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CHRONOTHERAPY THROUGH REGULATION OF CIRCADIAN RHYTHMS- AN OVERVIEW

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ABSTRACT: The objective of chronotherapy is to optimize medical treatments taking into account the body's circadian rhythms. Drug delivery systems that precisely control the release rates or target drugs to a specific site have an enormous impact on the health care system. Over the past few years, pharmaceutical industry has focused its research in the development of various Chrono therapeutic delivery systems. By choosing the optimal time to achieve the desired effect, treatment opportunities may arise, and undesirable side effects minimized. Hence, the long-term interest of both the public and the industry is to develop new and more effective methods on the current study focus – Chrono pharmaceuticals. The present article covers findings about the effects of biorhythms on various disorders, and their implications for drug therapy and also the design of novel chrono pharmaceutical drug delivery systems that might be able to release the therapeutic agents at predetermined intervals.

INTRODUCTION: Chronotherapy is the concept of optimizing the timing of drug administration according to target receptor/gene expression to maximize therapeutic efficacy and minimize the side effects. Chrono is derived from the Greek word *khrono* which means time. Hence, chronotherapy aims to reset a deregulated circadian rhythm (biological clock) of an individual to normal sleep/wake cycles. Increasingly, chronotherapy also refers to administering medications in accordance with circadian rhythms to achieve optimal effects along with reducing unwanted side effects in the body (treatment scheduling).

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Recently; chronotherapy has received increased attention because of a deeper understanding of the importance of circadian rhythms in health and diseases for humans. In multicellular organisms including humans, cellular oscillators in the brain and peripheral tissues interconnect to form a circadian network that coordinates rhythms in physiology and behaviors such as sleep-wake, body temperature, blood pressure, hormone production, neural, and immune systems [1].

Modern lifestyles often lack regular patterns of working, eating, and sleeping. The subsequent rhythm disruptions increase susceptibility to cardio-metabolic, digestive, immune, neuropsychiatric disorders, as well as cancers, reflecting the adaptive benefits of circadian rhythms [2, 3]. Rhythms of life: circadian disruption and brain disorders across the lifespan [4]. Studies with animal models containing genetic mutations of clock genes, or animals exposed to circadian

desynchrony regimens, reinforce the causal relationship between circadian disturbances and pathology [5-7]. In addition to the pathological impact of circadian disruption, symptoms of several medical conditions, including neurological (e.g. epilepsy), cardiovascular (e.g. high-blood pressure, myocardial infarction, stroke), and inflammatory disorders (e.g. asthma, sepsis, rheumatoid arthritis), show time of day variations [8-10]. The mechanisms, in some cases, may be due to rhythmic expression of disease genes and in other cases due to cycling in other aspects of physiology. Moreover, responses to physiological and pathological stimuli such as diet, exercise, and pathogenic infections often show circadian rhythms [11-13].

Given the links between circadian dysregulation and pathology, investigators have sought ways to enhance circadian rhythms for disease treatment, by targeting the circadian clock with non-pharmaceutical interventions such as bright light, time-restricted feeding, or exercise. The fact that target genes of many medications are expressed rhythmically also provides a molecular rationale for timed drug treatment to increase effectiveness and reduce toxicity. These drugs may directly target clock genes or molecules that cycle under the control of the clock "output molecules" (14 Hawley *et al.,* 2020; .15 Miller and Hirota, 2020; 16 Borrmann *et al.,* 2021; 17Rogers *et al.,* 2021.). On the other hand, some drugs can alter or disrupt circadian rhythms [14-17].

The objective of chronotherapy is to optimize medical treatments taking into account the body's circadian rhythms. Chronotherapy is referred to and practiced in two different ways:

- To alter the sleep–wake rhythms of patients to improve the sequels of several pathologies;
- To take into account the circadian rhythms of patients to improve therapeutics.

Chrono pharmaceutics includes pharmaceutical application of "Chronobiology" in drug delivery. Chronobiology is the study of biological rhythms **Fig. 1** and their responses to other metabolic functions of body. There are three types of mechanical rhythms in our body:

Circadian rhythms: The term "circadian" was obtained from Latin words "circa" meaning "about" and "dies" meaning "day". Oscillations in our body that are completed within 24 hours are termed as circadian rhythms.

Ultradian Rhythms: Oscillations that are completed in a shorter duration of less than 24 hours are termed as ultradian rhythms (more than one cycle per day).

In Radian Rhythms: Oscillations that are completed in more than 24 hours are termed as in radian rhythms (less than one cycle per day).

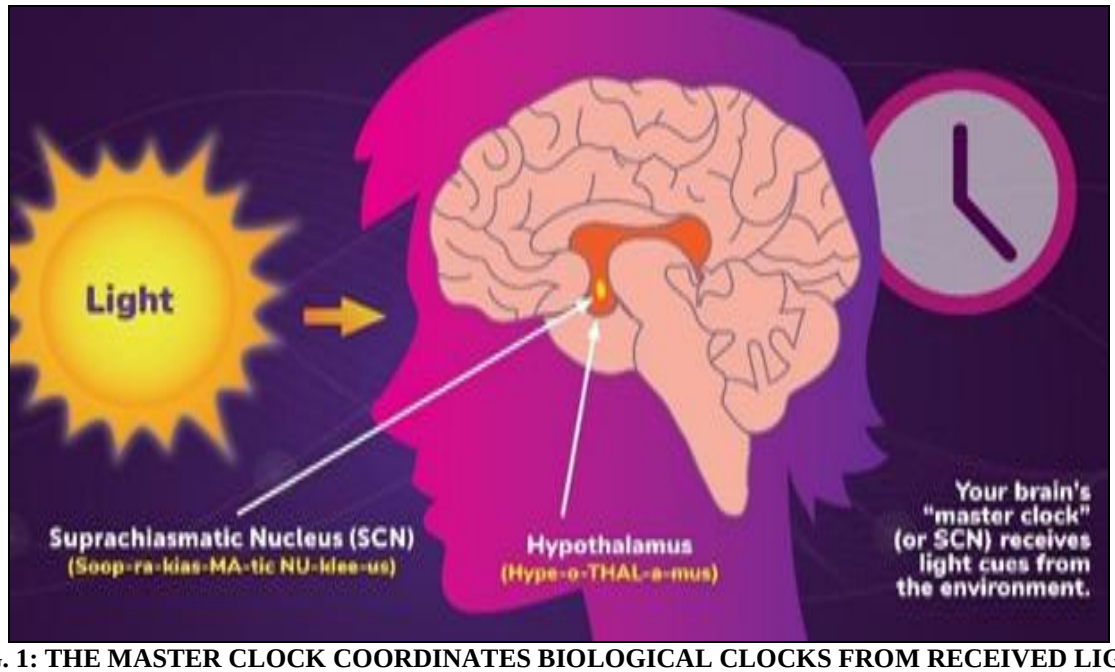

FIG. 1: THE MASTER CLOCK COORDINATES BIOLOGICAL CLOCKS FROM RECEIVED LIGHT

Circadian Rhythm: All living beings have an approximately 24 hour light/dark cycle that maintains biological processes, which is known as the circadian rhythm. In humans, the circadian rhythm is maintained by an internal biological clock (also known as the circadian clock) in the hypothalamus region of the brain. The circadian rhythm, whilst being produced by the internal biological clock, is also entrained by external environmental signals, such as daylight. Natural factors in our body produce circadian rhythms. For humans, some of the most important genes in this process are the Period and *Cryptochrome* genes. These genes code for proteins that build up in the cell's nucleus at night and lessen during the day. Studies in fruit flies suggest that these proteins help activate feelings of wakefulness, alertness, and sleepiness. However, signals from the environment also affect circadian rhythms. For instance, exposure to light at a different time of day can reset when the body turns on *Period* and *Cryptochrome* genes.

Circadian rhythms can influence important functions in our bodies, such as:

1. Hormone release
2. Eating habits and digestion
3. Body temperature

However, most people notice the effect of circadian rhythms on their sleep patterns. The suprachiasmatic nucleus (SCN) controls the production of melatonin, a hormone that makes you sleepy. It receives information about incoming light from the optic nerves, which relay information from the eyes to the brain. When there is less light for example, at night the SCN tells the brain to make more melatonin so you get drowsy. Changes in our body and environmental factors can cause our circadian rhythms and the natural light-dark cycle to be out of sync. For example:

1. Jet lag or shift work causes changes in the light-dark cycle.
2. Light from electronic devices at night can confuse our biological clocks.

Various forms of Chronotherapy:

Dazzling Light Therapy: It entails being exposed to 10 to 90 minutes of intense fluorescent illumination each morning from a specially made light box. While receiving therapy, patients are allowed to engage in other activities like reading. Although it is quite easy to give, each person may require a different light dosage and treatment time of day [3]. The first-line therapy for seasonal mood disorders is bright light therapy [18]. With only moderate success, it has also been used to treat non-seasonal depression.

Wake Therapy/ Sleep Deprivation Therapy: It entails alternating nights of recovery sleep with periods of full sleep deprivation for one to three cycles (the entire night and the following day) [19]. Wake therapy and sleep restriction therapy were introduced in the 1970s, and this was a big advancement because it quickly reversed depressed symptoms (within 24 hours). Since, then, numerous studies have documented the effectiveness of this treatment in reducing depressed symptoms; it seems to be beneficial for 40–60% of patients.

Ahead of Sleep Therapy: A normal sleep/wake cycle (for example, 11 pm to 7 am) must first be obtained and maintained before bedtime and wake time are advanced (for example, from 5 pm to 12 am midnight). Both patients using antidepressants and those not have had success with this therapy when combined with wake/sleep deprivation therapy. In individuals with delayed sleep phase disorder (DSPD), sleep phase advance therapy has also been found to reset the circadian clock. These individuals have trouble falling asleep around midnight and having trouble getting up in the morning.

Triple Chronotherapy: To assist alleviate depression symptoms quickly and effectively, triple chronotherapy combines bright light therapy, sleep restriction therapy, and sleep phase advance therapy. In a human research, triple chronotherapy was used to treat 13 individuals who did not react to antidepressants and experienced a quick reduction in depressed symptoms. The triple chronotherapy had no apparent short-term adverse effects in these patients. In a pilot research with 10 intensely suicidal depressed individuals, triple chronotherapy also decreased depression and suicidal symptoms. These studies only involve a tiny number of participants, despite their promise.

The advantages of triple chronotherapy need to be established through larger, well-designed research.

Chronotropic System Design: To create chronotropic systems that produce the appropriate drug-release profile in a pulsatile manner, numerous approaches have been devised.

Time-dependent Chronotropic Systems with Timed Releases: These kinds of devices display an abrupt medication release following a specified lag time. These systems can be further divided into the following subtypes based on the design approaches used.

Reservoir Systems with Reputable Polymer Coating: These systems can have an exterior rupturable barrier and be either single units or multiparticulate reservoir systems. When water enters the systems, a hydrostatic pressure builds up that causes the surrounding polymeric layer to rupture, releasing the drugs from the system's core. Swelling agents, gas-producing effervescent agents, or osmogenes can all be used to create the pressure needed to rupture the covering. Depending on the type of medicine, the drug's release mechanism is dependent on either diffusion or dissolution. Both kinds of dose formulations include an osmotic agent, a super disintegrant, and the medicine itself. The cores are then sealed with a top water-insoluble semipermeable layer that serves as a rate-controlling membrane for water inflow into the osmotic core and a protective polymeric rupturable layer.

Chronotropic Systems Dependent on Changed Membrane Permeability: Drug release in these kinds of systems is accomplished by altering the permeability of the polymeric coating layer in the presence of specific counterions in the surrounding media. A pulsed-release device was created by Narisawa *et al.* in response to changes in the Eudragit RS's diffusion properties. They investigated and supported the finding that theophylline cores coated with Eudragit RS release the drug very slowly when placed in pure water, but significantly more quickly when submerged in an organic acid solution containing succinic acid, glutaric acid, tartaric acid, malic acid, or citric acid.

Reservoir Systems with Soluble/Eroding Polymer Coating: The thickness of the coating layer in these systems regulates the amount of time before medication release. The lag time before drug release will depend on the thickness and viscosity grade of the HPMC layer in a chronotropic system that comprises of a drug-containing core layered with HPMC and a top layer of enteric coating. A high degree of drug solubility relative to dose is necessary for quick release of drug following the lag period since the drug release mechanism in these sorts of systems is dissolution.

Low Density/Floating Systems: These methods use low density, floating, pulsatile dose forms that are kept in the stomach for lengthy periods of time (four to twelve hours), unaffected by changes in the immediate environment or the rate at which the stomach empties. These dosage forms can either be single units (floating tablets) or multiparticulates (beads, pellets, granules, and microspheres) with the capacity to bind to the stomach. These systems are particularly helpful for medications that are either absorbed from the stomach or need local distribution in the stomach **Fig. 2**. Polysaccharides are typically well accepted in gastro retentive delivery systems due to their ease of formulation and ability to create the required drug release profile.

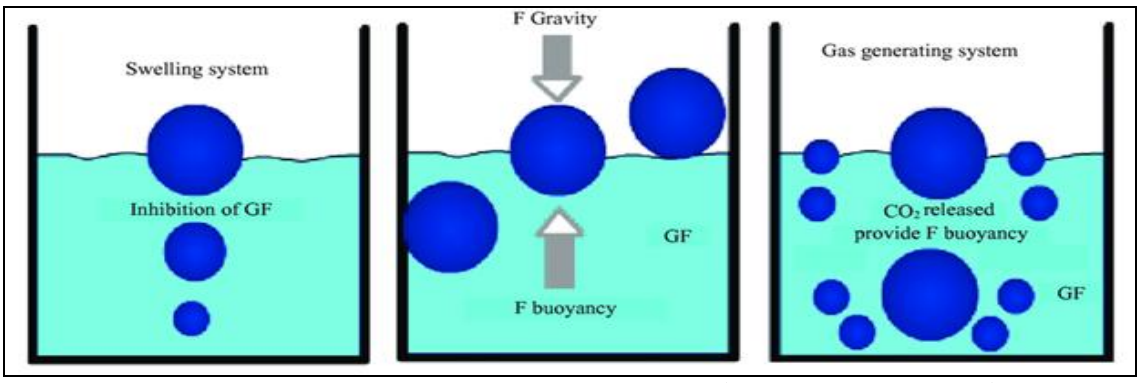

FIG. 2: MECHAISM OF FLOATING OF BEADS (GF=GASTRIC FLUID)

Systems that Depend on External Stimuli (Pulsatile Drug Delivery Systems): Pulsatile drug delivery systems are essentially time-controlled drug delivery systems where the system manages the lag time independent of environmental element such as Ph, enzymes, gastro-intestinal motility, *etc*. Drugs typically release in an immediate or gradual manner.

Temperature Sensitive Pulsed- Release Delivery Systems: Due to the numerous metabolic processes that each type of cell in the body performs, their physiological temperatures vary. When compared to other cells, some cells, such as tumor cells, have slightly differing temperatures (either higher or lower), with their cellular temperature being raised as a result of their greater metabolic rate. By utilizing a thermo-responsive hydrogel technology, a pulsatile drug delivery system for tumor targeting can be created.

Inflammation Induced Systems: A stimulus is any physical or chemical stress (injury, fracture, *etc*.) that may cause inflammation because it releases hydroxyl radicals from cells that are sensitive to inflammation. To support this, Yui and colleagues developed an inflammation-responsive pulsatile drug delivery system that reacted to hydroxyl radicals and degraded in a controlled way.

Instead of using normal tissue, they used hyaluronic acid, which is specifically degraded by hyaluronidase or free radicals present at inflammatory sites in abundance. Thus, the use of Non-steroidal anti-inflammatory medicines (NSAIDS) mixed with hyaluronic acid gels as a new implantable drug delivery system made it possible to treat patients with inflammatory disorders like rheumatoid arthritis.

Enzyme Dependent Pulsatile-Release Systems: Since, the rate of drug release is reliant on the catalysis of polymeric membrane by enzymes generated by colonic micro flora, such devices are often developed for colonic administration of drugs. Due to the fact that these systems are independent of pH shifts along the gastrointestinal track, they are more precise for targeting.

Glucose Concentration Dependent Insulin Release Systems: Different systems that responded to changes in glucose concentration were created. A pH-sensitive hydrogel with glucose-oxidase enzyme bound in it is one of these stimuli-induced systems. Glucose-oxidase turns glucose into gluconic acid as blood glucose levels rise, which alters the pH of the system.

pH Sensitive Pulsatile Drug Delivery Dystems: The most popular and adaptable method to achieve a desired lag time before medication release in a chronotropic system is pH dependent polymers.

They provide a consistent and predictable drug release profile whether they are single-unit or multiparticulate dose forms. These systems benefit from the fact that the pH environment varies depending on where in the digestive tract you are.

Dosage forms used for Chronotherapy: For desired medication release, a number of commercially accessible chronotherapeutic drug-delivery methods have been created. They are given in the evening and postpone the release of the medications until the morning hours, when the disease symptoms are the worst.

The importance of parenteral chronotropic systems is growing. The insulin pump, which is used to inject insulin for the treatment of diabetes mellitus, is the application that is utilized the most frequently. Another example of a chronotherapeutic system is time-scheduled intravenous infusion regimens for cytotoxic drug administration.

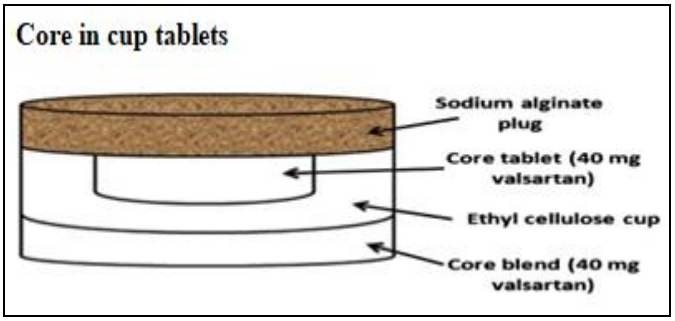

FIG. 3: CORE IN CUP TABLETS

These systems consist of an impermeable outer shell, a top cover layer-barrier made of a soluble polymer, and a core tablet containing the active substance **Fig. 3**. The medication release is caused by the cover layer eroding.

Compression Coated/Press Coated Tablets: By press-coating or compression coating, formulations with delayed release and intermittent release can be

produced. **Fig. 4** These systems employ hydrophilic derivatives of cellulose. The main downsides of this method include the necessity for relatively large amounts of coating ingredients and the challenge of positioning the cores accurately throughout the coating process. A diltiazem hydrochloride formulation was created by to be used in the treatment of hypertension and ischemic heart disease symptoms that worsen with time. The tablet is made up of a core that carries the medication and a coat made by compressing hydroxyethyl cellulose. The findings indicate that diltiazem was rapidly released following a several-hour delay.

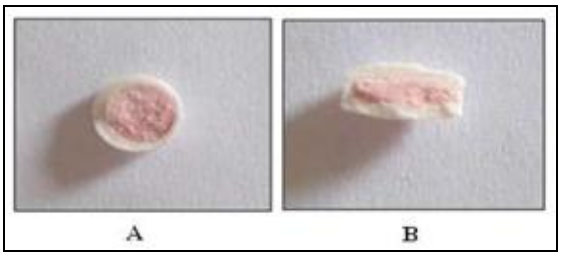

FIG. 4: VIEW OF TABLET-IN-A –TABLET TECHNOLOGY COMPRESSION COATED/PRESS COATED TABLETS

Double Coated Hard Gelatin Capsules and Double Coated Tablets: These are rupturable pulsatile drug delivery systems in form of hard gelatin capsules or tablets which releases the drug in time-controlled manner. Capsules are filled with active pharmaceutical ingredient either for single pulse or multi-pulse release (in form of multiparticulates) and coated with a swelling layer followed by an external water insoluble semipermeable polymeric coating **Fig. 5**. A threshold hydrodynamic pressure due to water absorption is required to rupture the outer coating (rate controlling step) and allowing the release of contents in surrounding medium and fulfills the purpose of desired lag time required in chronotherapy of disease.

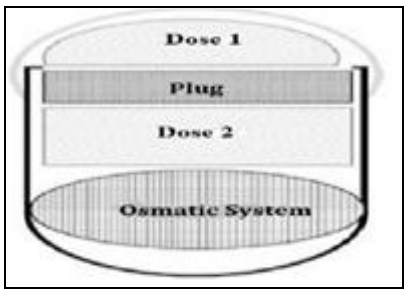

FIG. 5: DOUBLE COATED HARD GELATIN CAPSULES AND TABLETS

Chrono Modulating Infusion Pumps: These systems have a drug-containing core that also comprises a disintegrant (low bulk density solid or liquid lipid substance). A polymer made of cellulose acetate coats the core. Water seeps into the system's core and pushes the lipid material out when it comes into touch with it. When lipid material is depleted, internal pressure builds up until a threshold stress is reached, which leads to coating rupture and medication release for chronotherapeutic applications **Fig 6**.

FIG. 6: OPTIMIZING CHEMOTHERAPY WITH SMART INFUSION PUMP: ADDRESSING CLINICAL NEEDS FOR CHRONO-CHEMOTHERPY

Pulsincap Systems: Pulsincaps are made up of a medication that is sealed with a hydrogel plug, a water-insoluble body, and a water-soluble cap **Fig. 7**. The medicine is released into the small intestine or colon once the enlarged plug is removed from the capsule at a predefined period after ingestion.

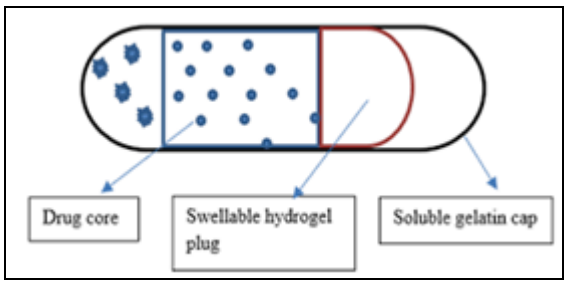

FIG. 7: OVERVIEW ON PULSATILE DRUG DELIVERY SYSTEM

Controlled-release Microchip: A microchip device has the capacity to store one or more compounds inside of it in any form (solid, liquid, or gel), with the compounds being released as needed. Each reservoir on the microchip is protected by a thin membrane made of a substance that acts as an anode in an electrochemical reaction **Fig. 8**. On the chip's surface, there are additional electrodes that operate as cathodes in an electrochemical reaction. Each reservoir is loaded with a substance that will be released. An electrical voltage of around 1 volt is placed between the anode covering a reservoir and a cathode when release from that reservoir is needed.

Electrochemistry causes the anode membrane to disintegrate. Now that this reservoir is open,

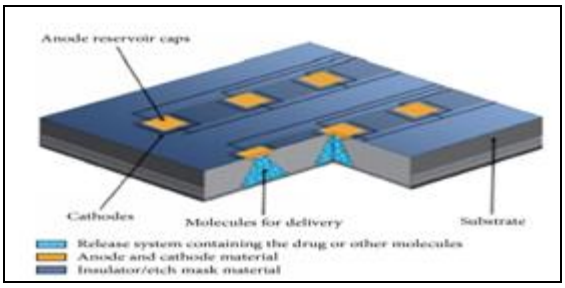

FIG. 8: MICROCHIP TECHNOLOGY IN DRUG DELIVERY

Hydrogels as Carriers in Chronotherapeutic Systems: Due to their physicochemical and biological characteristics, hydrogels are exploited as chronotherapeutic carriers. Three-dimensional structures called hydrogels have a high water absorption capacity. They are made of hydrophilic polymers that can swell. Hydrophilic group-containing hydrogels swell to a significant extent. Changes in swelling medium parameters such as temperature, ionic strength, and pH can all have an impact on the swelling of stimuli-sensitive hydrogels. Both diffusion-controlled (Fickian) and relaxation-controlled swelling are possible in hydrogels. The creation of chronotherapeutic delivery systems involves the use of a variety of hydrogels, such as stimuli-sensitive hydrogels, temperature-sensitive hydrogels, hydrogels that respond to physical stimuli, like light, magnetic field sensitive hydrogels, hydrogels that respond to chemical stimuli, analyte-sensitive hydrogels, *etc*.

Emerging Science of Chronotherapy [20]: Chronotherapy is not a cure-all and is not appropriate for all treatments or illnesses. However, it might present a vital route for sharpening and even enhancing several treatments. The extensive influence of circadian rhythms on physiology highlights the need of applying two main strategies to convert mechanistic understandings into therapeutic practice. First, it is important to raise people's knowledge of how rhythm disturbances caused by environmental and physiological factors affect physiology and make people more susceptible to disease **Fig. 9**. A treatment strategy that considers circadian control is the second field of medicine that should be created in light of circadian insights **Fig. 9**. In this analysis, we divide chronotherapeutic methods into two groups: (1) Targeting clocks; using non-pharmaceutical or pharmaceutical methods to influence circadian rhythms or other circadian components; (2) Clocks.

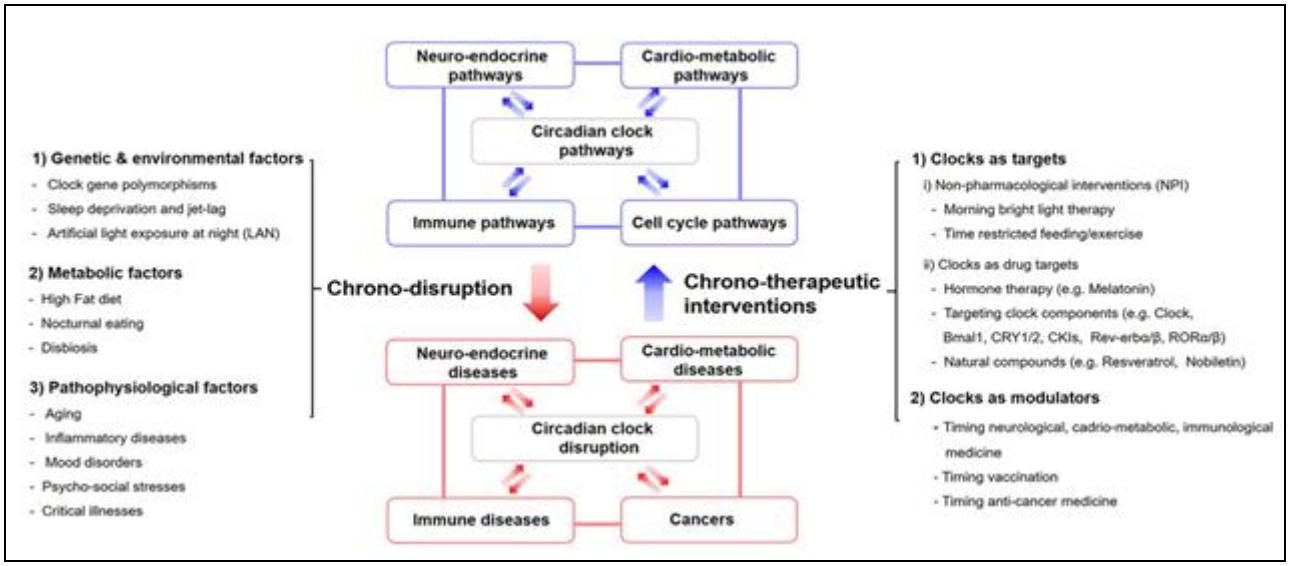

FIG. 9: CIRCARDIAN-DISRUPTIVE FACTORS AND CHRONOTHERAPEUTIC INTERVENTIONS IN PHYSIOLOGY AND DISEASE. ABBREVIATION: CRY=CRYPTO CHROME; ROR=RECEPTOR-RELATED ORPHAN RECEPTOR.RECIPROCAL INTERACTION OF CIRCADIAN CLOCKS WITH OTHER PHYSIOLOGICAL PATHWAYS CONSTITUTE SYSTEMIC CIRCARDIAN PHYSIOLOGY .MULTIPLE FACTORS THAT DISRUPT CIRCADIAN RHYTHMS CAN INCREASE THE RISK OF DISEASE ONSET AND SEVERITY, WHICH IN TURN FEES FORWARD TO CAUSE MORE CHRONO- DISRUPTION. CONVERSELY, SEVERAL TYPES OF CHRONO -THERAPEUTIC INTERVENTIONS CAN BE IMPLEMENTED TO ENHANCE OR RESTORE CIRCADIAN RHYTHMS AND THEREBY REDUCE DISEASE PROGRESSION AND IMPROVE THE RESPONSE TO TREATMENT; CKI=CASEIN KINASE 1

Clocks as Target: The circadian system composed of the brain and peripheral clocks can be synchronized through a wide variety of environmental and systemic cues such as light, feeding, hormones, and exercise. Exploiting such rhythm synchronizers can enhance body clock functions, thereby improving circadian rhythms and perhaps reducing susceptibility to diseases that are particularly sensitive to internal desynchrony.

Enhancing Circadian Rhythms to Improve Health: Circadian rhythms can be enhanced through non-invasive interventions such as bright light or scheduled meal times, making them an ideal target for improving basic health and fitness, in other words, preventive medicine.

Chrono-Phototherapy: Light is the most well-established means to entrain circadian rhythms, although no specific treatment or light device is FDA approved. Morning bright light exposure, has been widely touted as a way to treat sleep disorders (e.g. advanced or delayed sleep phase syndromes), neuropsychiatric disorders (e.g. autism spectrum disorder, attention deficit hyperactivity disorder, seasonal affective disorder, dementia), associated with genetically, environmentally, and pathologically perturbed circadian rhythms.

Chrono-Diet: Restricting food intake to a specific daily interval synchronizes some peripheral clocks and has become a popular way to improve metabolic health. The health benefits of clock-modulating diets have been increasingly recognized as has the dynamic cross-talk between circadian clocks and metabolic pathways.

Clock-enhancing Diets and Cancer: In addition to anti-aging benefits, preclinical evidence indicates that CR may have anticancer effects by reducing tumor progression, enhancing the death of cancer cells, and increasing the effectiveness and tolerability of chemo and radiotherapies.

Chrono-exercise and Aging: As with TRF, exercise is gaining attention as a potential chrono-therapeutic intervention in the prevention and treatment of multiple diseases.

Chrono-exercise and Metabolic Health: Skeletal muscle has an intrinsic circadian clock that is critical for regulating metabolic activity.

Future Perspectives: Despite the significant progress made in the study of circadian rhythms and chronotherapy, there are still significant informational gaps between patients receiving care, community pharmacists, and doctors regarding prescription-related details, awareness of circadian rhythms, application, and attitudes toward the use of chronotherapy in practice [21, 22]. In order to effectively apply this therapy in the clinical setting and maximize patient benefits, physicians and community pharmacists might both play crucial roles in supplying patients with the right information on the best dose intervals. Notably, by using novel drug delivery techniques, such as modulating drug release in a pulsatile fashion (delivery of an immediate pulse of drug after a delay, ensuring that the maximum amount of the drug is released at the appropriate timing), or by maintaining the necessary drug concentration.

CONCLUSION: For this therapy to work, the internal circadian timing must be accurately characterized. The future of this therapy will therefore be determined by improvements in biological time measurement technology, general assessments of circadian rhythmicity, and the appropriate application of this rhythmic variable to predict biological times. In circadian research, the use of machine learning algorithms in conjunction with predictive mathematical models of regulatory networks may make it possible to more effectively use and extrapolate biological data as well as uncover predictive circadian factors. The discovery of biomarkers inside genes that are expressed during the circadian cycle may be made possible by this information, which may then be applied to precisely estimate when to administer drugs to treat various disorders [23].

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CONFLICTS OF INTEREST: Nil

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