WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.453
Volume 14, Issue 8, 116-128. Review Article ISSN 2277–7105

ACETYLCYSTEINE AND ACEBROPHYLLINE FIXED DOSE COMBINATION CHRONOTHERAPY FOR COPD AND NOCTURNAL ASTHMA: REVIEW

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Article Received on
22 February 2025,

Revised on 14 March 2025,
Accepted on 04 April 2025

DOI: 10.20959/wjpr20258-36078

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ABSTRACT

The alarming rise of respiratory diseases worldwide has brought attention to the critical need for effective management strategies. Interestingly, our bodies have an innate time-keeping system, known as the circadian rhythm, which synchronizes our physiological processes with the day-night cycle. When this delicate balance is disrupted, lung function can be severely compromised. Fortunately, a promising approach known as chronotherapy has emerged, which involves tailoring treatment to an individual's unique circadian rhythm. By doing so, healthcare providers can optimize the efficacy of medications while minimizing unwanted side effects. In this review, we'll delve into the latest advancements in chrono-targeted therapies, offering new hope for those suffering from chronic respiratory diseases.

INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is a relentless and debilitating lung condition that's wreaking havoc on global health. Defined by the Global Initiative for Obstructive Lung Disease (GOLD) as a progressive disease marked by irreversible airflow limitation, COPD is a ticking time bomb that's expected to become the third leading cause of death worldwide by 2030. The disease is a complex interplay of small airway damage and lung tissue destruction, with each patient experiencing a unique combination of symptoms. The consequences are dire: COPD is already the fourth leading cause of death in the United States, affecting over 16 million people and imposing a substantial economic and social burden on families and communities. Despite these alarming statistics, there's hope on the

horizon. Recent advancements in pharmacological treatments have significantly improved outcomes for COPD patients. Current therapies, including bronchodilators and anti-inflammatory agents, have been shown to alleviate symptoms, enhance lung function, and improve overall quality of life. But managing COPD is about more than just treating symptoms – it's about empowering patients to take control of their disease. The primary goals of COPD treatment are to increase exercise capacity, reduce disease exacerbations, and improve patient well-being. By achieving these goals, we can help patients with COPD live fuller, healthier lives, despite their diagnosis.[1-3]

In 2017, Jeffrey C. Hall, Michael Rosbash, and Michael W. Young were jointly awarded the Nobel Prize in Physiology or Medicine for their discoveries regarding the molecular mechanisms that regulate circadian rhythms.[16-17] The circadian clock plays a vital role in governing daily physiological processes, and research has shown that the timing of immune system activation—whether through infection, vaccination, or surgery—significantly impacts the body's response. Many inflammatory diseases, including asthma, exhibit distinct daily patterns in symptom severity. Aligning drug administration with these biological rhythms to enhance effectiveness and minimize side effects is known as chronotherapy. This review article explores recent advancements in circadian biology and their implications for the treatment and management of asthma and chronic obstructive pulmonary disease.

Acebrophylline

Acebrophylline, which combines Ambroxol and Theophylline-7-Acetate, is a xanthine-based bronchodilator used to treat bronchial asthma and COPD in adults. It modifies mucus secretion by decreasing the thickness of the 'gel' phase and increasing the 'sol' phase, enhancing mucociliary clearance through improved ciliary movement. The drug also inhibits intracellular phosphodiesterase, leading to increased cAMP levels, which helps relax bronchial muscles. Furthermore, Acebrophylline selectively inhibits phosphatidyl choline, phospholipase A, TNF-alpha, and leukotrienes. By blocking these pro-inflammatory mediators, it effectively reduces airway inflammation and obstruction, particularly in chronic stages of respiratory diseases**.**

Acetylcysteine

NAC is a thiol compound, which provides sulfhydryl groups. NAC can act as a precursor of reduced glutathione and as a direct reactive oxygen species scavenger, hence regulating the redox status in the cells. In this way NAC can interfere with several signaling pathways that

play a role in regulating apoptosis, angiogenesis, cell growth and inflammatory response. Mucus hypersecretion has been reported in COPD and in other respiratory conditions. Two pathological processes have been described to play an important role in COPD, namely oxidative stress and inflammation. Both of these processes can induce mucin gene expression leading to mucin production. NAC, therefore, may influence mucin expression by acting on oxidative stress and inflammation, and play a role as a mucolytic agent. In this review we focus on the mucolysis of NAC in the management of COPD.[7-10]

Asthma and Circadian rhythm

Asthma is a disease with a strong circadian rhythm; it is characteristic of asthma that symptoms worsen in the early hours of the morning around 4:00 am. Nocturnal Symptoms in asthma are common and are an Important indicator for escalation of treatment. Sudden death in asthma also tends to occur Overnight.

Physiological parameters of airway resistance, forced expiratory volume (FEV1), and peak expiratory flow (PEF) are commonly measured in respiratory clinics and as outcome measures in drug trials. Both FEV1 and PEF vary in a circadian manner in healthy individuals at approximately 4:00 am. However, in asthma, the amplitude of the circadian rhythm of both FEV1 and PEF is greatly magnified.

Circadian rhythm in copd

Given the considerable heterogeneity of COPD, effects of the circadian rhythm has been observed to a lesser extent in this context than in asthma.[35] In healthy subjects, circadian fluctuations in lung function parameters, such as FEV1 and PEF, show their lowest levels around 4 a.m. These circadian rhythms are more pronounced in patients with obstructive lung diseases, but they are less evident in COPD compared to asthma. Further observations have indicated elevated rates of intubation, particularly during the early morning hours, among COPD patients in emergency departments. Moreover, research has demonstrated that environmental risk factors, particularly cigarette smoking, can trigger a chronic inflammatory response by disrupting various components of the circadian clock.

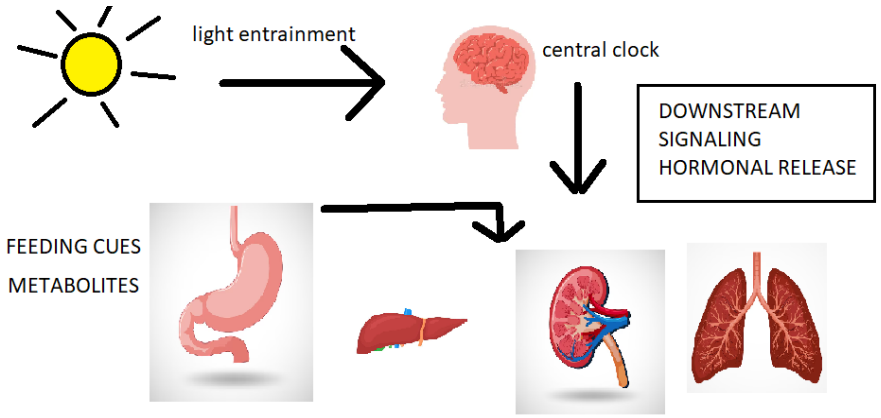

Figure 1: Representation of central and peripheral clocks.

The body has both central and peripheral clocks. The central clock, located in the suprachiasmatic nucleus (SCN) of the brain, processes light and dark signals and transmits this information to peripheral clocks, which are present in nearly all cells. This communication occurs through a network involving neural pathways, hormone secretion (such as glucocorticoids), and metabolic signals influenced by rhythmic feeding patterns. While light serves as the primary cue for synchronizing the SCN, feeding-related metabolic signals play a crucial role in regulating many peripheral clocks.

Chronotherapeutic approach

Asthma and COPD are respiratory diseases that exhibit pronounced diurnal variability, with symptoms often worsening at night and in the early morning hours. Therefore, chronotherapeutic treatment could be advantageous for patients.

In cases where patients experience a significant exacerbation of symptoms during the nocturnal period, it is essential to modify the pharmacological treatment regimen to ensure its effectiveness during sleep. Even for patients whose symptoms do not worsen at night, there may be an optimal timing for medication administration that maximizes efficacy and minimizes toxicity.

The Global Initiative for Asthma (GINA) guidelines (85) emphasize individualized therapy based on severity and control, recommending inhaled corticosteroids (ICS) as the cornerstone of treatment. Although asthma symptoms often follow a circadian pattern, with worsening at night or early morning.

Circadian rhythms (CRs) are primarily controlled by a core group of clock genes. These include basic helix-loop-helix (BHLH) Period–ARNT–Sim (PAS) domain-containing transcription factors, such as the *circadian locomotor output cycles kaput* (CLOCK) gene and the *brain and muscle ARNT-like protein 1* (BMAL1) gene. These genes regulate the transcription and translation of various other genes and proteins, including three period (*PER1–3*) genes and two cryptochrome (*CRY1* and *CRY2*) genes. Together, these elements form transcription-translation feedback loops (TTFLs), which serve as the molecular foundation of CRs.

In response to a zeitgeber (a time cue), transcription of *BMAL 1* and *CLOCK* increases in the nucleus. This triggers the heterodimerization of BMAL 1 and CLOCK proteins in the cytoplasm. These BMAL1-CLOCK complexes then move into the nucleus, where they bind to Enhancer Box (E-Box) sequences in clock-controlled genes, initiating a regulatory cycle. This process leads to the synthesis of negative regulators PER and CRY, which form PER-CRY heterodimers. These heterodimers subsequently enter the nucleus and inhibit BMAL1-CLOCK-mediated transcription, ensuring the rhythmic regulation of CRs.

Additionally, BMAL1-CLOCK dimers influence other clock-related proteins, including *differentiated embryo chondrocyte-1* (DEC1) and *differentiated embryo chondrocyte-2* (DEC2), which represent a fifth gene family involved in the interplay between circadian rhythms and the immune system. The BMAL1-CLOCK heterodimer also stimulates *DEC1* by binding to the E-box in the presence of external cues.

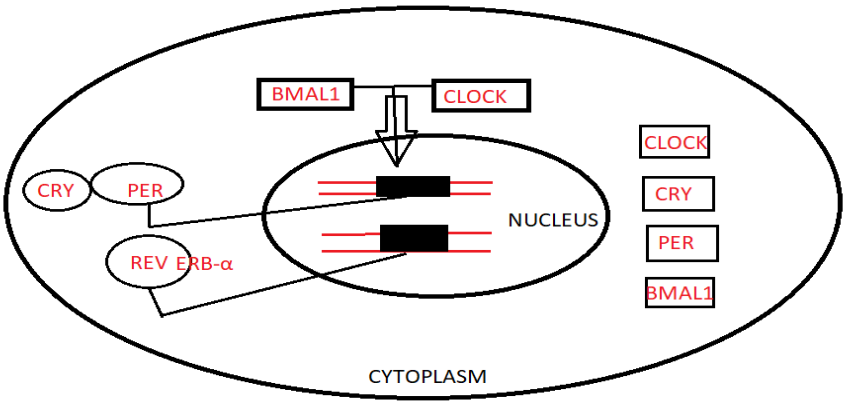

Figure 2: The molecular circadian clock.

Both central and peripheral clocks rely on the same molecular mechanisms to regulate daily rhythms. These clocks operate through interconnected feedback loops of transcription and

translation, resulting in the roughly 24-hour rhythmic expression of key clock genes in each organ. CLOCK and BMAL1 promote the transcription of period (PER1/2) and cryptochrome (CRY1/2) genes. As PER and CRY protein levels rise, they form complexes that move into the nucleus, where they inhibit CLOCK/BMAL1 activity, thereby suppressing their own transcription. The degradation of PERIOD and CRYPTOCHROME proteins introduces a delay before the next transcription cycle begins. This interplay between positive regulators (CLOCK and BMAL1) and negative regulators (PER and CRY), which are expressed in opposite phases, establishes circadian timing at the molecular level. The molecular clock influences physiological processes by regulating the transcription or repression of target genes, with BMAL1 being further modulated by its rhythmic interaction with REV-ERBα.[34-35]

Lung-on-a-Chip: A powerful tool for respiratory research

The lung-on-a-chip model, in particular, holds great promise for advancing our understanding of respiratory diseases. By incorporating rhythmic endocrine regulation, these systems can simulate the complex interactions between drugs, organs, and hormones, enabling the development of personalized and effective treatments.[37]

Future directions: Personalized Chips and Multisystem homunculi

The possibility of creating personalized chips using individualized samples and interconnecting different organ-on-chip models to form multisystem homunculi opens up new avenues for research. These innovations will enable scientists to study complex physiological interactions and circadian rhythms in unprecedented detail, driving the development of novel and effective therapeutics.

Nocturnal asthma

Definition

Nocturnal asthma is characterized by an exacerbation of asthma symptoms, such as coughing, wheezing, shortness of breath, and chest tightness, specifically during the night or early morning.

Prevalence

It's estimated that a significant portion of people with asthma experience nocturnal symptoms, with some studies suggesting that up to 60% of asthmatic patients experience nocturnal asthma.

Impact

Nocturnal asthma can lead to poor sleep quality, daytime fatigue, and difficulty managing asthma symptoms, ultimately affecting overall quality of life.

Causes and Factors

Circadian rhythms

The body's natural 24-hour cycle (Circadian rhythm) can influence lung function, with peak lung function occurring in the afternoon and minimal function in the early morning. This natural variation can be exaggerated in nocturnal asthma, leading to airway narrowing and increased symptoms at night.

Hormonal changes

Fluctuations in hormones like cortisol and melatonin, which also follow circadian rhythms, can contribute to airway inflammation and increased asthma symptoms at night.

Environmental triggers

Exposure to allergens, irritants, or pollutants in the bedroom environment, such as dust mites, pet dander, or mold, can trigger or worsen asthma symptoms at night.

Medication timing

The effectiveness of asthma medications can also vary throughout the day, with some medications wearing off during the early morning hours, potentially leading to a resurgence of symptoms.

Table 1: Chronopharmaceutical technologies for the treatment of asthma.

Technology	Chronopharmaceutical technology	Chronotherapeutic studies
Proventil Repetabs® (Bayer-Schering, Berlin, Germany)	Pulse-release LABA tablet design. An outer coat of 2 mg albuterol surrounds an inner subcoat. A third "barrier coat" is insoluble in the acid of the stomach, but soluble in the alkaline small intestine, thus exposing the core of the tablet containing an additional 2 mg albuterol. Half the dose is released within the first 6 hours, and the rest is released during the next 6 hours.	Proventil Repetabs® given twice a day (4 mg in the morning and a larger dose at nighttime) demonstrated a significant reduction in nocturnal PEFR dip and nighttime symptoms when compared to placebo.

Bambuterol (Bambec®, Astra Draco, Sweden)	Once-daily prodrug of terbutaline; lasts for 24 hours. After absorption, bambuterol is protected from hydrolysis by an esterase-inhibiting function built into the prodrug molecule.	Bambuterol is slowly metabolized in the liver
Hokunalin® Tape (Abbott Japan Co, Ltd, Osaka, Japan)	Transdermal chronodelivery system for Tulobuterol, a LABA. Maintains an effective drug concentration over 24 hours	Application of patch between 7 pm and 9 pm for 6 consecutive days leads to markedly improved morning PeFR, compliance, and allergic airway inflammation.
Dutimelan® (Sanofi, Paris, France)	A different mix and concentration of synthetic glucocorticoids. The stronger 8 am dose consists of 7 mg prednisolone acetate and 4 mg prednisolone alcohol, while the 3 pm dose consists of 3 mg prednisolone alcohol and 15 mg cortisone acetate.	In a 1-month course of treatment, Dutimelan significantly improved airway caliber without causing adrenocortical suppression.

DISCUSSION

COPD was frequently observed in subjects over the age of 41 years and pulmonary function test was preferred for diagnosing COPD. The majority of the respondents recommended the N-acetylcysteine and acebrophylline (NAA) combination for a variety of bronchitis conditions, emphasizing its effectiveness in managing not only acute exacerbations but also chronic manifestations such as hyper mucus secretion. There are numerous studies highlighting the use of Nacetylcysteine for reducing acute exacerbations in COPD patients.[7-10]

The survey findings can be considered as the first of their kind suggesting the therapeutic value of the NAA combination, as there was no clinical evidence on the combination of NAA for the treatment of COPD.

Oral N-acetylcysteine has gained significant recognition as a potent and efficient mucolytic agent. It serves as a precursor for innate glutathione reservoir, actively supporting the scavenging of reactive oxygen species. It also exerts control over cell signal transmission and gene expression linked to inflammation through redox-sensitive pathways. By restoring the equilibrium between cell oxidation and antioxidation in COPD cases, NAC plays a pivotal role in preventing the intensity of the inflammatory response.

Acetylcysteine-600 mg once daily dosage of this monotherapy was found to be effective in improving the quality of life in Indian COPD patients, according to a randomized controlled trial.[11] On the other hand, acebrophylline monotherapy was also proven to have a clinical improvement in dyspnoea, amount of sputum, and frequency of reliever medication.[12]

CONCLUSION

It is emphasized that N-acetylcysteine and acebrophylline combination as a promising approach for managing COPD patients, demonstrating potential benefits in treating both acute and chronic bronchitis. Noticeable improvement is typically observed within a week of initiating this therapy, with a suggested duration of 10–15 days. Incorporating adjuvant treatments such as amoxicillin clavulanic acid, montelukast, and levocetirizine alongside the NAA combination to effectively manage mucus in conditions like asthma, bronchitis, and COPD.

NAC serves as a precursor to glutathione, a crucial antioxidant that helps neutralize reactive oxygen species (ROS) and reduce oxidative stress, protecting lung tissues from damage. By reducing oxidative stress and modulating inflammatory pathways, NAC helps lower inflammation in respiratory conditions. Acebrophylline contains theophylline, which inhibits phosphodiesterase (PDE-4), leading to increased cyclic AMP (cAMP) levels. Elevated cAMP levels cause relaxation of bronchial smooth muscles, leading to bronchodilation. It also acts as an adenosine antagonist, reducing bronchoconstriction. Thus it is a promising strategy for COPD and Asthma.

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