



REVIEW ARTICLE

NOVEL DRUG DELIVERY SYSTEM

**CHRONOTHERAPY- CLOCK OF CURING**

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**ABSTRACT**

The present review deals with treatment to various disorders with normal body rhythms like Ultradian, Circadian, Infradian & Seasonal. The basics of Chronotherapy and its advantages and disadvantages following the marketed technologies for the drug-chronotherapy are focused. The rational therapy to various diseases like: Hypertension, Bronchial asthma, Peptic ulcers, Myocardial infarction, Arthritis, Cerebrovascular accidents & Hypercholesterolemia by Chronotherapy is also enlightened. The regulatory concern on Chrono-Pharmaceuticals is glanced.



## KEYWORDS

ChronoPharmaceuticals, Bio-rhythms, Chronotherapy & Chronotherapeutics.

## INTRODUCTION

The treatment of the disease to the fullest not only depends on the medicine but it also depends on the time and month of administration. The action of body defense system depends on the various factors like age, gender, genetics etc. Some people of the medical community recently studied about the role of biological rhythms against diseases. These rhythms of our body clocks are called as biological clocks<sup>1</sup>, which change with the environment. These biological clocks are also controlled by our genetic makeup. These clocks are responsible for the changes in our body throughout the day like blood pressure, blood coagulation, blood flow and other functions of the body<sup>2</sup>.

There are some other rhythms<sup>3, 4, 5</sup> which affect our body such as

**Ultradian:** these are the cycles shorter than a day. Ex: 90 minutes sleep cycle

**Circadian:** This lasts for over 24 hours. Ex: sleeping and waking patterns.

**Infradian:** cycles longer than 24 hours. Ex: monthly menstruation

**Seasonal:** such as *seasonal affective disorder (SAD)*, this causes depression during the short days of winter in susceptible people.

### CHRONOTHERAPY

Chronotherapy refers to the treatment of biological rhythms coordination. It deals with chronobiology. As nature has its seasons which changes rhythmatically, likewise every person's body has its own rhythms which are governed either by genetics or by the environmental changes. By determining these biological rhythms of a person one can increase or decrease the dose of the drug thereby avoiding the unwanted effects of the particular drug.

### CIRCADIAN RHYTHMS

As mentioned above human body consist of a 24 hour in-built cycle, these are called Circadian rhythms. Researchers had found out that these circadian rhythms are useful for the treatment of various pathophysiological conditions of human body.

### CHRONOTHERAPEUTICS

Chronotherapy refers to the treatment which works in accordance with the bodies biological rhythms which are known to be natural. And the study of treatments of such a kind is called chronotherapeutics.

### DRUG CHRONOTHERAPY

Drug chronotherapy is not the usage of the novel medication but it's the use of the old drugs in a different way. The main aim of this drug chronotherapy is to use the old drug differently which gains more results. It includes either revising the drugs profile and reformulating it in such a way that it got the delayed release into the blood stream or using the additional pumps which help in the delayed release. Such changes are made to get the enormous benefits<sup>6</sup>.

### Advantages of Chronotherapy<sup>7</sup>

- Chronotherapy is drug-free
- Chronotherapy is more effective when a person sleeps for several hours.
- While Chronotherapy patients often fall asleep this improves their condition and confidence as well.
- Chronotherapy is different from other treatments because it got the beginning, middle, and an end. So one can predict easily the point at which it will work.
- It gives you a new schedule like getting up and sleeping early which will be quite unusual for some days but it will give u a period to adjust psychologically.



### **Disadvantages of Chronotherapy<sup>8</sup>**

- It develops a non 24 hours sleep wake syndrome after the treatment as the person sleeps for over 24 hours during the treatment. It's not quite common but the degree of risk is not known.
- Person may also be sleep deprived sometimes.
- Person become less productive during chronotherapy and staying awake till the other schedule will be bit uncomfortable.
- You will have to take some time off from your busy normal schedule as its time taking therapy.
- Medical supervision is mandatory for this therapy. And regular consulting of sleep speacitists is recommended.
- One has to keep himself awake till the next sleep schedule.so he have to get himself busy so that he stay awake till the other schedule.
- Person going through the therapy may feel unusually hot or cold sometimes.
- Have to consult the doctor regularly to avoid side effects

### **MARKETED TECHNOLOGIES:**

There are various types of pharmaceutical technologies used for the preparation of drugs for chronotherapy<sup>9, 10 & 11</sup>. Technologies used for the parenteral route in chronotherapy include the use of chrono modulating infusion pumps (Panomat™) and controlled release microchip strategies. And technologies used for oral administration are-Ceform™. There are other methods like three dimensionalprinting (3dp) which includes usage of erodible polymers for the controlled release and changing the physiochemical properties of the drug. The most recent was the floating pulsatile system using high internal phase emulsion based porous material for chronotherapy<sup>12</sup>. Low density floating multiparticulate pulsed-release dosage forms are also available<sup>13</sup>. The desired release of ranitidine hydrochloride from the tablet with a coating successfully explains the combined principles of floating and pulsatile used in chronotherapy<sup>14</sup>. Many marketed products in the form of transdermal drug delivery system

having chronopharmaceutical applications are available<sup>15</sup>; some of them are ChronoDose™, crystal reservoir<sup>16</sup> and thermo responsive membrane systems<sup>17</sup>. For rectal route-aminophylline delivery system was reported and many novel chronopharmaceuticals has been used for this purpose<sup>18</sup>.

### **CHRONOTHERAPY IN VARIOUS DISEASES<sup>19</sup>**

Like our body has an inbuilt 24 hour cycle in the same way some diseases will also follow the circadian patterns, chronotherapy is very useful in treating such type of diseases by adjusting the dose and the time of drug administration according to the circadian rhythms. The following is the list of some diseases which can be more significantly cured by chronotherapy

- Hypertension
- Bronchial asthma
- Peptic ulcers
- Myocardial infraction
- Arthritis
- Cerebrovascular accidents
- Hypercholesterolemia

#### **Hypertension**

Heart rate and blood pressure will be high at the time we wake up in the morning i.e. A.M and it will begin to decrease in the afternoon and it reaches to the minimum at midnight<sup>20, 21</sup>. But the blood pressure is comparatively high in case of hypertension patients upon awakening. This physiological condition is described as morning surge or A.M. surge<sup>22</sup>. The systolic blood pressure rises up to 3mmHg/hour for 4-6 hours after getting up called post-awakening and the diastolic blood pressure also rises up to 2mmHg/hour<sup>23</sup>.

#### **Myocardial Infarction**

The release of the catecholamine's, cortisol, increase in platelet aggregation and the vascular tone will be high in the morning. These are the main reasons for the outburst of the myocardial infraction in the morning with 34% events taking place from 6 A.M till noon. Acute cardiac arrest and transient



myocardial ischemia takes the lead as well in the morning<sup>24, 25</sup>.

### **Cerebrovascular accidents**

Cerebrovascular accidents are more common in the morning hours between 10A.M to 12 noon and it will decrease considerably from noon to midnight. The main aim of chronotherapy in these conditions is to deliver the drug in the higher doses in morning and little lower dose at noon and in midnight times. Various ACE inhibitors like Atenolol, Nifedipine and amlodipine are more effective when administered during night<sup>26</sup>.

### **Bronchial asthma**

Asthma have the more circadian variations when compared to the other diseases.so various chronotherapy studies have been undertaken and one of the study shows that the intake of the time released theophylline i.e. theo24 at 3 P.M achieved a therapeutic dose at night and the toxic levels during the day was avoided<sup>27</sup>.

### **Arthritis**

According to the chronotherapeutic studies the more desirable results has been achieved for rheumatoid arthritis when the dose was given in the evening.

Cyclooxygenase inhibitor-2 will relieve the pain effectively when taken in the morning<sup>28</sup>

### **Peptic Ulcer Disease**

A histamine antagonist when given at night shows the better result unlike when given at regular intervals around the clock. This is because the more acid secretion, more pain and perforation of gastric and duodenal ulcers are more subjective at night rather than in day time<sup>29</sup>.

### **Hypercholesterolemia**

The morning doses were recommended at first for HMG CO-A inhibitors but after the discovery of circadian rhythms the profile was reevaluated and the evening doses were recommended as the cholesterol intake and cholesterol biosynthesis is more in the evening hours even in fasting state<sup>30</sup>

### **REGULATORY CONCERN**

Although the chronopharmaceutical products are more useful over the normal products they are some regulatory problems, this is because the MR formulations have a unique challenges from the normal formulations and manufacturing. They require a more precise drug profile and characterization for the controlled release delivery<sup>31</sup>

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