



Review article

Chronobiology and chrono pharmacology with reference to consequences and management of shift work

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ABSTRACT

The conventional aim of pharmaceuticals is becoming outdated due to developments in chronobiology and chrono pharmacology, as well as global market restrictions. The availability of suitable technologies could be the main constraint in the creation of drug delivery systems that complement the circadian rhythm. The interest in the systematic study of the chronobiology is relatively recent and has developed rapidly in the last two decades. Chronobiology exhibit conceptual biological periodicity may conserve in the genomes of shift workers. Authors stated that the shift work affects our biological and psychological functioning with reference to regarding health and diseases. Author review the accessible literature concerning the chronobiology and chrono pharmacology with reference to consequences and management of shift work. Although shift work is advantageous for all those workplaces that operate around the clock, the most unfortunate part is that it takes its toll on employees and their families.

Keywords: Chronobiology, Biological periodicity, Shift workers, Psychological, Circadian rhythm

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INTRODUCTION**Chronobiology**

Chronobiology is scientific restraints which use to examine and measures the mechanisms of biological clock including important periodic signs of life from unicellular organisms to multicellular organisms [1]. The term chronobiology has coined by Halberg [2] for daily rhythm, however, it is applied for biochemical, physiological and behavioural rhythms. Chronobiology includes chrono pharmacology, chronophysiology, chrono pathology, chronotoxicology and chrono therapy among others [3]. Applied Chronobiology takes into its fold problems associated with transcontinental travels and shift work. The latter is extremely important because currently about 30% of the total global work force works in shifts. This work culture has a number of deleterious effects on human physiology, psychology and longevity. All harmful effects of shift work that one would envisage in an individual could be imputed to de-synchronization of its biological rhythms [4].

Biological rhythms are vitally available in all organisms, ranging from production/degradation of molecules to fluctuations within and between whole populations. It includes circatidal rhythms, circalunar rhythms, circannual rhythms and circadian rhythms. Circadian rhythms are the determined and significant biological rhythms because it reveals in all the kingdoms, cyanobacteria (Proteista), Bacteria (Monera) fungus (Fungi), plants (Plantae), and

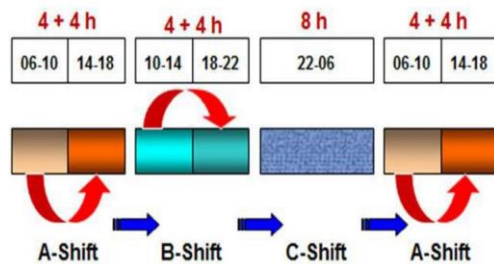
animals (Animalia), are affected by the daily change of day and night. Circadian rhythm may be de-synchronize due to biological oscillators such as clocks and zeitgeber, entrainment, circadian clock and shift work. [5]. the biological clock or supra-chiasmatic nucleus (SCN) has been independently studied by several authors [5,6]. The circadian system allows the orientation in the fourth dimension i.e., non-image-forming retinal pathways and integrates information about intensity, duration, and spectral composition of light. As pacemaker, the SCN sets the phase of oscillators of many physiological and endocrine rhythms in the body. Simultaneously, SCN releases certain molecules which use to hypothesized to transmit behavioural circadian rhythm [7].

Chronobiology is strongly associated with certain genes such as clock, per1, per 2, per 3, Tim, cry1, cry2, BMAL1 [8,9,10]. They are accountable for exert circadian mechanism almost all species investigated and substantial homology exists between for example *Drosophila* and mammals. Oscillation of clock genes is control and coordinated by SCN.

Biological clock and shift workers have acknowledged maximum attention during the last couple of decades [4,11,12]. Shift work has got the maximum attention with reference to call center and business process outsourcing. This work culture has a number of

deleterious effects on human physiology, psychology and performance. A variety of shift work has been adopted in organizations that remain functional around the clock, notably sectors managing health, security, transport, entertainment, telecommunication, material production [13,14]. Grossly shift work could be of four types: (a) rotating, (b) stable/ permanently displaced, (c) on call, and (d) split [4]. In rotating shift system traditionally, a worker works in more than one shifts (morning or afternoon or night) for a given duration (in hours), switching from one shift to another either clockwise or counter-clockwise after a specified interval. The working length of a particular shift may vary: It could be short (normally of 8 hours) or could be long (exceptionally 12 hours). In many countries in certain sectors 12-h shift is a routine feature. In some shift system rotation is completely absent. This type is called as stable or permanent shift [14]. There may be few variants, for example asymmetrical shift in which duration, length and timing of shift is not known beforehand. On-call shift is a special work system of shift in which workers are called during emergency. Split-shift is the system in which an individual works in two spells per day and each spell may last for about 4 hours. A rest period of few hours is allowed between the spells. This type of shift is uncommon (Figure 1) [4].

Figure 1: Split Rotational pattern (From Achari *et al.*, 2012 with permission)



Consequences of shift work

Physiological consequence of shift work is reflected in disruption of biological rhythms [13,15]. In humans, numerous physiological functions, namely body temperature, heart rate, respiratory rate, blood pressure, digestive activity, appetite, water balance, and the secretion of hormones follow a circadian rhythm, as do many psychological processes and mental functions that include mood, memory, manual dexterity and alertness [15]. The rhythm of wakefulness and sleep is governed by intricate neural and physiological mechanisms. There are precise centers in the brain that send out signals to many effectors in the body to regulate sleep-wake rhythm on a daily basis [16,17]. Studies have shown that it is indeed difficult on the part of rotating/ night shift workers to have sufficient sleep in the day and attentiveness in the night. It would be worthwhile to reiterate that shift work affects human health and performance through the disruption of circadian rhythms. Consequently, human behavior and physiology undergo alteration dramatically [18]. Internal de-synchronization of several rhythms in shift workers has been

reported. De-synchronization in a given variable is often marked by alteration in three important circadian rhythm parameters, such as phase, amplitude and 24-h average [19, 20].

The sleep-related problem in shift workers is multi-faceted. It may involve a wide range of complications, such as inadequate quality and quantity of sleep, excessive daytime sleepiness and circadian rhythm sleep disorder [16, 17]. Shift workers are most likely to suffer from insomnia like sleep disorder [21]. Night shift workers exhibit severe sleep deprivation due to continuous shift duty. Further workers on quickly rotating shift experience lesser sleep problems than those on slow rotating schedules. In a nutshell, night shift workers experience deterioration of both quality and quantity of sleep [4]. Further there is strong relationship between sleep and age as well as gender. Older shift workers exhibit less sleep problem than that of their counter parts. Female shift workers experience more sleep disturbances than males [22].

Shift workers suffer from number of clinical problems, notably cardiovascular and gastrointestinal complications. Shift workers reveal cardiovascular death due to myocardial infarctions [23] and angina pectoris [15] early in the morning [24]. Shift workers especially night shift and rotating shift workers have their food at wrong time of the day. They experience abnormal patterns of gut motility and gastric acid secretion. This could be the reason why shift workers often suffer from gastrointestinal complications, such as gastric upset, disturbed appetite, gastritis, constipation, diarrhea, poor eating, dyspepsia, epigastria pain, gastro duodenitis, and peptic ulcer [25]. Further, a significant association was acknowledged between shift work and cancer [26]. Shift workers tend to accumulate more carcinogens in their blood as compared to their day-working counterparts. Authors hypothesized that the increasing incidence of breast cancer in the developed world was due to light exposure at night.

Non-clinical problems that usually shift workers suffer from are mostly related to performance parameters and status [17]. Performance variables themselves exhibit circadian rhythms [27]. Night shift work has been shown to be associated with poor reaction time, mental arithmetic, higher error rate in performing addition and fewer signal detections. Performance shift workers towards the different shift pattern were reliant on many factors such as demands of the task, type of shift system [28].

Shift workers exhibit number of psychological and psychosocial problems. They face the burden of family dysfunctions that cause social disorganization. Authors also reported that many shift workers not able to continue their jobs on grounds of social issues than that of medical. On-call shift workers often negotiate disturbed psychological equilibrium with reference to family and

social life [29]. It has been observed that due to complication of shift schedules and their pattern spouses and children of shift workers exhibit anxiety and mental health then that of their other relatives of day workers. Further authors stated that due to unavoidable schedules of shift workers restrain anxiety and mental health in their spouses and children [29,30]. Shift workers and their associates also reveals number of psychological and psychosocial problems such as depression, helplessness and stress [25,29].

Individuals of human species could be either morning type (*Homo sapiens larkensis*) or evening type (*Homo sapiens owlensis*) or neither type are considered as chrono type [31]. Attempts have been made to ascertain if consideration of variability in chronotype among shift workers would help in the effective optimization of human shift work. Morning and evening types differ significantly with reference to circadian organization of their physiological and biochemical rhythms. In morning type peak of circadian rhythm in body temperature occurs earlier in the day as compared to evening type with the peak appearing later in the day. According to Kleitman [32] morning type and evening type explain some of the variations in adaptability to shift work. Morning type appears to experience more problems to cope with night work while evening type experiences fewer problems in adapting to night work. Morning type people face difficulty adapting to shift work due to sleep deficiency and its accompanying pathological symptoms. On the basis of phase position of circadian rhythms, a statistically significant difference between morning type and evening type has been noticed in rhythms of oral temperature [32].

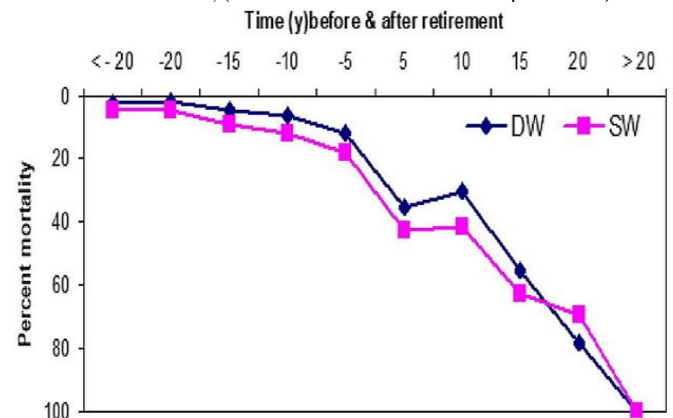
Most of the psychosocial and psychological problems such as extraversion, introversion, socialization and psychoticism were discussed by Eysenck [33]. He developed number of personality traits, for example 2-factor super traits (neuroticism and extraversion), 3-factor super traits (extraversion, neuroticism, and psychoticism). There is yet another 5-factor model that includes neuroticism, extraversion, and openness to experience, agreeableness and conscientiousness. This model that includes five "big" traits is considered dominant in descriptive models of personality issues relating to selection of models for measuring personality have been debatable. Two factor model developed by Eysenck is one of the best to measure personality trait among all [33]. Shift work does not allow the shift workers to have complete participation in the social activities, because it is designed for daytime workers. Social cues are of primary importance for entrainment of circadian rhythms. This shift system and their shift schedules results in an increase in the level of psychosocial interruption. Female shift workers have been viewing more critical complications as they have an overall responsibility of the family members and their child specially [29,34].

There are many studies that document incidence of social dissatisfaction for the family and their family members. Shift work has been associated with increased rates of divorce [35]. However, relationship between circadian types and personality, social satisfaction, social disruption, and job satisfaction has been partially worked out. Author knowledge is fragmentary regarding relationship between shift work tolerance or shift work coping ability and personality traits. This interesting area of investigations needs focused attention [34].

Longevity and shift work

The consequences of shift work produce number of negative issues in human health and safety [11,18,36,37]. It impairs performance thus leading to manifestation of chief industrial accidents [36,38]. Shift work has been strongly related to several clinical and non-clinical impediments [15]. Although it is presumed that shift work might produce life shortening effects, there is complete lack of knowledge validating a direct association between longevity and shift work. [18]. Authors computed longevity of each worker from the dates of birth/retirement and death. Percent mortality was also computed for day workers and shift workers. Both longevity and percent mortality were plotted as function of work type (Figure 2). Percent mortality (all-cause) was more in shift workers. A statistically significant reduction in longevity ($P < 0.001$) was noticed in shift workers which were amounted to 3.94 years (Figure 2). The significance of the findings reported here is that they are based on direct measurement of lifespan in shift workers and their day-working counterparts, who worked in the same organization [18, 31].

Figure 2: Higher mortality (all-cause) in shift workers ^{DW}Day workers; ^{SW}Shift workers; (From Pati and Achari 2007 with permission)



Chrono pharmacology

Chronotherapeutic is significantly related to *in vivo* medication accessibility is timed to complement disease rhythms in order to improve patient outcomes while reducing side effects. It is focused on the finding that the peak-to-trough rhythmic behavior in disease symptoms and risk factors, pharmacokinetics and pharmacodynamics of medications are symbiotic. The chronobiology and chronotherapeutic are interrelated to each other because

medication time and patient's circadian rhythm is reciprocal. Therefore, one has to clear that the precise period in which patients take their drug could be much more important than previously thought. The practice of administering medicine at evenly distributed time periods during the day, in order to retain stable drug levels throughout a 24-hour cycle is a common thought according to the researchers. However, some of them even claim that certain drugs may perform well if their administration is synchronized with day and night. When the possibility of serious medical events or the starkness of diseases and their effects is known to differ predictably across 24 hours or other time periods, a chronotherapeutic solution is recommended. Large-scale clinical studies have demonstrated that dosing in regard to the circadian time structure will increase the efficacy and protection of such traditional drugs^[39].

The chrono biology and chrono therapy of methylprednisolone tablets with reference to hypothalamic-pituitary-adrenal suppression were discussed in the 1960s. Further, single morning doses of H₂-receptor would protect from peptic ulcer and gastritis. Similarly, evening doses of HMG-CoA reduces cholesterol production in the gastrointestinal tract and work as antagonists. The comparison to the afternoon, the chance of an asthmatic attack is almost multiple times better in patients at 4:00-5:00 in the morning. The use of new technologies allows for the temporal regulation of opioid levels in response to patient needs. Corporation started selling theophylline chronotherapeutic ally engineered administration of these unique dosage for nocturnal asthma^[40].

Numerous studies have reported 24-hour trends in cardiovascular diseases. Circadian patterns in blood pressure in stable subjects—nocturnal dropping of cardiac pressure and a fast increase between 5:00 a.m. and 9:00 a.m. Patients with hypertension typically have common signs, but their mean cardiac pressure get enhances due to malfunctioning of medication. Malignant hypertension and a bad prognosis are often related to a lack of nocturnal decreasing. It is lower in males and becomes smaller when they grow older.

Long-acting antihypertensive agents took at bedtime help regain blood pressure regulation in the morning and restore the natural circadian cycle of blood pressure (non dipper-dipper). Heart problems such as angina pectoris, cardiac arrest, ischemic and myocardial infarction are common within the morning exercise in diurnally engaged patients than that of day or night. Vasospasm events of Prinzmetal angina, are more frequent during night, as are the signs of patients with congestive cardiac arrest. The morning dose of enalapril shows better results for day time hypertension, while evening dose exhibit greater effect on evening night time hypertension. Further, the evening doses of isradipine reveal better

results for diabetic patient have a severe renal disease. At the same time evening doses of isradipine exhibit very good result for the patient suffering from circadian disruption. The impacts of quinapril and ramipril on blood pressure are often affected by the time of administration; a morning once-a-day dosing schedule decreases sleep-time blood pressure moderately, while an evening dosing schedule reduces it excessively, particularly with quinapril. The effect of diltiazem on blood pressure varies based on when it is taken; the overnight once-daily intake schedule has a strong influence on nighttime blood pressure, while the evening one has a strong effect on it in the morning and afternoon^[41].

The impacts of the circadian rhythms on drug activity were not discussed earlier in the field of medical sciences. Therefore, the conventional aim of pharmaceuticals is becoming outdated due to developments in chronobiology and chrono pharmacology. The availability of suitable technologies could be the main constraint in the origin of drug delivery systems that counterpart the circadian rhythm Chrono pharmaceutical drug delivery systems has emerged as a treatment for a variety of diseases in the last decade and became the Chrono pharmaceuticals^[42].

Circadian rhythms exist in chronic states of disorder, much as they do in physiological processes. The enhanced risk of illness symptoms during the 24-hour period has been reported in epidemiological studies. Chronotherapeutic have been seen to have potential applications in the treatment of a variety of diseases such as allergic, arthritis, upper respiratory infections, cardiovascular problems, gastrointestinal complications, cancer. Patients suffering from allergic rhinitis always complain that the worst symptoms troubles in the morning. Evening dose is more suitable for severe patients of antihistamine then that of morning dose, as is often prescribed, might have greater success in controlling morning pain^[43].

Chronotherapy

Non-Steroidal Anti-inflammatory Drugs (NSAIDs) can be more successful at relieving discomfort in people with rheumatoid arthritis and associated debilitating joint conditions if they have medication before 5-7 hours the pain starts. If arthritis patients are in a lot of pain in the morning, taking NSAIDs before bedtime can improve.

Similarly, anti-asthma medication looks as if medicated in the night than that of day. The deterioration of nocturnal asthmatic symptoms seems to be influenced by a number of circadian-dependent causes. Theophylline absorption is even sluggish at night, according to studies. Modern methods to disease control also benefited from greater knowledge of the chronobiological effect on asthma pathology. Anticancer agents are cytotoxic to both stable and diseased tissues.

The sensitivity of non-malignant and malignant cells to these agents can be influenced by the biological cycles, as one would predict. Furthermore, authors stated that stable tissue and cancerous tissue have distinct “susceptibility rhythms” to medications. As a consequence, “proper” drug therapy timing can minimize host toxicity, improve the tolerance of drug and thus improve malignant cell control. Malignant cell resistance may be predisposed by pharmacodynamic and pharmacokinetic properties, as well as rhythmic improvements in DNA and RNA production, RNA translational activity. It seems that when treating cancer, the timing of medication delivery has a direct effect on patient effectiveness.

CONCLUSION

It has been unequivocally established that chronobiology and chrono pharmacology are symbiotic constituents which affects the human psychological and physiological processes. Shift workers may treat with chronotherapy to get the healthier results. However, the chronotype, life style, and longevity preference of shift workers has not yet been addressed adequately. It is also not known if shift work modulates human personality with special reference to personality traits. Further, issues involving social satisfaction, social disruption and job satisfaction among shift workers and more especially among Indian shift workers are not yet properly evaluated. It is also not known if shift work has any negative effect on human longevity. It is indeed striking that in a country like India, where about 30-40% of its total work force might be working shifts, research in the domain of shift work is yet to develop.

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DECLARATION

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