effects and/or minimise the adverse effects across the day and night.[4]
- **Chronotoxicology:** The study of kinetics, dynamics, toxicological responses and side effects of drugs, poisons or toxic substances relative to temporal rhythms occurring in living organisms.[5]

# Chronobiology: Biological clock of the body[6]

- Physiological function and the pathophysiology of diseases are influenced by biological rhythms.
- The concentration of biomolecules in living systems shows numerous systematic and random variations. These variations are typically classified based on their frequency into:
    - Ultradian (<24 h): Cortisol level
    - Circadian (approximately 24 h): Sleep Walk cycle
    - Infradian (>24 h): Menstrual cycle

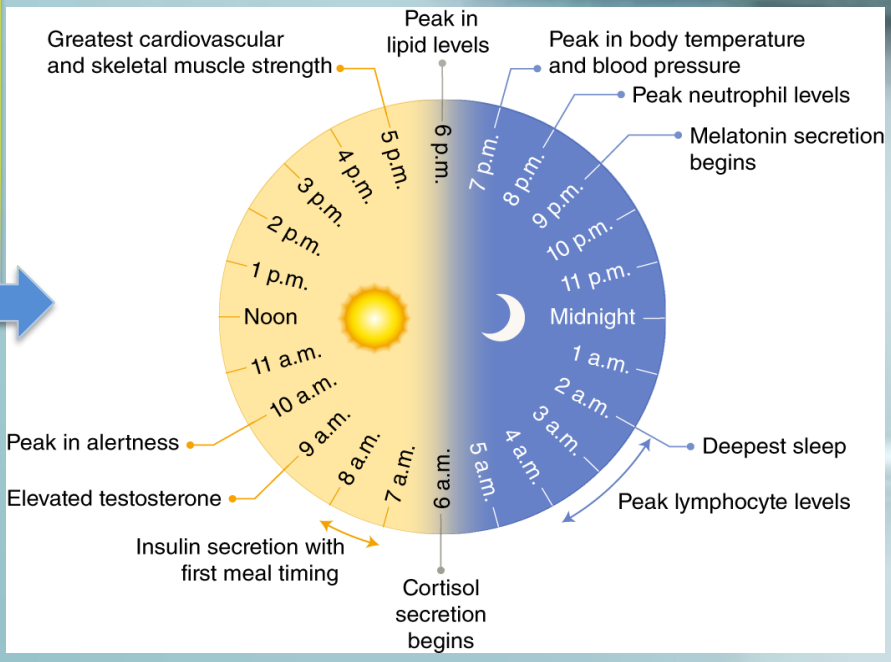



## Circadian clock: It regulates the following functions on a 24-hour cycle[6]

- Homeostatic systems
- Individual aspects of cellular physiology
- Neurotransmitter release
- Sleep
- Hormone levels
- Appetite, control of gastric and intestinal digestion, absorption and metabolism
- Cardiac Function
- Immune regulation

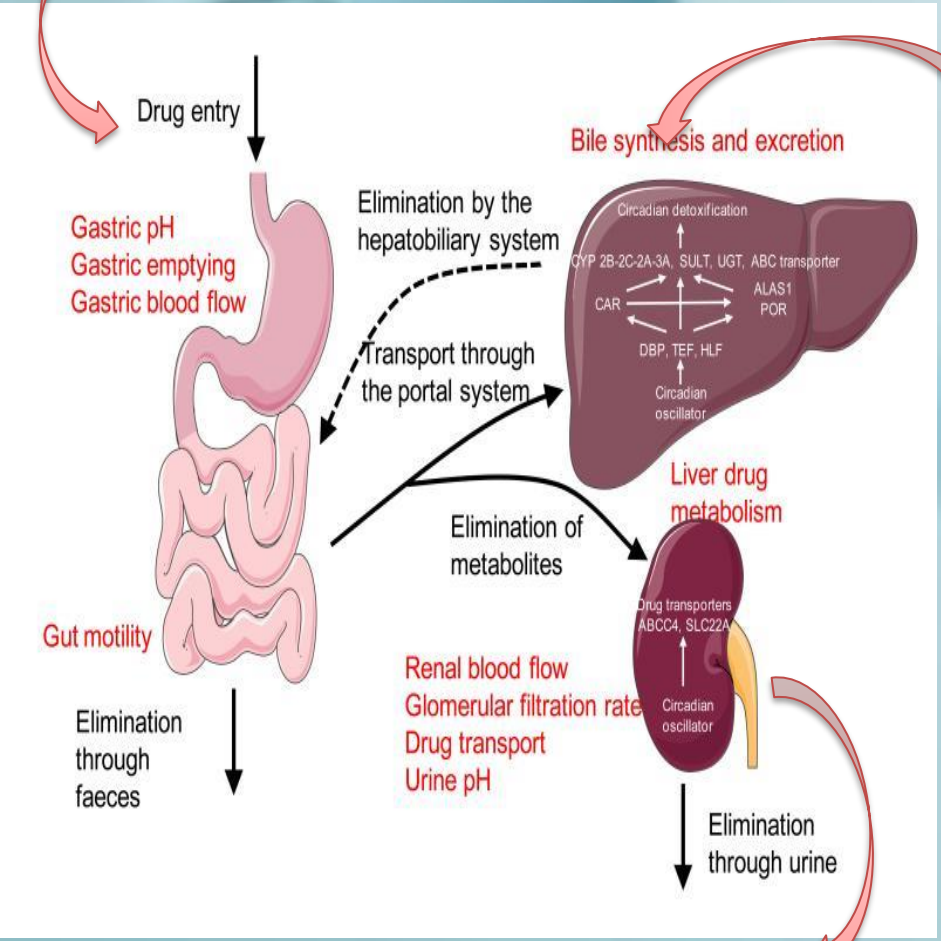


# Chronopharmacokinetics[7]

- It studies the temporal changes in absorption(A), Distribution(D), Metabolism(M), Excretion (E) taking into account the influence of time of administration on these different steps.

**Absorption:** Temporal variations in drug absorption in the gastrointestinal tract are influenced by circadian changes in factors such as gastric acid secretion, gastric emptying time, drug transport, and gastric blood flow.

**Distribution**: Temporal changes affect plasma protein binding and drug distribution.




**Metabolism:** Temporal variation in enzymatic activity (Cytochrome P450) in the liver, hepatic blood flow influence drugs metabolism. The activity of hepatic phase I cytochrome enzymes (CYP2B10, CYP2E1, CYP2A4, CYP2C22, CYP2E1, CYP4A3) and the activity of phase II enzymes (such as UDP-glucuronosyltransferase, glutathione S-transferase, N-acetyltransferase, and epoxide hydrolases) varies with the circadian rhythm.

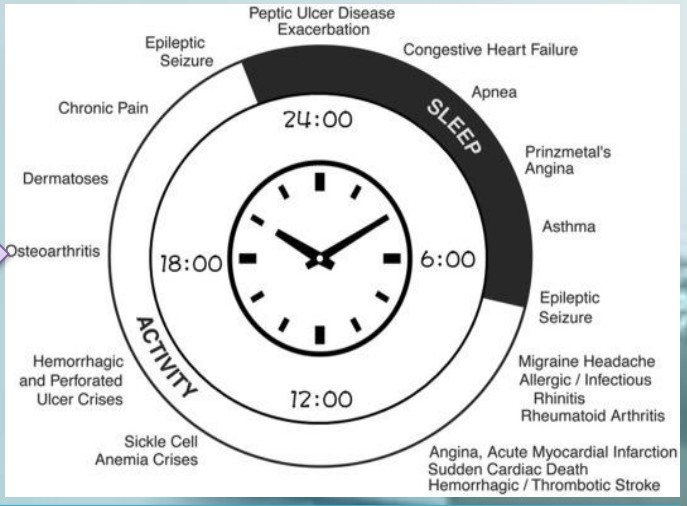
**Excretion:** Renal drug excretion affected by temporal variation in glomerular filtration, renal blood flow, the glomerular filtration rate, urine flow and the urine pH.

# Chronobiology of disease occurrence[6,7]

Chronobiology is the study of biological rhythms and their influence on health and disease. It examines how the timing of biological processes, affects disease occurrence and progression.

- **Worsening of diseases/symptoms observed at nighttime includes the following:**
  - **Allergic rhinitis:** Symptoms of allergic rhinitis, even skin testing results vary according ot the time of the day.
  - **Asthma:** Chronopharmcological studies shows that the development asthma symptoms and bronchospastic attacks is more common from midnight to early morning. This is due to temporal variation in significance cholinergic dominance, lowest cortisol level, reduction of small bronchial diameter, and supine position during sleep.

**Chronobiology of disease occurrence**




- **Cardiovascular diseases:**Circadian variation is significantly associated with adverse cardiovascular events, with a higher risk of myocardial infarction and sudden cardiac death occurring more frequently in the early morning hours.
- The reasons for this pattern include elevated morning cortisol levels, which enhance adrenergic sensitivity, increased platelet aggregation, and decreased intrinsic thrombolytic activity in the early morning.
- Blood pressure fluctuates according to a circadian pattern, typically rising in the morning and gradually declining throughout the day, reaching its lowest point around midnight, especially during sleep.
  - **Hypercholesterolemia:** Research indicates that cholesterol synthesis in the liver generally follows a circadian pattern with increased activity during the night or early morning hours, aligning with the body's overall metabolic processes.

# Chronotherapy

**Chronotherapy** involves the tailored timing of doses to match the body's natural daily rthythms and behavioral pattern in order to increases beneficial effects and or minimize any adverse effects across the day and night.[4,6]


## Drugs more effective when administered at evening/night

**Statins**: Hypolipidemic drugs, particularly HMG-CoA reductase inhibitors (with the exception of atorvastatin), should be administered in the evening to maximize efficacy. This timing is optimal because hepatic cholesterogenesis occurs primarily during the evening and night, leading to a greater reduction in serum cholesterol compared to morning doses.[4,6]

**Non-sedating antihistamines,** when administered once daily at bedtime, can more effectively control overnight exacerbations of allergic rhinitis**.**[4,6]

**Long acting NSAIDs** such as ketoprofen and indomethacin, are optimally administered at bedtime to enhance their therapeutic effects and minimize adverse drug reactions in rheumatoid arthritis.[8]

**ACE inhibitors** are found to be safer (lower incidence of side effects such as dizziness, orthostatic hypotension) when administered at bedtime compared to in the morning.[9]

**5-Fluorouracil (5-FU**) administration in the early morning can boost its efficacy by aligning with peak cell proliferation.[10]

## Drugs more effective when administered at morning

**Beta-blockers:** Blood pressure often peaks sharply in the early morning due to increased catecholamine levels and heightened adrenergic receptor expression at this time. This temporal pattern supports the effectiveness of beta-blockers administered in the morning to manage hypertension.[11]

**Triptans:** Migraine episodes frequently occur in the early morning and can be effectively managed with triptans when administered during these early hours.[12]

# Chronopharmacology- Therapeutic Drug Monitoring

Therapeutic drug monitoring (TDM) reveals how the timing of administration can influence the maximum concentration (CMax) of a drug.[11] The following are some of documented reports regarding chronopharmacokinetic differences of drugs during the therapeutic drug monitoring procedure[4]:

- **Antiepileptic Drugs**
  The maximum concentration (Cmax) and absorption rate of valproic acid (VPA) are higher in the morning compared to the evening. Urinary concentration of VPA peaks between 2a.m. and 6 a.m., while it is lowest in the afternoon and evening.[13]
- **Antihypertensive Drugs**
  The maximum concentration (Cmax) of antihypertensive drugs, such as nifedipine, propranolol, and verapamil, is higher and occurs more quickly when these medications are administered in the morning.[8,10]
- **Antimigraine Drug:**
  The maximum concentration (Cmax) of sumatriptan is higher when administered in the morning at 7 a.m. compared to the afternoon.[14]
- **Cyclosporine**
  The "C max" achieved after tacrolimus night dose was significantly lower than after morning dose administration. The concentration must be determined 2 hours after morning administration, while blood samples at night should be collected to determine lower concentrations.[10]

## TIME FOR A CHANGE ?

Understanding of how biological rhythms influence disease progression and drug therapy is advancing. However, chronopharmacology remains a relatively underappreciated and underutilized field in drug development, regulation, and clinical practice. Chronopharmacology could streamline drug development, speeding up the delivery of effective medications. Additionally, existing treatments could be optimized by incorporating chronopharmacological principles. To fully unlock the clinical potential of chronopharmacology, more evidence is needed.[1]

**As William Shakespeare** wisely said, "**Make use of time, let not advantage slip.**"
Embracing chronopharmacology might help us do just that.

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## QUIZ corner!!!!

1. **Identify the disease from given image and specify which hormone is likely to be affected?**

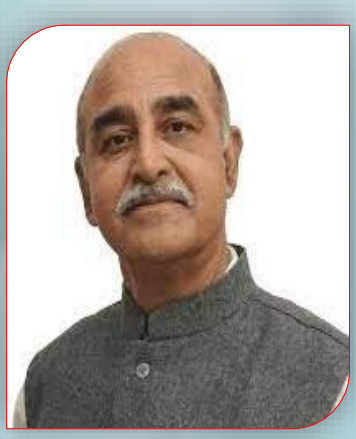
2. **Which of the following is an example of a drug that might be given at a specific time of day to optimize its effect?**

   A) Paracetamol for fever
   B) Beta-blockers for hypertension
   C) Antidepressants for mood disorders
   D) Drotaverine for renal colic

3. **All of the following anticancer drugs' efficacy can be optimized using the principle of chronotherapy, EXCEPT _____**

   A) Cisplatin
   B) Methotrexate
   C) Tamoxifen
   D) Cyclophosphamide

Answer: 1- Jet lag syndrome, Melatonin, 2- B, 3- C



## Message from the Executive Director

"I heartily congratulate the department of pharmacology for bringing this informative newsletter on clinical pharmacology and therapeutics on "Chronophramacolgy". My best wishes to the entire team.

Dr. (Col) CDS Katoch, Executive Director, AIIMS, Rajkot.

## Team Pharmacology

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