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RESEARCH ARTICLE

A study of chronopharmacological relevance of antihypertensive drugs at a tertiary care hospital - A prospective observational study

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ABSTRACT

Background: Chronopharmacology is the science dealing with the optimization of drug effects and minimization of adverse effects by timing the medications in relation to the biological rhythm. Blood pressure (BP) in normotensive person raises in the early morning, gradually dips by noon, and peaks again by evening to show a greater fall during midnight. To maintain a steady Blood pressure throughout the day necessitates to have knowledge of chronopharmacology and drugs following it. **Aims and Objectives:** The aim of this study is to evaluate the relevance of drug administration to patients with the standard chronopharmacological guidelines. **Materials and Methods:** Data were obtained from clinical case records of patients admitted in wards of Department of Medicine at K.V.G Medical College Hospital, Sullia, from December 2014 to June 2016 based on inclusion and exclusion criteria. **Results:** The study involved a total 744 subjects of either gender, of which 68.10 % (n = 506) were males and 31.98% (n = 238) were females with their average age being 55.97 and 55.96 years, respectively. Chronopharmacological relevance was found with 28 drugs, of all antihypertensives were 25 including diuretics, i.e., 17 antihypertensives and 7 diuretics. Nifedipine, a calcium channel blocker to be administered in the morning, all of the 100% of subjects received the drug in the morning with excellent relevance to chronopharmacology. Amlodipine to be administered ideally in the morning was seen to be followed in 98% of subjects, while a fixed drug combination (FDC) of amlodipine and olmesartan (10 mg/40 mg) to be taken at night showed 100% correlation for chronopharmacology. Enalapril, an angiotensin-converting enzyme inhibitor,was given to 10 patients, of which 80% of patients received them at bedtime and followed appropriate chonopharmacology for the drug. Telmisartan, an angiotensin receptor blocker, has shown only 30% relevance as bedtime administration. Beta blockers such as propranolol and metoprolol showed only 79% and 50% of bedtime and morning relevance, respectively. Diuretics are ideally prescribed in the morning. FDC of furosemide with amiloride (40 mg/5 mg) and furosemide with spironolactone (20 mg/50 mg) have followed the chronopharmacology in 100% of subjects. Furosemide alone was administered in the morning in only 60% of subjects. **Conclusion:** A very few antihypertensive and all of the diuretics have shown chronopharmacological relevance with their time of administration. A few like telmisartan and other FDC of diuretics have shown poor relevance to chronopharmacology. This could be because of the lack of knowledge of chronopharmacology and circadian rhythm. In conclusion, the timing of drug administration is in good relevance to standard chronopharmacology. This study has provoked the need for updating the knowledge of chronopharmacology and its application in clinical practice for a better patient recovery and good quality of life.

KEY WORDS: Chronopharmacology; Antihypertensive; Diuretics, Fixed Drug Combinations; Chrono Therapeutics; Angiotensin-converting Enzyme Inhibitor; Angiotensin Receptor Blockers

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INTRODUCTION

Chronopharmacology is the science dealing with the optimization of drug effects and minimization of adverse effects by timing the medications in relation to the biological rhythm.[1]

This concept was first outlined by Alain Reinberg and Franz Halberg in 1971. The first scientific approach of the importance of synchronization of the therapy with the "biological clocks" took place in 1814.[2]

Circadian rhythm also called as biological rhythm is defined as oscillations in the biological, physiological, and behavioral function of an organism with a periodicity of 24 h. Circadian rhythms are endogenous in nature and are known to persist under free-running conditions.

Diseases such as hypertension, myocardial infarction (MI), congestive heart failure, and stroke follow the body's circadian rhythm.[3] It may also be very important in influencing the responses to various medications. Some of the manifestations are in the night time and some other seen during the daytime. The disease occurrence is independent of time of day, month, or year. As a result, the time of the day when medications are administered is not a key focus for health-care professionals in diagnosis or prescribing.[4] However, during the last couple of decades, much progress has been made in the field of sleep and circadian medicine, and the concept of biological rhythms is being viewed as a possible complement to homeostasis.

It is important to maintain constancy in the blood concentration of drugs so as to maintain the constant efficacy of drug. This fact explains the need for the pharmacology to fetch better results from the same drug. Chronopharmacology plays a significant role here. A thorough understanding of the circadian rhythm and its application for drug administration serves productive utilization of drug. Thus, chronopharmacology is synchronization of drug therapy with the biological rhythm. However, knowing the temporal variability (ultrafine, circadian, infradian, circaseptan, circatrigintan, and circannual) of the manifestations and the security of drug utilization constitutes the reason of a new approach of the therapy - chronotherapy.

Health-care practitioners are well aware of the normal homeostasis of the body.

Understanding of the molecular control of circadian rhythms and subsequent signaling pathways has allowed for new therapeutic drug targets to be identified. In turn, a better understanding of how to more efficaciously and safely utilizes current drugs.[5] A constant concentration of drugs is an assumed means of achieving constancy in therapeutic effect and drug safety.[6] Clinical studies show that the magnitude of the predictable-in-time (rhythmic) differences can be so great that it can be a strong determinant of time during 24 h, severe morbid, and mortal events occur and when the symptoms and signs of many chronic medical conditions flare.[7] Thus, circadian time has to be taken into account as an important variable influencing a drug's pharmacokinetics and its effects or side effects.

Cardiovascular System (CVS)

Blood pressure (BP) shows a dip in the noon and profound dip at the night but peaks during 6–9 a.m. and 6–7 p.m.[8] Surge in heart rate is seen soon after waking and commencing daily activity in the morning and there on reaches peak between 10 and 12 a.m. After that, heart rate gradually begins to decline and maintains a lower level during the whole night [Figure 1]. In diurnally active patients, angina, acute MI, sudden cardiac death, and ischemic and hemorrhagic stroke occur more frequently during the initial 3–5 h of morning activity than at any other time of the day or night.[9] The 24-h pattern in MI is a result of the predictable timing of environmental triggers, the change in posture, and physical and mental loading occurring in the morning. These are largely responsible for the rapid increase in BP, heart rate, and myocardial oxygen demand.[10] The risk of these events is relatively lower during the rest of the day, especially during the sleep period. The phasing of the circadian rhythms in sympathetic tone, neuroendocrine function, blood coagulation, and coronary vessel inflammation and reactivity also plays an important role.[11]

The renin-angiotensin system plays a key role in the regulation of the CVS. Angiotensin II levels affect peripheral vasomotor tone, and therefore, cardiac afterload. The activity of the renin-angiotensin system has a circadian rhythm, and the pattern of its circadian rhythm coincides with the circadian pattern for heart rate and BP.[12]

At the same time, some authors have found that the incidence of thrombosis also shows diurnal variation, with a significant peak of onset at 7–8 a.m.[13] Studies have shown that platelet aggregation peaks in the morning around the time of

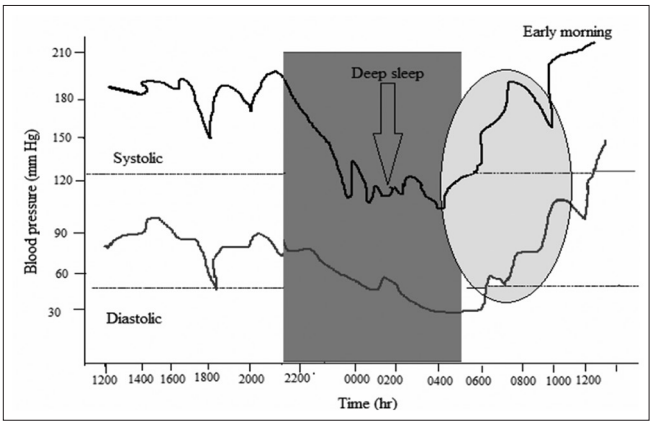

Figure 1: Circadian rhythm of blood pressure[17]

wakening and then begins to decrease, remaining at a lower level throughout the rest of the 24 h. This circadian change is believed to be another factor associated with the morning increase in thrombotic cardiovascular events.[14] Although the circadian peak of the BP rhythm differs in terms of clock time, it is comparably timed when referenced to the worker's sleep-wake routine. The peak of the rhythm occurs approximately 10–11 h after one arises from sleep, whether it is during the night or day.[15]

Applying the knowledge of circadian function and regulation to the relevance of disease has enabled a chronotherapy approach in the timing of administration of conventional drugs to synchronize the rhythms in disease activity with the efficacy of the drug.

The goal of chronopharmacology is as follows:[16]
- Optimization of therapy by considering rhythm dependencies.
- Prevention of overdosing and unnecessary side effects of any class of drugs.
- Prediction of time variability in manifestation and severity of diseases.
- Matching the timing of treatment with intrinsic timing of illness.
- Thus improve efficacy and safety of medications.

Thus, the study aims at observing and recording the time of drug administration in relation to the circadian rhythm of the body and to evaluate the relevance to chronopharmacology, hence bring about the change in the pharmacotherapy in accordance with the chronopharmacology.

Objectives

The objective is to study the chronopharmacological relevance to the time of drug administration in general medicine inpatients at K.V.G Medical College and Teaching Hospital (KVGMCH), Sullia, Dakshina Kannada.

MATERIALS AND METHODS

Place of Study

The study was undertaken in coordination with the teaching and non-teaching staff of the Department of General Medicine at K.V.G Medical College and Teaching Hospital, Sullia, Dakshina Kannada.

Design and Duration of Study

A prospective, non-interventional, observational study was undertaken from December 2014 to June 2016. Accordingly, a special pro forma was designed, and data were obtained from medical case records of patients suffering from various disorders admitted in the wards of General Medicine, K.V.G Medical College and Teaching Hospital, Sullia, Dakshina Kannada, Karnataka.

The Institutional Ethics Committee clearance was obtained for this study.

Data collection was undertaken with the following inclusion and exclusion criteria.

Inclusion Criteria

1. Patients admitted in General Medicine wards of age group 14 years and above of either gender for chronic disease conditions at KVGMCH were included in the study.

Exclusion Criteria

The following criteria were excluded from the study:
1. Outpatients are excluded from the study.
2. Patients below 14 years of age.
3. Patients receiving emergency treatment in the wards of General Medicine at KVGMCH.
4. Patients being treated for acute infectious conditions.
5. Pregnant women.

Data Collection

The investigator met and sought the help of staff and the Head of the Department of General Medicine with regard to the conduct of this study. The investigator duly recorded data of patients attending admitted in the wards of General Medicine. Drug therapy prescribed to those patients was recorded. The data were obtained from patients' case reports. After the demographic data was noted, details regarding the type of illness, duration of illness, drug/drugs prescribed, dose of each drug, frequency of administration, timings, duration, route of administration, relation to food (before/after food), and other associated systemic illness and adverse drug reactions if any, either pertaining to present illness or an interaction of drugs taken for other chronic illness were obtained. The duration of data collection was restricted to maximum 5 days of the hospital stay of the patient.

The relevant data were collected in a pro forma by the investigator in person from the medical case records and also direct patient monitoring from the Department of General Medicine at KVGMCH, Sullia.

The specially designed pro forma provides information about the following:
1. Demographic data:
   - Name, age, address of the patient, OP/IP number, and date of examination/admission of patients.
2. Disease data:
   - Onset and duration of illness.

3. Data pertaining to drug therapy**:**
   - Drug/drugs prescribed, dose, frequency, duration, timings, and route of administration.
4. Data pertaining to other comorbid illness the patient is suffering from if any
5. Data pertaining to adverse effects of drugs, if any

Statistical Analysis of the Data

- Descriptive statistical analysis was done using Microsoft Office Excel 2010.

RESULTS

A total of 1064 patients were screened in the wards of the Department of General Medicine, of which 744 subjects were chosen to be the study subjects based on the inclusion and exclusion criteria. The study involved a total of 744 subjects of either gender. Among the study subjects, 68.10% (n = 506) were males and 31.98% (n = 238) constituted females. The average age of male and female was found to be 55.97 and 55.96 years, respectively. These subjects were treated for various illnesses like respiratory conditions such as chronic obstructive pulmonary disease, bronchial asthma, chronic bronchitis, pleural effusion, allergic bronchopulmonary aspergillosis, lung fibrosis, sinusitis, pulmonary edema, pulmonary TB, and bronchiectasis. Cardiovascular conditions such as hypertension, coronary artery disease, ischaemic heart disease, MI, dilated cardiomyopathy, cor pulmonale, rheumatic heart disease, congestive cardiac failure, constrictive pericarditis, and left ventricular hypertrophywere seen.

A total of 114 drugs were recorded in the current study. Table 1 shows the drugs of each system used for the treatment of various illnesses. Of the 114 drugs recorded, those having chronopharmacological relevance were 28 which were studied thoroughly. Of all, antihypertensives were 25 including diuretics. Table 2 shows the ideal time of administration of drugs for the 25 drugs at different dosage and dosage forms studied in the current study. Antihypertensive drugs used were 17, of which 7 showed chronopharmacological importance as illustrated in Figure 2. Nifedipine (n = 18), a calcium channel blocker to be administered in the morning, all of the 100% of subjects received the drug in the morning with excellent relevance to chronopharmacology. Amlodipine (n = 92), to be administered ideally in the morning was seen to be followed in 98% subjects; while a fixed dose combination of amlodipine and olmesartan (10 mg/40 mg) to be taken at night showed 100% correlation for chronopharmacology. Enalapril, an angiotensin-converting enzyme inhibitor, given in 10 patients showed that 80% had relevantly received at bedtime. Telmisartan (n = 6), an angiotensin receptor blocker (ARB), has shown only 30% relevance as bedtime administration. Beta blockers such as propranolol and metoprolol showed only 79% and 50% of bedtime and morning relevance, respectively.

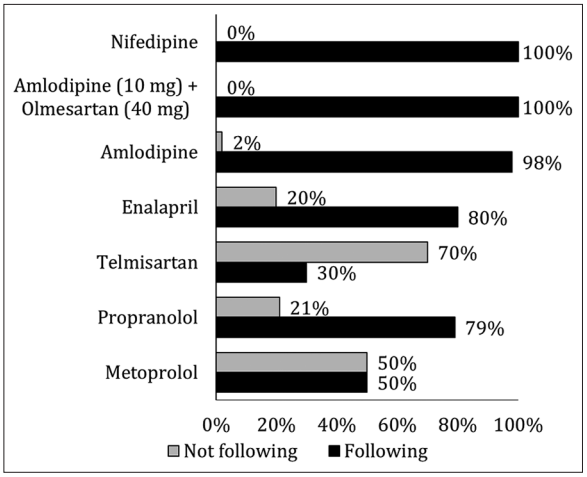

Figure 2: Percentage relevance to chronopharmacology for antihypertensive drugs

Table 1: List of drugs prescribed

System	Number of drugs used	Percentage of drugs
RS	12	10.5
CVS	17	14.91
Renal	8	7.01
GIT	16	14.03
CNS	15	13.1
Steroids	3	2.63
Autocoids	18	15.78
Hormones	7	6.14
Blood	7	6.14
Vitamins	9	7.89
Antihelminthic	2	1.75
Total	114	

CVS: Cardiovascular system, GIT: Gastrointestinal tract, CNS: Central nervous system, RS: Respiratory system

As shown in Figure 3, diuretics are ideally prescribed in the morning. Fixed dose combination of furosemide with amiloride (40 mg/5 mg) and furosemide with spironolactone (20 mg/50 mg) has followed the chronopharmacology in 100% of subjects. Furosemide (n = 110) alone was administered in the morning in only 60% of subjects.

DISCUSSION

The study has evaluated the relevance of "time of administration" of various drugs to its chronopharmacology. That is whether the drug administration is at appropriate time at which the drug shows maximum therapeutic effect and minimum adverse effects. Of the 28 drugs with chronopharmacologic importance, 16 drugs (57.14%) have followed their ideal timings of administration to the fullest. To study these 28 drugs, they were categorized based on the systems, as respiratory drugs, antihypertensive, diuretics, gastroprotective agents, CNS drugs,

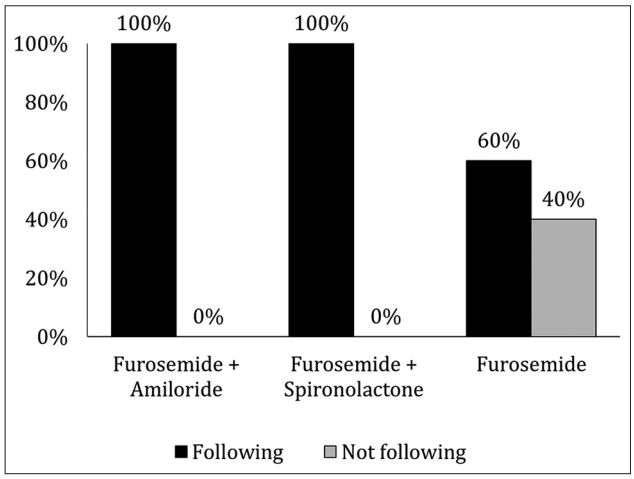

Figure 3: Percentage relevance to chronopharmacology for diuretics

Table 2: The ideal time of administration of drugs for the 25 drugs at different dosage and dosage forms studied in the current study

Drugs	Preferred time of day
Amlodipine	Morning
Nefidipine	Morning
Telmisartan	Bedtime
Propranolol	Bedtime
Metoprolol	Morning
Enalapril	Bedtime
Amplodepin+olmesartan	Bedtime
Furosemides	Morning
Furosemide+amiloride	Morning
Furosemide+spiranolactone	Morning

autacoids, steroids, anticoagulants, and hormones. Not all the drugs recorded have chronopharmacology. Only the drugs for which various clinical trials have proved to have a difference in efficacy when administered at different timings were studied thoroughly. Of the total of 17 antihypertensive drugs, 7 drugs were studied for their chronopharmacologic effect. Calcium channel blockers such as amlodipine and nifedipine have more effect on BP with morning administration. In the current study, 98% relevance is seen with amlodipine. ACE inhibitors such as perindopril and enalapril have established to have ideal timing at bedtime administration as they have a better effect in reducing the BP with bedtime dose.[8] In our study, enalapril is prescribed and has been administered at bedtime in 80% of patients at the correct time. This marks a good relevance to guidelines. Enalapril reduces the bedtime and also morning BP effectively with bedtime dose. ARBs such as telmisartan, valsartan, and olmesartan have got chronopharmacologic importance as evident by the previous studies as bedtime to be more efficacious.[17] In the current study, telmisartan is given rightly in only 30% of patients with hypertension. Remaining 70% were given only single dose in the morning. This deviation from chronopharmacology is serious and needs to be addressed to get a better control of BP. The fixed dose combination of amlodipine with olmesartan (10 mg/40 mg) was given rightly at bedtime in all patients. This fixed drug combination (FDC) has been shown to more effective at bedtime to decrease the nocturnal BP.[21] Beta blockers such as atenolol and metoprolol have shown their best effect with morning dose.[8] However, propranolol is better with evening dose.[32] In this study, metoprolol has shown 50% relevance and propranolol showing 79% relevance to ideal time. Furosemide, furosemide + amiloride, and furosemide + spironolactone FDC have shown best efficacy with morning dosage.[17] Among diuretics received by the patients in the current study, both FDCs have 100% relevance but only 60% in case of furosemide single drug. Ideally, diuretics given in the morning produce a better relief of edema and congestion in cardiac and renal conditions.[17]

The physiological activities in the body adhere to this circadian rhythm to produce a normal homeostasis. The approximate peak time of circadian rhythm of selected biological variables in persons who adheres to a normal routine of daytime activity from ~6–7 a.m. to ~10–11 p.m. alters with nighttime. The activity in light and sleep in darkness daily routine determines the phasing of all circadian rhythms. Figure 4 illustrates theses variation in circadian rhythm of the physiological processes in the body.

The morning peak of the rhythm in vasoactive entities contributes to the morning peak time of the circadian rhythms in heart rate, BP, arterial compliance, and vascular resistance in normotensive and uncomplicated essential hypertension persons. The morning peak of the circadian rhythm in blood catecholamine's gives rise to the morning peak of the circadian rhythm in platelet aggregation.[17]

ACE inhibitors such as perindopril and enalapril have established to have ideal timing at bedtime administration as they have a better effect in reducing the BP with bedtime dose.[18]

Circadian Rhythms in Various Systems and Disease Processes

Similarly, clinical studies involving amlodipine and nifedipine demonstrated a reduction in BP throughout 24 h whether ingested in the morning or evening.[23] However, in a prospective, 12-week, double-blind, randomized, cross-over study of mild-to-moderate essential hypertension patients (n = 60), the nocturnal BP fall was greater with morning than with evening administration.[24] Other calcium channel blockers such as nicardipine, nitrendipine, verapamil, and diltiazem should be administered in the evening (they do not excessively decrease BP values during the night). Diltiazem has greater efficacy by morning administration, compared to the 12.00 a.m. administration in Prinzmetal angina.[16] The combination of amlodipine/

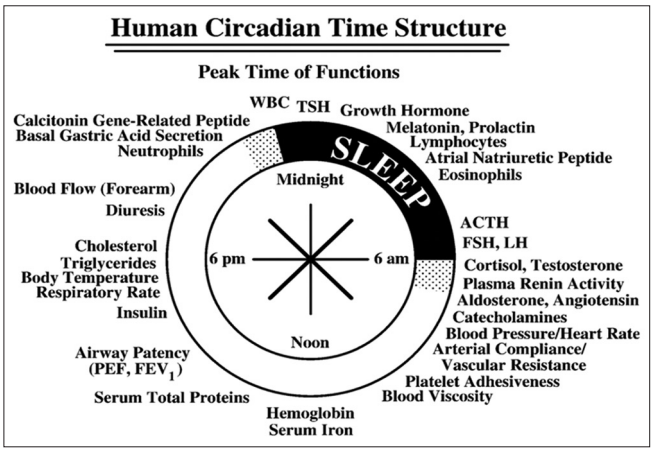

Figure 4: Time of day when physiological or biochemical functions are at peak. PEF - peak expiratory flow rate; FEV - forced expiratory volume; WBC - white blood count; TSH - thyroid-stimulating hormone; ACTH - adrenocortical tropic hormone; FSH - follicle-stimulating hormone; LH - luteinizing hormone[3]

hydrochlorothiazide,[25] amlodipine/olmesartan,[26] and amlodipine/valsartan[27] showed higher effectiveness for bedtime than morning administration. However, in a study conducted by Asmar *et al*., the authors reported no significant differences between morning and evening administration of amlodipine/valsartan.[28] In the case of atenolol, a chronopharmacokinetics trial investigated the effect of a 50-mg dose in 13 hypertensive patients and found no significant differences for morning versus night-time administration. Puzzutto *et al*. showed that atenolol and metaprolol produced better BP control with morning dose, while BP was elevated when evening dose of atenolol was given.[8] Nebivolol and propranolol had a higher effectiveness after the evening dose compared to morning administration.[29] Torasemide (loop diuretic with long duration of action) and hydrochlorothiazide showed a better effect on BP pattern after bedtime dose.[30] By administering the thiazide diuretics in the morning (before 09.00), the risk of hypokalemia is significantly decreased.[8] American diabetes association recommends bedtime administration of at least one antihypertensive drug.[31] Furosemide, furosemide + amiloride, and furosemide with spironolactone FDC have shown best efficacy with morning dosage.[17]

Limitations of the Study

This current study did not take into account the dose of each drug and their dosage forms. The study has involved only patients attending tertiary care hospital where drugs are minimal in availability and also has focussed mainly on the timing of administration of drug as the main objective. This could be addressed in the future studies in the field.

Future Prospective

Newer drug delivery systems are presently in the vogue. These drugs are called as chronopharmaceuticals. Chronopharmacology applied to different drug delivery systems, and their beneficial effects could be studied in the future.

CONCLUSION

Antihypertensive such as nifedipine (100%), amlodipine (98%), enalapril (80%), propranolol (79%), telmisartan (70%), and metoprolol (50%) showed good relevance. Furthermore, a combination of amlodipine with olmesartan showed 100% relevance, while Metoprolol (50%) and telmisartan (30%) have a poor relevance to chronopharmacology. Diuretics were administered accordingly in all patients. Furosemide (60%), furosemide + amiloride, and furosemide + spironolactone both followed 100% chronopharmacology. FDCs of diuretics have followed chronopharmacology, but furosemide single prescription has only 60% relevance. This could be because of the lack of knowledge of chronopharmacology and circadian rhythm. In conclusion, the timing of drug administration is in good relevance to standard chronopharmacology. This study has provoked the need for updating the knowledge of chronopharmacology and its application in clinical practice for a better patient recovery and good quality of life. This study also highlights the importance of timing of medication in human health for already existing drugs and new drug substances that act on the peripheral clock. This will in turn help us to establish chronopharmacologic and chronotherapeutic approaches to more appropriate extent. The current study adds a scope for improvement in the therapeutic outcome if chronopharmacology is considered in treatment. In view of the current research and investigations, the chronopharmacologic aspect plays a major role for the optimal utilization of the available drugs to fetch an improved therapeutic effect when followed in clinical practice.

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