Chronotherapy in clinical practice: A review.

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Abstract

The body functions are controlled by the circadian clock; later it was discovered that the pathological condition of several diseases also exhibited certain rhythm in the body. Based on this, chronotherapy was introduced targeting the administration of a drug according to the biological rhythm of the body function as well as the pathological rhythm of the disease condition. Conclusively, Chronotherapy has the advantage of minimizing the drug's side effects and also decreasing its dosing frequency. In addition research is still ongoing towards advancements in drug formulations to deliver the drug in time and rate controlled manner. Profoundly, comprehensive studies are recommended for developing a structural individualize chronotherapy approach.

Keywords: Circadian clock, Chronotherapy, Bright light therapy, Sleep deprivation therapy, Chronotherapeutics, Chrono-drug delivery.

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Introduction

The circadian rhythm controls all biochemical processes and functions of the body and the pathological state of disease conditions follows this rhythm for diseases like asthma, cancer, hypertension, rheumatoid arthritis, and depression.

The chronotherapy is the administration of a drug or treatment to provide maximum therapeutic effects with minimum adverse effects by analysing this pattern and administering drugs according to circadian rhythm [1].

In clinical practice, chronotherapy in is an emerging area in the health system where health professionals aim at treating patients, according to the biological rhythm of the disease condition. In contrast to the conventional therapy of prescribing frequent doses of medication, chronotherapy focuses on the apt delivery of drugs to the target site at the right biological time [2].

A new development in chronotherapeutic approach is, the time and rate controlled delivery technologies of drugs, which are developed to mimic the biological pulsatile delivery of substances into the body at the target site.

These include pulsatile and press-coated technology for infusion and oral dosage forms respectively. Novel technologies like targeting rhythm engineering and modelling, rhythmic biomaterials and system design are currently the blooming area of chronotherapy [2, 3].

This review discus in depth about the importance of chronotherapy in various diereses management; it's present and future trends.

Literature Review

Circadian clock

All living organisms have a biological rhythm; the fundamental feature of life is controlled by an internal clock in the body called the circadian clock. The word circadian meaning circa-around, dien- day, and circadian rhythm is an 'around-the-day rhythm' which is controlling all biochemical processes are in the body. Apart from a 24 hour pattern, Ultradian rhythm (<24 hour) and Infradian (>24 hour) patterns are also seen in the biological processes present in the body [4]. The circadian rhythm is controlled by a central pacemaker called Suprachaismatic Neuron (SCN) locate in the hypothalamus. This internal pacemaker is responsible for the biological processes at the cellular level which includes processes like sleep-wake cycle, glucose, lipids and drugs metabolism, immunological process, bone formation, hormone regulation, timing of the cell-division cycle, and the physiological rhythms such as heart rate, blood pressure and body temperature. Unfortunately, the disturbances in the rhythm of these processes can develop several diseases like sleep problems in the elderly, Familial Sleep disorder (FASPS) and possibly cancers [4, 5, 6].

The clock genes that influence the oscillation are:

- Per (Period) gene
- Cry (Cryptochrome) gene
- Bmal (Brain and muscle ARNT- Aryl hydrocarbon receptor nucleus translocator) like protein
- CLOCK (Circadian Locomotor Output Cycles Kaput)
- ROR (Related Orphan Receptor)
- Rev-Erb (Nucleus receptor, reverse strand of ERBA gene)

The interaction among the genes is done through a positive and negative transcriptional and translational feedback loop. Ordinarily, gene interaction starts from the beginning of the circadian day by the formation of a heterodimer complex called, BMAL/CLOCK this complex then attaches to the two large interconnected loops. One of these interconnected loops is known as Per/Cry (PC) loop, which constituting two genes such as Per and Cry genes; the other one is RoR/REV-ERB/ Bmal (RBR) loops constituting three genes. Basically, these genes get translated into subsequent proteins; accordingly, the Per/Cry complex protein inhibits the CLOCK/Bmal-1 mediated transcription and regulates the expression of all core clock genes, subsequently, it does bringing the process to the end for completing one rhythm. Conversely, the robustness of the second loop-RBR loop was identified recently, which it's also capable to generate oscillation in the body clock [4, 5, 6].

Chrontherapy in depression

Depression arises due to the abnormal levels of adrenocorticotropic hormone and cortisol secretion, which ultimately brings variations in sleep/wake patterns and the daily frame of mind. Basically, the biological rhythm drives and synchronizes hormone secretion, neurotransmitters, and body temperature in daily pattern. Chronobiological disruption in depression is characterised by altered food intake, memory dysfunction, stress-decreased functioning of psychomotor activity, subsequently, these changes in the circadian rhythm lead to neurobiological, behavioural, and loss of internal temporal order [7]. The circadian pacemaker, Suprachaismatic Nucleus (SCN) contains the high concentration of serotonin and melatonin receptors and the imbalance of these neurotransmitter system is one of the reason for depression. The chronotherapy based treatment helps to resolve this imbalance by harmonizing circadian rhythm [8].

The current conventional treatment for depression is antidepressants, the Selective Serotonin Receptor Inhibitor (SSRIs) inhibit the reuptake of 5-HT into the presynaptic neuron which is the first line treatment. Tricyclic antidepressants inhibit the reuptake of nor epinephrine and 5-HT, and has an affinity for adrenergic, cholinergic, and histaminergic receptors. Another class of medications are Monoamine oxidise (MAO) inhibitors, which increases epinephrine, 5HT and dopamine concentrations within the neuronal synapse by inhibiting the MAO [9].

The main focus of chronotherapy is the resynchronization of circadian rhythm by restoring the neurotransmitter system. Moreover chronotherapy treatment has a positive impact on patients experiencing symptoms of depression [10]. Chronotherapy in depression include Sleep Deprivation (SD), Wake Therapy (WT), Sleep Phase Advance (SPA) Light Therapy (LT), and Dark Therapy (DT). These techniques control the exposure to environmental stimuli which influence the circadian clock. Melatonin is an endogenous hormone secreted by the pineal gland, which helps to regulate the circadian pattern according to light and at the signal of darkness. There are melatonin agonists available in the market for its deficiency, namely Agomelatin, Ramelteon and Tasemelteon. Since it possess the rhythm regulating property, it is useful as chronobiotics for the improvement of depressive symptom [11]. Bright Light Therapy (BLT) works based on neurobiological principles and can be used as first line treatment for Seasonal Affective Disorder (SAD) and MDD (Major Depressive Disorder). Normally, BLT use white light intensity of 2,000-10,000 Lux with the time duration of 30-120 minutes per day in the morning and the exposure duration is mainly based on the therapeutic response of patient. Sleep deprivation involves remaining awake for long periods to reduce depressive symptoms, whereas, triple chronotherapy produces a rapid improvement and it involves the combined use of BLT, SD, and SPA [8].

Chronotherapy based lithium salt treatment for bipolar disorder shows better therapeutic effect and long term psychiatric management. The benefits of chronotherapy in depression are its efficacy, rapidity of action, lack of side effects, low risk and cost. Increased use of these techniques may shorten hospitalization, reduce the need for prescription, and increase rate of recovery [12].

Chronotherapy in hypertension

Hypertension account a major risk factor for myocardial infarction and cerebrovascular events, which are presenting a high rate of mortality .The factors which causing fluctuations in BP are classified into two and those are internal and external factors, the internal factors are humoral mediators (melatonin, cortisol, renin, vasoactive intestinal peptide, and atrial natriuretic peptide) and the activity of the ANS . The external factors like stress, shift work, change of time zone determines the daily variability's of BP (blood pressure) like physical and mental activity, emotional state, and food intake. Disruption of circadian rhythm/desynchronization leads to the misdemeanour of basic functions, the development of pathological conditions in the body, and the risk of development of hypertension and cardiovascular diseases. Checking BP during sleep is the best method to forecast CVD (cardiovascular disease) risk and organ damage. The risk factor for CVD and cerebrovascular diseases are in those patients with insufficient and inordinate sleep time relative BP decline or increased BP at night.

According to Kario.et.al, MBPS is the Morning Blood Pressure Surge which can be calculated by two methods, the first method is called the Sleep Trough MBPS, which is the rise in BP during sleep (it is the average of the difference between morning BP and the lowest nocturnal BP). The second method is the rise in BP before awakening called the Prewaking MBPS (It is the difference between morning and reawakening BP) [13]. Target organ damage and cardiovascular events are associated with pronounced MBPS and morning hypertension. Violation of the regulatory mechanism occurs due to the short term BP variability, including emotional stress, exercise like external factors. Short term BP variability is another parameter determined by Ambulatory Blood Pressure Monitoring (ABPM). Under the influence of external factors, the short term BP variability reflects the adaptive capabilities of BP regulation [14].

The Anti-hypertensive drug selection depends on the degree of BP elevation and presence of compelling indications for selected drugs. Angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), calcium channel blockers (CCBs), and Thiazides diuretics are acceptable as first-line options. Beta-Blockers are used to either treat a specific, compelling indication or as combination therapy with a first-line antihypertensive agent for patients without a compelling indication [15].

Individualized chronotherapy of antihypertensive are based on patient chronotype. Hyperperfusion of the internal organ, pronounced MBPS, physiological circadian rhythm impairment of BP with an increased risk in cardiovascular events are all consequences of excessive reduction of BP due to antihypertensives. Majority of physicians have lack of knowledge about how to interpret BP levels at night time during sleep [16].

The effect of Beta-blockers on reducing BP is negligible; nevertheless, a study was conducted on 82 hypertensive patients dividing them into morning and evening groups according to the time of administration of Nebivolol. From the results, it was found that there was no significant reduction in BP between morning and evening groups, though a marked reduction in daily BP readings was seen in the morning group compared to evening group. Contrary to this, the author has an opinion that ingestion of Nebivolol during the evening is the most optimized treatment compared to morning intake, which can prevent the distortion of circadian BP pattern. Later, M.C. Acelajado et al concluded through that Nebivolol has effect on reducing the daily BP readings (morning, evening and 24 hour BP) when ingested in the mornings and evenings and even at night time. In-fact, the night time BP is more dependent on the activity of RAAS system in the body, so taking drugs at bed time is considered efficacious. But then it was found that the deestrification process of the ACE-inhibitors which is activated in the liver reduces metabolism during sleep time which can lead to the delayed activation of ACE-inhibitors [13]. Therefore, this factor should be considered during antihypertensive chronotherapy to optimize the treatment and to get an improved BP control.

Melatonin is an endogenous hypotensive factor which regulates the circadian rhythm, accordingly, in hypertensive patients the use of exogenous melatonin with diminished circadian rhythm is an interest [17].

Moreover, the side effects of antihypertensive drugs can be reduced through a treatment optimization by adapting individual BP chronostructure. Overall, to effectively treat hypertension, the administration time is likely significant in relation with circadian BP rather than changing the drug combination [18].

Chronotherapy in asthma

Asthma is a chronic inflammatory disorder of the airways in which cellular elements play a major role, particularly, the mast cells, Eosonophill's, T-lymphocytes, and epithelial cells. This inflammatory response produces recurrent episodes of airway obstruction, which is characterized by the symptoms of asthma such as breathlessness, wheezing, cough, and chest tightness. The symptoms of the inflammatory disorder often worsen at night and in the early mornings. The array of the damage process occurring in asthma pathogenesis is: Inflammation of the airway, airway obstruction (reversible/ non-reversible) bronchoconstriction, mucus accumulation, airway remodelling, and hyper responsiveness. Apart from these inflammatory cells, inflammatory mediators are involved in asthma, which have an importance contribution in the pathological features of asthma. They are histamine, prostaglandins, and leukotrienes which have the properties of constricting smooth muscles, increased microvascular leakage, mucus secretion, and also in attracting other inflammatory cells [19, 20]. The first line drugs for treating the exacerbation of asthma is beta-2 agonists, which is available as both short-acting and long-acting administered according to the severity of the disease. In severe exacerbation, oral/systemic corticosteroids is the treatment of option and also a promising therapy. Other agents used in treating asthma attacks are anti-cholinergics, leukotriene modifiers, theophylline, mast cell stabilizers and Anti-immunoglobin therapy [21].

The evidence on the association between the circadian rhythm and asthma is recognised after studying the worsening of asthma in inpatients at night. There is a circadian pattern in the airway calibre and inflammation. One of the parameters for detecting airway obstruction is Peak Expiratory Flow (PEF) and its showing fluctuations over a day in healthy individuals and also patients with asthma. In addition, Bonnet & colleagues revealed the circadian variation of airway responsiveness with maximum bronchial responsiveness to methacholine and histamine bronchial challenge, during 3 am and 4 pm. Likewise, there is also a variation in the inflammatory cells present respect to circadian pattern, which is seen higher at 4 am than 4 pm [22].

Explicitly, the asthma attacks usually worsen at night-time compared to the day-time. This variation in the disease severity is due to the changes in the circadian pattern which observed in the lungs function, in both, normal individuals and in asthma patients. The PEF value is higher around 4 pm, but declines at 4 am, subsequently, show a contribution to the asthma attack in the morning time. Moreover, the cortisol level reaches its maximum in day time and has a low level during midnight. This variation is seen in all individuals, but in-fact, the maximum anti-inflammatory effect of cortisol's on the inflamed bronchial airways, makes the difference in asthmatic patients. In addition, the circadian pattern of the sympathetic hormone epinephrine shows increasing in their levels during the noon and decreasing at early morning hours. Since, epinephrine contributes in the airway muscle relaxation and inhibiting the inflammatory mediators from mast cell, likely its circadian pattern will affect the disease control. Overall, considering the rhythms of events in the asthma condition; accordingly, giving the medication with respect to those rhythms variation are apparent reasons to consider chronotherapy in the asthma condition. From the previous studies, it is evident that 4 pm-4 am/3 pm-3 am is the start-end-

point in the event of asthma conditions. The lungs shows very low function level at 4am but independent of treatment the PEF reaches its normal level at 4pm. In this condition, targeting drugs in timely- manner, as explained in chronotherapy, the nocturnal asthmatic condition can be improved. Chronotherapeutic administration of corticosteroids is a promising treatment for asthma exacerbation, particularly when considering its ability to block the release of inflammatory cells in the lung. However, a double-blind placebo controlled study conducted by Baem.et.al, design with a single dose of 50 mg Prednisone at dose timings 8am, 3pm, and 8 pm which is compared with placebo, the dose given at 3pm shows a decreased FEV value and also improved inflammatory condition. Also from other studies, it is concluded that 3 pm daily dosing of inhaled corticosteroids is effective as 4 times daily dosing. Moreover, it was evident that a single evening dose of short-acting Albuterol showed efficacy in controlling nocturnal symptoms in asthma patient. Efficiently, Albuterol combination along with this long-acting inhaled beta-2 agonist, Salmeterol, resulted in improvement of the lung function in particularly overnight.

The conditions of the disease changes in a 24-hour period and thus the asthma exacerbation can be treated according to this change in pattern. Conclusively, asthma is known to be the disease, which is better treated after understanding the circadian pattern and accordingly, administering the drugs in a chrono-therapeutic manner [23, 24].

Chronotherapy in rheumatoid arthritis

The Immune system is regulated by the biological clock and changes in the immune system may cause the variations in the circadian rhythm. The circadian clock regulating the cellular components, the inflammatory pathways, CD4+, T-lymphocytes, and IL-6 plays major role in the severity of rheumatoid arthritis. The CD4+ and T- lymphocyte leads to the altered proliferation and cytokine secretion by the circadian oscillators [25, 26] Central clock produces circulating mediators such as glucocorticoids, thereby, increasing the production of IL-6. Thought, the central clock doesn't produce the circulating mediator solely, however, the local clock does control the production of this mediator. The desynchronization between the environment and internal clock is likely disrupting the circadian clock, which subsequently, will alter the inflammatory response cascades rhythm. An interested study conducted to find the relation between the body clock pattern and symptoms of rheumatoid arthritis, concluded that change in the circadian pattern will alter the symptoms and probably contribute to the pathogenesis of the disease.

The symptoms of rheumatoid arthritis include pain, stiffness and disability which are high during the day time in majority of the patients, moreover, circadian plays a major role in the development of symptoms as well as the inflammatory processes. The secretion of proinflammatory cytokine, TNF-alpha; IL-6 from monocytes and macrophages are initiating the production of C- reactive protein in hepatocytes, which is an indicator of the inflammatory responses. In rheumatoid arthritis patient, the levels of these indicators are high during the early morning [27]. The clinical symptoms of rheumatoid arthritis are low from 12 pm to 3 pm and high at 5-6 pm because of the production of melatonin and cortisol. The excess production of the TNF-alpha and IL-6 at the night time may worsen the intensity of the rheumatoid arthritis symptoms in the morning time.

Melatonin and cortisol are related to the production of cytokine i.e. melatonin increases the production of cytokine, whereas, cortisol decreases the production of cytokine. Patients who are suffering of morning stiffness, the serum level of melatonin and cytokines are likely at the peak in the early morning, with very low cortisol levels, therefore, morning stiffness may present signficantly. Normally the circadian rhythm of melatonin and cortisol balances the production of cytokine. However, lack in cortisol level may leads to the over expression of cytokines due to high melatonin concentrations [27].

In rheumatoid arthritis patients, the Disease-modifying anti-rheumatic drugs (DMARD's), Non Steroidal Anti Inflammatory Drugs (NSAID's), and glucocorticoids are the first-line drugs to gain relief from pain and inflammation symptoms. The DMARD's include Methotrexate, Hydroxychloroquinine, Sulfasalazine, and Leflunamide. The biological DMARD's include Etanercept, Infliximab, Adalimumab, Certolizumab, and Golimumab are also effective in rheumatoid arthritis management. In addition to the pharmacological treatment, the occupational, and physical therapy are also recommended for efficient improvement in the symptoms control [28].

Exogenous glucocorticoid is supplemented in the patient who has a lack of endogenous cortisol, the long term use of exogenous glucocorticoids may lead to suppression of the Hypothalamus-Pituitary-Adrenal (HPA) axis function and affects the normal cortisol production. Positively, the night time administration of the modified release prednisone dosage regimen produces a better efficacy compared to the immediate release prednisone dosage regimen, moreover, didn't resulted in adverse effects compared to the placebo and/or regular prednisone dosage regimen. Like glucocorticoids chronotherapy approach, clinical studies have also found that the administration of DMARD's and NSAID's at night will more likely provide profound therapeutic effect [29, 30].

Chronotherapy in cancer

The DNA damage of an organism activates the circadian that control proteins and it may lead to the activation of cell proliferation and genotoxic stress. In addition, the damage in DNA contribute to cell cycle arrest or apoptosis by the activation of ATM/ATR (Ataxia Telangiectasia Mutated / Ataxia Telangiectasia rad 3 related) and CHK1/2 (Check point kinase ½) which follow by switch on the P53 tumour suppressor protein. Human cells, which are insufficient in BMAL1, these cells are incapable to suppress P53. The PER1 (period 1 gene) have a role in tumour suppression, particularly when combine with DNA damage activated checkpoint proteins. Ionizing radiation causes expression of P21 nuclear

translocation of PER1 and induces the C-Myc (called as master regulator which regulates cellular growth and metabolism) expression. One of the tumours for DNA damage induced apoptosis is over expression of PER1 and inhibition of PER1 reduces apoptosis of the same cells [31].

Another circadian protein known as Time Less (TIM) and its interacts with ATR, CHK1 and ATRIP, significantly, this interaction is accelerated by DNA damage. Loning Fu et al conducted study on mice, found that mper2 gene behaves as a tumour suppressor and it is achieved by the regulation of DNA damage response pathways. In mice per 2 gene is regulating the circadian rhythm, therefore, in mice having deficiency of mper2 gene are at great risk of getting cancer [32]. In case of human colon cancer, the circadian clock regulate genes such as per1 and cycle in D are down regulated and increased ß catenin target genes does cell proliferation. Patrica A wood et al study found that the down regulation of PER2 genes in mice caused colorectal cancer. This study suggested that PER2 gene product down regulated the ß catenin target genes which led to the suppression of tumerigenesis in the small intestine and colon [33]. H. Hua et al study found that over expression of PER2 gene reduces the growth of the LLC and apoptosis in mice [34].

Cancer and the circadian clocks are interconnected, based on this principle many studies are conducted. The studies finding indicated that shift workers are more prone to get cancer, mainly the women who work night shifts, particularly more than three nights per month are at the risk of getting breast cancer. Probably, it may due to the changes in circadian rhythm as well as the production of melatonin. Various studies conducted in mice and humans, found that the destruction of SCN or chronic jet lag may lead to the changes in circadian rhythm, subsequently, may promote tumour growth. Elisabeth et al conducted a study in mice having disrupted or enhanced circadian rhythm found that increment of P53 and reduction of C-Myc expression and those mice expressed diethylnitrosamine -initiated hepatocarcinogenesis. Positively, the synchronization of circadian rhythm achieved by meal time adjusting and phase shifting of transcriptional rhythm clock genes resulted in the reduction of cancer progression in mice [35].

Sephton et al conducted a study for detecting the relationships between diurnal variations of salivary cortisol in metastatic cancer. In this study, the amount of cortisol in the saliva of patients who had metastatic cancer was assessed; also the amount detection of natural killer cells was carried out. The study concluded that, the diurnal cortisol system is abnormal in metastatic breast cancer patient, also a reduction in the natural killer cells resulted in the disease progression [36]. Interestingly, dosing times according to the circadian clock influenced the extent of toxicity of anticancer drugs. Nocturnal animals, especially mice or rats are synchronized with the changes of 12 hours of light exposure. Hours After Light Onset (HALO) are usually used to express the time.

The drugs administered according to the circadian rhythm in mice and rodents showed less toxicity, particularly, in case of platinum complex (e.g. Cisplatin, Carboplatin) they showed less toxicity at the middle of nocturnal activity. Additionally, the Anthracyclin compound, Pirurubicin showed the least toxicity at the time of 7 HALO. Another anthracycline compound mitoxantrone showed less haematological toxicity 8 hours later, i.e. 15 HALO. The Vinca alkaloids showed least toxicity at 14 HALO. Cancer patients have altering circadian rhythm; this alteration of circadian rhythm depends on the type of cancer, tumour growth, and phase of differentiation. The cancer cell produce cytokines and growth factors; these cytokines and tumour growth factors are likely lead to the alteration of the circadian rhythm [37]. Explicitly, chronotherapy based cancer therapy showed better outcomes and least toxicity; especially has more beneficial for patients who maintaining their endogenous circadian rhythm [38].

Exigency of chronotherapeutics in diseases management

The chronotherapeutic approach is the delivery of medication at different times in 24 hours, to coordinate the desynchronized rhythm in the disease condition. Chronotherapeutics considers the chronopathology, chronopharmacology of medications and the human circadian time structure for the delivery of the drug at the correct time structure into the targeted site, thus minimizing adverse effects. The area of chronotherapeutics also determines the frequency at which a drug is to be delivered, so that it can bring better therapeutic outcomes in the neuroendocrine system [39].

Chronotherapeutics were not only limited to newly marketed medications, but also can implement in already established medications. The main difference with respect to the conventional therapy is the unequal morning and evening administration of a sustained release tablet instead of single dose. Other field in which chronotherapeutic application are implemented is in the area of chronobiotics, where special drugs are administered to improve or reorganise the altered circadian rhythm in individuals. Another aspect, which goes hand-in-hand is chronoprevention, but is different from chronotherapeutics. In chronotherapeutic process, the drug is delivered at a rhythm in order to reverse or improve or decrease the already existing pathological condition of the disease. But in chronoprevention, the main target is the avoidance of the disease, or its pathological changes or other harmful events, which can lead to establishment of an acute or chronic disease condition [40,41].

Impact of chronopharmacology in enhancing the drug effect

Chronopharmacology is an area in chronotherapy explaining the pharmacokinetic and pharmacodynamic effect of the administered drugs. The administration of drug is according to the biological rhythm of the disease condition in chronotherapy, which also takes into the consideration the effect of the biological rhythm on the behaviour of the drug in the body, thus realizing the importance of pharmacodynamics of the drug. In Chronokinetics, the effect of the rhythm

variations in the drug's absorption, distribution, metabolism and elimination of medications is studied. In Chronodynamics, how the difference in the outcome of medication is related to rhythms in free-to-bound fractions of the drug, the number of target receptors and the secondary messenger system present in the body are more in concern. Chronotoxicology is the area, which is dealing with the occurrence of adverse effects and their connection with the rhythm and how it is leading to intolerance of the patient to the drug. This difference in the adverse effect outcome of a drug is variably seen in cancer drug administered patients. The advanced knowledge in all these areas of chronotherapeutics, for sure, can change the health outcome of the disease [36].

A new advancement in the area of the chronotherapy is the chronotherapeutic drug delivery system, which is intended for the controlled drug release by advanced formulation. Clinical chronotherapeutics is the base for the introduction of the 'action-delivered-at-time' delivery pumps and designs of new formulations that can target specific circadian time windows. The drug- delivery developments, which shows marked improvement is the pulsatile-drug delivery technology and the press-coated tablet for infusion and tablet respectively. In the pulsatile-delivery system, the delivery is targeted in a pulsatile fashion, i.e. an immediate release phase after a prolonged lag phase. This is usually given as infusions of hormones to mimic the pulsatile action of them in the body. For this lag-phase delivery, for eg: in asthma patients, the drug is delivered at the evening time in order to release the drug at midnight, where the symptoms are more likely to get worsens.

Another development in the chrono-drug delivery system for oral dosage form is the press-coated tablets formulation. Normally, for the extended or controlled release, a solvent layer is coated around the core tablet; unfortunitly, this faces many disadvantages in delivery due to the destruction of coating in several areas in the body. In order to overcome this problem, a press-coated drug delivery is being recognised as a novel approach for the chrono-drug delivery systems. In press-coating technique, an outer coat is formed around the inner core by the process of compression, which is efficiently capable of deliver the drug in a time and rate-controlled manner [3][39,41,42,43].

Pharmacoeconomics merits of considering chronotherapeutics

The advancement in chronotherapeutics and chronodelivery of drugs brings improvement in the outcome of the disease condition. This approach is used in various diseases from earlier time and the outcome is compared with those obtained from standard conventional therapy. A comparison study performed between chronochemotherapy and FOLFOX regimen for metastatic colorectal cancer patient. The study results stated that though costly drug delivery materials are required for the chronotherapeutic, it is balanced by efficacy, safety and better tolerability of the drug. Another study comparing combination of chronotherapy and standard therapy for colorectal cancer concluded that the duct cost may be increased due to chronotherapy, but in fact, the indirect and intangible cost is minimal [31,44]. According to William et al study, the mean treatment cost for patient is higher for immediate release prednisone and modified release prednisone when compared to night time prednisone and regular prednisone regimens respectively [45].

Present and future of chronotherapy

Chronotherapy is a term that was established decades; the influence of circadian rhythm in some disease condition and its application in chronopharmaceutics is not well established. For disease like asthma, cancer, and rheumatoid arthritis, it is proved that the disease condition can be well managed by considering the disease condition's circadian pattern. Presently, the area of chronotherapy is well developed and formulated; also chronotherapeutic drug delivery systems are available in the market. However, for the future, the focus is on individualization of chronotherapy according to the patient's chronotype and developing new technologies in the area of chrono-drug delivery system is a great of importance in enhancing the clinical outcome.

Individualization the therapy by recognizing individual's circadian rhythm will make a huge impact on the treatment of disease. Since today there is a general approach for chronotherapy in all patients i.e., by considering the normal rhythm in humans. Each individual is unique in their chronotype and can have unique body rhythms for their biochemical process, should be taken into consideration while deciding the therapy.

In pharmaceutical drug development, after pulsatile and press-coating drug delivery, the researchers are working with drug loaded carriers in chronotherapy. This type of chrono-administration of the drug delivery can be aided for target delivery, such as breast cancer; thereby increasing the efficacy and decreasing the side effects.

Table 1. *The drugs administration time based on different diseases circadian rhythm*.

Disease	Drugs	Administration time
Hypertension	Beta-blocker	Evening/night
	ACE inhibitor	Bed time
	Angiotensin II receptor blocker	Bed time
	Calcium channel blockers0	Bed time
Asthma	Modified release Prednisone	Evening (3 pm)
	Theophylline	Night (8 pm)
	Night time release prednisone	Night (10 pm-11 pm)
	Immediate release prednisone	Morning (7 am-9 am)
Cancer	Doxorubicin	Morning (6 am)
	Cisplatin	4 pm and 8 pm
	5-flurouracil	4 am

The current footrace in chronopharmaceutical drug research and the development is advance in:

- Rhythmic biomaterials and system design
- Rhythm engineering and modelling
- Regulatory guidance related to these types of modified dosage form

Although advanced time controlled delivery systems are developed, a productive insight is possible with the introduction of smarter biomaterials. Smarter biomaterials are those that can release drug in a rhythmic pattern with reasonable properties such as biodegradable and or biocompatible properties and shows good results and fast responses in the biological system. [42,43,46].

Conclusion

Chronotherapy in clinical practice is important for the management of many diseases, since the disease state is influenced by the biological rhythms of the patient. A chronotherapeutic approach will increase the efficacy of the drug, decrease the dosing frequency, and reduce the adverse drug reactions, which in ultimate will improve the outcome of the therapy and quality of the patient's condition. The chrono-drug delivery system advancement is the current area in chronotherapy for the appropriate drug delivery. Profoundly, comprehensive studies are recommended for developing a structural individualize chronotherapy approach.

Conflicts of Interest

The authors of this article has no any conflicts of interest.

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