TURKISH REPUBLIC OF NORTHERN CYPRUS
NEAR EAST UNIVERSITY
HEALTH SCIENCES INSTITUTE

Application of chronotherapy in Asthma: A systemic review

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Master Thesis

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MENTOR
Prof. Dr. Nurettin Abacioğlu

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Approval

Thesis submitted to the Institute of Health Sciences of Near East University in partial fulfillment of the requirement for the degree

Master of Science in Pharmacology

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Abstract

Asthma is accompanied by chronic airways inflammation and reversible airflow limitation. The nocturnal worsening of asthma has been a well-researched subject over the last century. A great number of literature suggest that 75% of patients with asthma report nocturnal symptom at least once per week, 64% report awakening at least three times per week, and nearly 40% report nightly awakenings. Chronotherapy on the other hand, is a behavioral technique whereby bedtime is steadily delayed, following the natural tendency of humans.

Methods: "Pubmed" and "Clinical trials" database were used to search eligible articles. Results from clinical trials on cases of asthma and its treatment with regards to circadian rhythm and bronchial asthma published between January 2010 to December 2019 were utilized. The age focus was restricted to younger adults and older adults, that is, patients between 18 years to 80 years old. Articles were limited to English language. Furthermore, duplicated articles were removed. Publication in English language studies carried out on Humans and articles that pertaining to chronotherapy were utilized. Search terms were ''Chronotherapy'', ''Chronopharmacology'','Chronopharmacokinetics'',''Chronopharmacodynamics'', ''Chronoefficacy'', ''Chronoformulation'', ''Morning and Evening'', ''Morning and Bedtime'' and their combinations.

An extensive search of the literature was conducted to identify publications focusing on chronotherapeutic aspects of drug therapy. Two investigators systematically review the database search independently by reading the title and abstract of the identified studies and screen out of the irrelevant ones. Included studies were read in full text for suitability of the criteria independently, variance was managed by consensus.

Preferred reporting items for systematic reviews and meta analysis protocol were followed while planning, providing objectives, selecting studies and analyzing data from the systematic review.

Results: Our search revealed a total of 591 journal articles, of which 10 articles were selected for review based on the inclusion and exclusion criterias.

Conclusion: This thesis work presented the scope of chronotherapy with regards to asthma treatment. It is believed that the knowledge and science of chronotherapy is increasing becoming an effective and recognized technique for asthma treatment and management. The current and ongoing studies on the use of chronotherapy is promising. This statistical review has highlighted several concepts and definitions within the field of chronotherapy. Using these definitions, a scope of the utilization of chronotherapy was done. It has shown that there is considerable evidence for the effect of time on the administration of drugs with regards to asthma patients. In such conditions, it may be prudent for professional practice guidelines to make due reference to chronotherapeutic principles. We believe that the knowledge of chronotherapy is growing and current researches within this are promisingly. However, it would be important to keep in mind that in any future clinical trials carried out, studies should also endeavor to explore gender, genetic and age related differences. Clinical curricula should incorporate a certain level of exposure towards the concept of chronotherapy, as this seems to be neglected.

Key words:
Chronotherapy, Asthma, Meta analysis

STATEMENT (DECLARATION)

Hereby I declare that this thesis study is my own study, I had no unethical behavior in all stages from planning of the thesis until writing thereof. I obtained all the information in this thesis in academic and ethical rules. I provided reference to all of the information and remarks made. I also ensure that their references where included in the reference list, therefore had no breech of the patent right and copyright infringement during the duration of my study and writing of the thesis.

Edeh Esther Victory

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Chapter 1

Introduction

Asthma is a complicated disease dependent on the interaction between genetic and environmental factors. According to Yokoyama *et al.* (2019), the percentage at which asthma can be inherited is as high as 50%. It is a intricate disease that is characterized by severe airflow obstruction, persistent airway inflammation, as well as, airway hyper responsiveness (Yokoyama *et al.* 2019).

Though asthma has been identified as a disease with high level of heritability, it prevalence in developing countries has become alarming over the last few decades. According to Polderman *et al.* (2015), it has been discovered that due to its rising prevalence rate, both environmental and genetic factors may be involved in its pathogenesis (Yokoyama *et al.* 2019).

Around the 1980s the importance of inhaled corticosteroids (ICS) become clear. This subsequently led to the realization that the inflammation of the airway was a characteristic of asthma (Yokoyama *et al.* 2019). It is an undeniable fact that continuous study of asthma has greatly influenced the usage of inhaled corticosteroids (ICS) in several countries around the world (Yokoyama *et al.* 2019).

However, during the late 1990s it was discovered that asthma can not be categorized as a single disease. Recent studies after the examination of induced sputum have shown that airway inflammation can be divided into 4 types, which include eosinophilic, neutrophilic, mixed, and pauci- granulocytic. When considering the treatment of severe asthma, chronotherapy could be considered as a method to reduce its symptoms (Yokoyama *et al.* 2019).

The harmonization of the biological rhythms with medical treatment can be referred to as chronotherapy (Awasthi *et al.* 2010). Basically, chronotherapy uses the biological rhythms of people to monitor and determine the exact timing and amount of drugs required for the optimization of the effectiveness of a drug (Awasthi *et al.* 2010). On the other hand, chronopharmacology can be defined as the study of the influence of biological rhythm on the effects of drugs, whereas chronobiology is the

study of the biological rhythms (Awasthi *et al.* 2010).

With research and advances in technology, the monitoring of the biological time humans became even more common (Awasthi *et al.* 2010). This brought about the idea that these rhythms could one way or the other affect the way the human body responds and reacts to drugs administered over the course of a day (Youan, 2009). The appropriate timing of administered drugs has the potential to diminish toxicity, as well as, improve efficacy.

The role of chronotherapy in the prescription and administration of drugs becomes even more relevant when the disease or illness being treated varies with time, such as asthma, congestive heart failure, arthritis, stroke etc (Ohdo, 2003).

Conventional methods have drug delivery have always focused on a fixed/constant drug routine, with the object of minimizing or monitoring drug intake and consequently adverse effects that may result from an overdose (Awasthi *et al.* 2010). However, chronotherapy explores the dosage of drugs administered as while as the duration and time schedules (Awasthi *et al.* 2010).

This study comprises five chapters, which include introduction to the key words pertaining to this research work, the purpose of the study, a detailed review on publications and research that have been carried out in relation to this study. Within the literature review, current findings on chronotherapy as it relates to asthma would be explained in details.

Aim of Study

- To investigate the optimum time interval for the administration of asthma drugs, using chronotherapy.
- To perform a meta analysis based on clinical trials that has been performed and published.
- Comprehensively draw conclusions on the most effective time interval for asthma patients based on the meta analysis carried out.
- Suggest improved strategies based on drugs, time intervals, age, as well as, the inclusion and the exclusion criteria's.

Chapter 2

2.1 Introduction

Chronotherapy is a process done by synchronizing the concentration of drug to rhythms associated with disease activity. This is done in order to increase the efficacy of the drugs and also reduce its adverse effects. The success of implementing chronotherapy on asthma patients is most often determined by its effects during the morning dip observed in the lung function measurements of PEFR or FEV1. In cases where the management of asthma patients are inadequate, the morning PEFR is remarkably lower than the evening PEFR (Durrington *et al*., 2014).

Majority of the drugs that are currently being used for chronotherapy are usually administered once at night. The timing is set in order to prevent chronic airway inflammation or limitations in the flow of air. Once daily administration also comes with added benefits for the patient including self-management and adherence.

According to Durrington *et al. (*2014), PEFR and FEV1 have been known to affect the symptoms at different times. Usually, the inflammatory process that results in the symptomology would have been triggered several hours before, characterized by the transcription of pro-inflammatory genes and the subsequent stimulation of the immune system. Chronotherapy can serve as an effective way to control asthma because it exhibits a marked time-day variation in its symptoms, airway inflammation and physiology (Durrington *et al*., 2014).

A well-grounded knowledge of the circadian rhythm of inflammatory biomarkers present in the blood or sputum may provide a basis by which the chronotherapeutic window can be narrowed down to for future references (Durrington *et al*., 2014).

2.2 Definitions

2.2.1 Chronopharmacology

According to Gupta *et al.,* (2013), chronopharmacology can be defined as the science that deals with the optimization of the effect of drugs, as well as, the minimization of the adverse effects of the timing for the administration of drugs with regards to biological rhythms. It can also be seen as an investigative science concerned with the

biological rhythm dependencies of medication (Gupta *et al*., 2013). The goal of this process is to improve the understanding and clarify the basis of the periodic drug administration and thus predict changes in both desired effects and tolerance of medication (Gupta *et al*., 2013).

2.2.2 Chronobiology

According to White and LaRocca (2002), chronobiology is the science that deals with the phenomenon of rhythmicity in living organisms. Basically the meaning of chronobiology is coined from three different words, which are; chronos which stands for time, bios which stands for life and logos which stands for the study of. Circadian rhythms monitors the physiology, behaviour and functioning of living organisms at several biochemical levels (White and LaRocca, 2002).

According to Gupta *et al.* (2013), chronobiology aims to optimize pharmacotherapeutics, by taking into consideration rhythms that depend on the medication kinetics and dynamics. It also aims to predict in time, the variability's associated with diseases in their manifestation and severity (Gupta *et al*., 2013).

2.2.3 Circadian rhythm

Gupta *et al.* (2013), defines circadian rhythm as an oscillation in the physiological, biological and behavioural function of the human body within a period of 24 hours. Currently, the concepts of chronobiology and chronopharmacology have become imperative and more relevant within the medical community.

The circadian variation in blood pressure and heart rate, as well as, in the occurrence of acute cardiovascular disease is very evident (ischemia, infarction, stroke and sudden death) (Gupta *et al*., 2013). However, biological rhythms can be seen to occur in events of dyspnoea in nocturnal asthma, in hormonal pulses, in the cordination of the immunological framework and in the procedures attached to cellular proliferation, the behaviour, physiology and function of living organisms at many biochemical levels (Gupta *et al*., 2013).

2.3 The Role of the Body Clock in Asthma Treatment

For the past 15 years, the zeal to understand the human biological rhythm and clock has increased dramatically (Huang, 2018). The knowledge and the understanding of the circadian clock are critical in regulating daily physiological processes. Recent discoveries have shown that the timing at which the human body's immune system is triggered by vaccination, infection and even surgery, is crucial to the way we respond (Durrington *et al*., 2014). Asthma has shown a marked time of day pattern in its symptoms. Synchronizing drug administration and treatment dosage to rhythms in disease activity, can help to increase efficacy, as well as, to diminish its adverse effects (Long *et al.,* 2018). Every human body clock allows for the generation of circadian rhythms. Circadian rhythms are behavioral patterns and physiology that usually follow a 24 hours cycle.

2.4 Asthma

Asthma is a disease usually characterized by chronic airway inflammation (Turner-Warwick, 1988). It is described by various respiratory symptoms such as shortness of breath, chest tightness, cough and wheeze (Turner-Warwick, 1988). Asthma is a common disease affecting about 18% of the world's population.

2.4.1 Asthma and circadian rhythm

Symptoms Asthma is a disease with a strong circadian rhythm; it is type of asthma in which its symptoms get worst during the early hours of the morning around 4:00 am (Cochrane and Clark, 1975) On the other hand, nocturnal symptoms are common and are an essential indicator for escalation of treatment, as sudden death in asthma patients tends to occur overnight (Sutherland ER, 2005).

Table 1: Summary of clinical studies showing the importance of circadian clock biology.

Clinical	Comments
Shift workers and regular jet-lag	Disorganization of the internal clocks with surrounding light dark levels. Studies (Epidemiological) have shown elevated amounts of risks for:

	Cardiovascular disease, prostate cancer, and breast cancer.
Critically ill patients in ICU	Patients who are critical ill in ICUs are nursed around the clock with no differentiation between night and day. Patients such as these with sepsis have weakened circadian melatonin rhythms
Chemotherapy infusions	The timing of chemotherapy infusions with circadian rhythms in patients with metastatic colorectal cancer has been seen to increase the effectiveness of chemotherapy and significantly reduced toxic side effects.
Vaccination	276 patients (over 65 years of age) vaccinated in the morning had greater antibody 1 month later than patients vaccinated in the afternoon.
Surgery	For patients undergoing aortic valve replacement, the occurrence of severe adverse cardiac incidents was much lower in the afternoon then for those done in the morning.
Wound healing	Skin wounds gotten during the circadian rest period healed less quickly than those wounded during the active period.

2.4.2 β_2-adrenergic agonist medication

The β_2-agonists (BAs) primarily lead to the relaxation of airway smooth muscle. This enables the increase of airflow and also relieves bronchoconstriction. Nevertheless, BAs are also characterized by their anti-inflammatory action. With the BAs, plasma epinephrine shows displays the lowest level of circadian rhythm at 4am and the

highest at 4pm for both healthy patients and patients with asthma. According to Krakowiak and Durrington, (2018) BAs, procaterol and fenoterol, all have been reported to strongly induce per-mRNA expression in human bronchial epithelial cells in vitro. Usually, BAs are inhaled and have been known to have short acting effects (Krakowiak and Durrington, 2018).

2.4.3 LABA tablet formulation

Terbutaline constitutes an LABA tablet formulation was one of the first drugs that were tested in chronotherapy trials. Daily doses were administered to asthmatics in synchrony with biological needs specified in terms of the circadian rhythm of their lung function (PEFR, FEV1). In a clinical trial noted by Koeter *et al.* (1985), five milligrams were administered in the morning at approximately 8 am when the lung function began to improve towards afternoon. At about 8 pm in the evening another ten milligram was administered, as soon as the lung function began to decline during the early hours of the morning. This chronotherapeutic routine considerable increased the 24 hours mean PEFR and FEV1 and almost averted the nocturnal decline (Koeter *et al.*, 1985).

2.4.4 LABA inhaler medication

Formoterol and salmeterol are aerosol LABA medications. However, they are associated a few adverse effects. Both medications have been know to have a duration of action of about 12 hours, although according to Kesten (1992), formoterol have been known to have a more rapid onset of affect.

Although, formoterol and salmeterol have similar composition in terms of their chemical structure, salmeterol possesses an elongated side chain that binds the molecule firmly to the β_2-adrenoceptor, allowing it to repeatedly excite the receptor Ball *et al.*, (1991). Overall, judging from the results of many large scale studies and clinical trials, it has been discovered that twice daily, within a time interval of 12 hours and a dosing of 50 μg salmeterol, compared to the dosing of 180 to 200 μg albuterol four times daily, results in better control of overnight and morning PEFR and FEV1, reduces daytime and night time asthma frequency, lowers patient dependence on BA aerosol rescue medication, and also improves night time sleep (Brambilla *et al.*, 1994). According to Brambilla *et al*., (1994), the chronotherapy of

LABA has not been comprehensively studied, hence making it a very interesting subject matter. According to the authors, it would be interesting to investigate the chronobiological effects of nighttime versus morning once daily dosing by these agents.

Amongst the ultra-LABAs are indacaterol and vilanterol, which have an active window of 24 hours. According to LaForce *et al*., (2009), several data have revealed that a single morning dose of indacaterol drastically improves the 24 hour trough FEV1, compared with twice-daily formoterol and placebo.

In a study conducted by Kempsford *et al*., (2013) to investigate the effect time has on dosing with consideration to morning and evening on lung function following administration of fluticasone furoate/ vilanterol 100/25 μg, showed no considerable differences between morning or evening dosing in patients with persistent asthma. This suggests that the timing of dosing with ultra-LABAs is not very significant. Nevertheless, any circadian effects of these long acting drugs may well be masked (Kempsford *et al*., 2013).

2.4.5 Systemic corticosteroids

Oral steroids are used as a short-term burst to manage acute deterioration in asthma patients. However, many patients with severe asthma are controlled on a long-term maintenance basis with oral corticosteroids.

According to Ceresa *et al*., (1969) chronotherapeutic investigations studying the use of synthetic steroids has to ensure pronounced endogenous circadian variation in cortisol levels is taken into account. It was noted that the administration of cortisol has a much greater effect in the morning as compared to its administration at night. In another study conducted to investigate how the time of administration of synthetic steroid affects the endogenous circadian rhythm of cortisol secretion. The administration of synthetic methylprednisolone by infusion at about 8 am and 4 pm resulted in no adrenal suppression. However, infusion at 12 am and 4 am resulted in very severe adrenocortical suppression. Infusion during 4 pm and 8 pm and also between 4 am and 8 am resulted in moderate adrenocortical suppression (Ceresa *et al*., 1969).

Beam et al., (1992) conducted a placebo-controlled, double blinded, crossover protocol to study the impact of the administration of either 50 mg prednisolone or placebo at 8 am, 3 pm, or 8 pm on FEV1 for patients with uncontrolled nocturnal asthma. Unexpectedly, the 50 mg prednisolone dose attenuated the nocturnal decline in FEV1 only when ingested at 3 pm. The ingestion of 50 mg prednisolone at 8 am or 8 pm was ineffective (Beam et al., 1992).

These results are consistent with other studies, Reinberg *et al.,* (1974) Revealing that the administration of synthetic corticosteroids at 3 pm are more effective in nocturnal asthma and cause less disruption to endogenous circadian cortisol rhythm.

2.4.6 Inhaled corticosteroids

Inhaled corticosteroids are characterized as the mainstay of asthma treatment. Inhaled corticosteroids are very effective in managing asthma symptoms in asthmatic patients regardless of the age and its severity (Barnes *et al.*, 1998). Inhaled corticosteroids come with their own advantage, which is that the corticosteroid is delivered specifically to the target area. Nevertheless, this is also dependent on the ability of the patient to use the inhaler correctly.

The deposition of the Inhaled corticosteroids in the oropharynx will lead to increased systemic absorption and the development of associated side effects. Inhaled corticosteroids inhibit inflammatory cytokines and decreases airway hyper responsiveness. It also reduces mast cells, T lymphocytes and eosinophil in the bronchial epithelium (Barnes *et al.*, 1998).

Numerous studies have been carried out with regards to the investigation of chronotherapy for inhaled corticosteroids. In one of the studies, triamcinolone acetate aerosol when administered to asthma patients at 3 pm (800 μg) was discovered to be at least effective compared to the conventional four-times-a-day (200 μg) treatment schedule (Pincus *et al*., 1995). In a second study conducted, Pincus *et al*., (1995) compared the administration of triamcinolone acetate (800 μg/day) four times a day, with single 8 am or 5.30 pm once daily dosing regimens in moderately severe nocturnal asthmatic patients. Both the four times a day and the 5.30 pm dosing

regimens improved the morning and evening PEF drastically, but not the single 8 am dose (Pincus *et al*., 1995). These results are also in agreement with chronotherapeutic studies investigating oral corticosteroids.

According to Nave et al., (2006), ciclesonide is a unique inhaled corticosteroids given once daily at night by a metered dose inhaler. Dosing with ciclesonide once daily in the morning or evening has been showed to drastically improve PEF and FEV1 without resulting in any adrenocortical suppression. Although, the evening dosing regimen best improved the morning PEF (Nave *et al.,* 2006). Once-daily ciclesonide (160 μg dose) has been revealed to be as effective when compared to the twice-daily dosage (88 μg dose) fluticasone in enhancing airway flow, reducing dependence on rescue medication and controlling asthma symptoms (Nave *et al.,* 2006).

2.4.7 Theophyllines

Although theophylline is a relatively weak bronchodilator, it has significantly strong anti-inflammatory effects. In asthmatic patients, theophylline prevents the late response to allergen. It increases the CD8+ cells in peripheral blood and also decreases T lymphocytes in the airways (Kidney *et al.,* 1995).

According to Darow and Steinijans (1987), the adverse effects of theophyllines differ depending on whether the drug is given in the morning or in the evening. The application of chronotherapy in the administration of theophylline involves the administration of medication in unequal amounts during the duration of 24 hours so that an increment in concentration is achieved during the night time. This basically implies that when the risk of asthma is greatest during the night time an increased dosage is required, whereas when the risk of asthma is lowest during the day time the dosage can be reduced (Darow and Steinijans, 1987).

According to D'Alonzo *et al.,* (1990), the asymmetric type of dosing reduces patient adherence; therefore, once daily preparations were developed. Euphylong and Uniphyl/Uniphyllin are given at night with the purpose of achieving peak concentration during the night and at early hours of the morning when the drop in PEF is at it's highest. When comparisons were made between once daily dosing in the evening (chronotherapy) and twice-daily, as well as, round the clock dosing in

asthmatic patients with a nocturnal dip on PEF, once-daily in the evening was found to be more effective for increasing the serum theophylline concentration at the time when lung function was worse, and this regimen improved the PEF (D'Alonzo *et al.*, 1990).

2.5 Chronotherapy in asthma

The efficacy of chronotherapy for asthma is most often dependent on its effects on the morning dip in FEV1 and PEF (Durrington *et al.*, 2014). However, other outcome measures are inflammation quality of life of the patient, exacerbations and nocturnal wakening. Current treatment procedures do not suggest chronotherapy instead; they provide a straightforward treatment algorithm, based on asthma symptoms (Durrington *et al.*, 2014).

According to Chung *et al*., (2014), inhaled corticosteroids (ICSs), regardless of the presence of long acting beta agonists (LABAs), are seen as the mainstays of pharmacological treatment for mild to moderate asthma. Severe asthma can be defined as asthma that necessitates treatment with increased dosage of inhaled corticosteroids plus a second controller and/or systemic corticosteroids to prevent it from escalating to the point where it is uncontrollable (Chung *et al*., 2014).

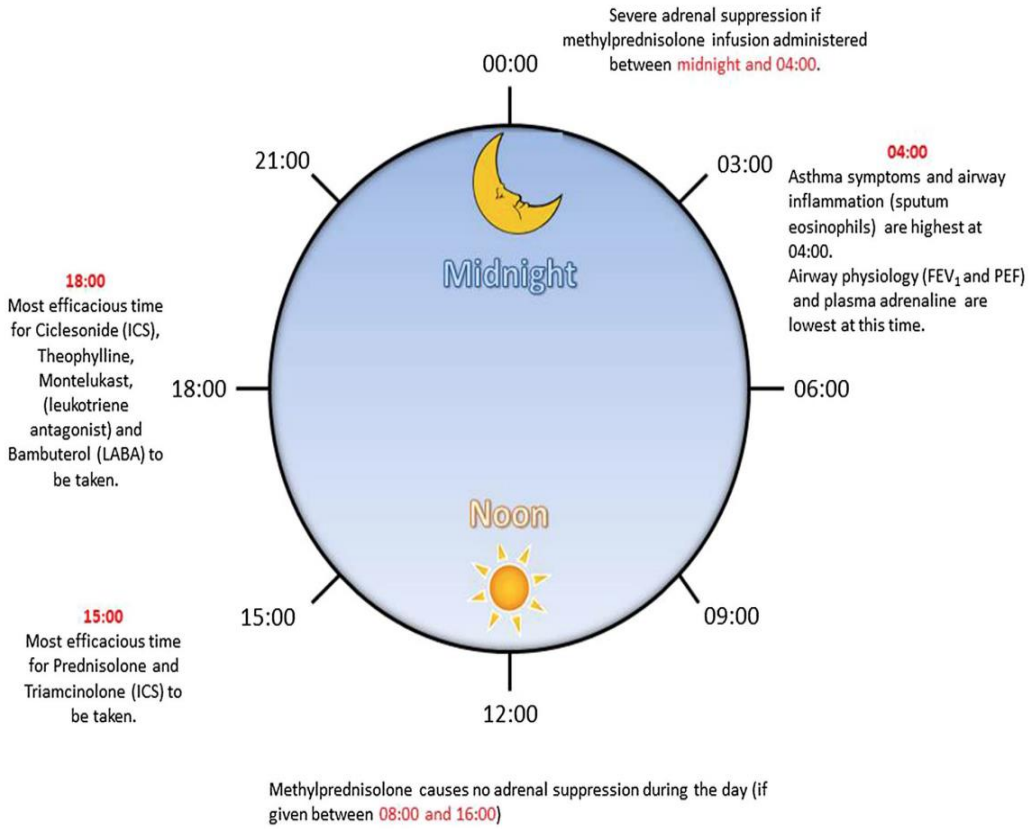

Figure 1: Asthma varies over 24 hours (Durrington *et al.*, 2014).

Figure 1 shows a summary of the changes that occur in asthma over 24 hours. At 4 am in asthma airways become more narrowed. This is accompanied by increased symptoms and increased airway inflammation also at this time (Durrington *et al.*, 2014). The most effective time to take steroids (systemic and inhaled) would most likely be around 3 pm. There is no adrenal suppression for steroids that are administered between 8 am and 4 pm, but there is adrenal suppression if administered at midnight and 4 am. If taken during the early evening rather than the morning theophylline, leukotriene antagonists or LABAs may be more effective (Durrington *et al.*, 2014).

2.6 Chronopharmaceutical technologies for the treatment of asthma

New technologies have been developed to permit the administration of medications at convenient times of day in order to help improve compliance, but allow the release of drug to be delayed to coincide with what is referred to as the morning dip in PEFR (Durrington *et al.*, 2014).

2.6.1 Application of Chronotherapy in asthma

Table 2: Chronopharmaceutical technologies for the treatment of asthma.

Technology	Chronopharmaceutical technology	Chronotherapeutic studies
Hokunalin Tape	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.
Proventil Repetabs	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	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, and terbutaline is generated in a controlled fashion during 24 hours	
Sustained-release albuterol.	Albuterol tablet with 12/24 hour dosing intervals. Contains a rate-controlling semipermeable membrane, and a core of albuterol and osmotic agent. An osmotic gradient draws water into the tablet, albuterol dissolves. It is released from the polymeric coated tablets, in which the hole has been drilled using a laser driller one just one side of the drug.	
Dutimelan	A different concentration of mix of synthetic glucocorticoids. Usually, the stronger 8 am dose consists of 7 mg prednisolone acetate, as well as 4 mg prednisolone alcohol. On	After a 1 month duration of treatment, the dutimelan greatly improved and enhanced the airway caliber without causing any adrenocortical suppression.

	the other hand, the 3 pm dosage is basically made up of 3 mg prednisolone alcohol as well as 15 mg cortisone acetate.	
Contin	Sustained release Uniphyl/Uniphyllin tablet. Complexes are formed between a cellulose polymer and a nonpolar solid aliphatic alcohol. Used for controlled-release formulations since it has a uniform porosity.	
Pastillation of doxofylline	A novel "pastillation" process applied to doxofylline, a new bronchodilator, derived from theophylline. Delivers an immediate "pulse" of drug after a delay of about 5 hours.	Evening dosing means maximal drug is released at the time of minimal PEFR.

Chapter 3

Materials and Methods

3.1 Inclusion and exclusion criteria

Results from clinical trials on cases of asthma and its treatment with regards to circadian rhythm and bronchial asthma published between January 2010 to December 2019 were utilized. The age focus was restricted to younger adults and older adults, that is, patients between 18 years to 80 years old. Articles were limited to English language. Furthermore, duplicated articles were removed.

The selection criteria for the inclusion of articles in the review included current publications (years 20010–Aug 2019), publication in English language, studies carried out on Humans and articles that pertaining to chronotherapy. Our search revealed a total of 591 journal articles, of which 10 articles were selected for review.

3.2 Search strategy

The major electronic databases were utilized amongst which were, PubMed and clinical trials. The bibliography of the included studies was hand search to identify additional studies. Abstracts of articles were then scanned and filtered using set inclusion and exclusion criteria. After selection for review, selected articles were re-read again from the point of view to classify them based on our operational definitions.

3.3 Search, data collection and analyzing

Research Database: PubMed and Clinical trials.

3.4 Data screening and extraction

An extensive search of the literature was conducted to identify publications focusing on chronotherapeutic aspects of drug therapy. Two investigators systematically review the database search independently by reading the title and abstract of the identified studies and screen out of the irrelevant ones. Included studies were read in

full text for suitability of the criteria independently, variance was managed by consensus.

3.5 Study Selection

3.5.1 Search terms

‘‘Chronotherapy’’, ‘‘Chronopharmacology’’, ‘‘Chronopharmacokinetics’’, ‘‘Chronopharmacodynamics’’, ‘‘Chronoefficacy’’, ‘‘Chronoformulation’’, ‘‘Morning and Evening’’, ‘‘Morning and Bedtime’’ and their combinations.

3.6 Study design

Randomized clinical trials that were published between the year 2010 to the year 2019. And two systematic reviews also included.

3.7 Population

Investigator independently reviewed all relevant articles to identify studies for inclusion. Data components collected directly from included article(s) were (a) patient characteristics (age sex), (b) trial inclusion and exclusion criteria, (c) medications used, does and route of administration, (d) timing of rate/rhythm control after drug administration, and (e) adverse events. Data extracted from relevant publications included: first author, data collection year, publication year, number of participants, mean age, follow up period and outcomes reported.

3.8 Outcomes measures

The major outcome of this review is any improvement in chronotherapy with regards asthma patients.

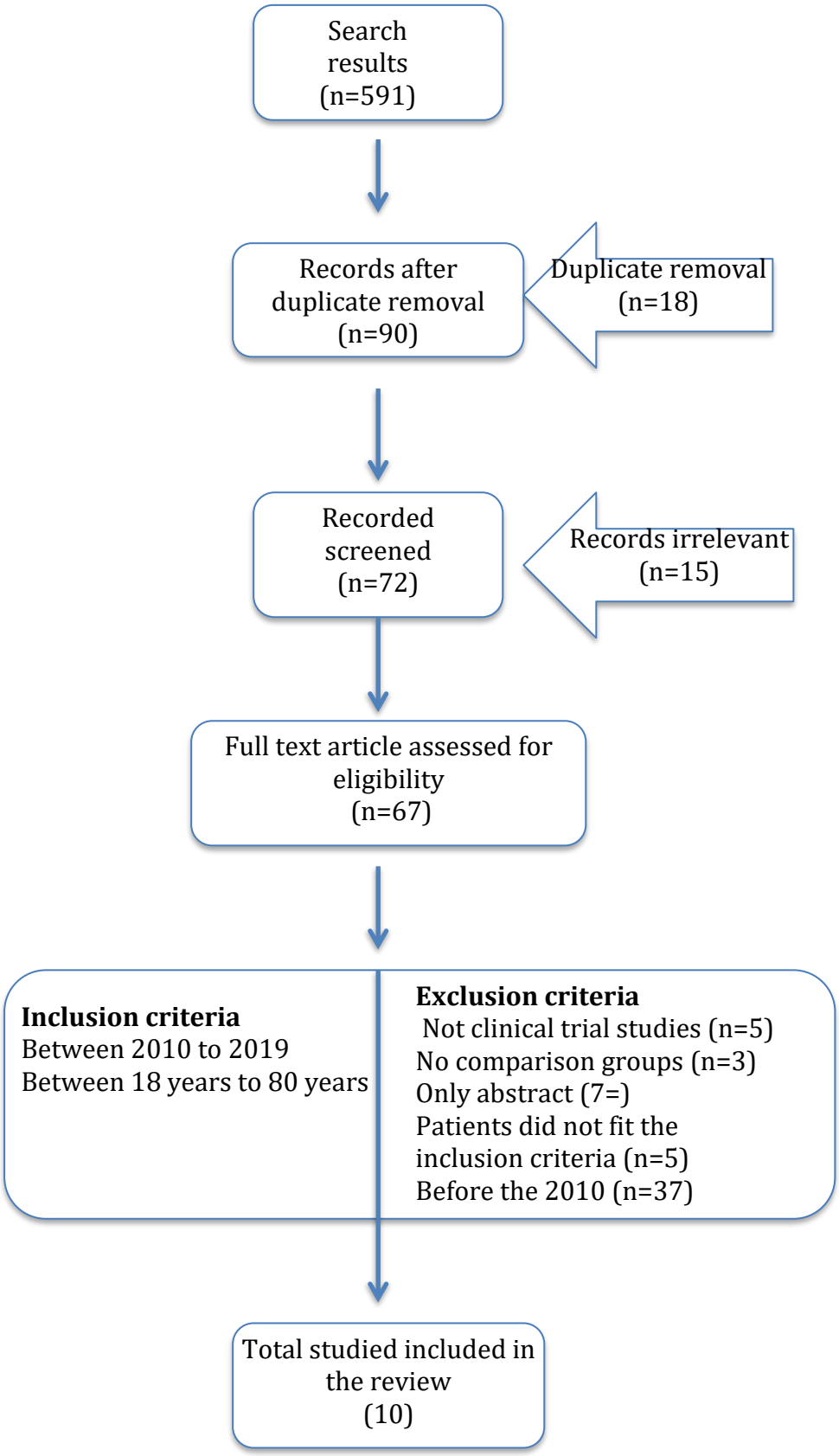
Search results (n=591)
Records after duplicate removal (n=90)
Duplicate removal (n=18)
Recorded screened (n=72)
Records irrelevant (n=15)
Full text article assessed for eligibility (n=67)
Inclusion criteria
Between 2010 to 2019
Between 18 years to 80 years
Exclusion criteria
Not clinical trial studies (n=5)
No comparison groups (n=3)
Only abstract (7=)
Patients did not fit the inclusion criteria (n=5)
Before the 2010 (n=37)
Total studied included in the review (10)

Table 3: Summary of the clinical trials examined

No	Author	Country	Population	Mean Age	Aim of study	Study Design	Primary Outcome	Results
1	GlaxoSmithKline (2016)	Australia	28	44	To investigate the effects of altering the time of day of dosing (morning or evening)	It was a randomized, triple, crossover assignment.	The primary outcome was the Pre-treatment AM and PM examination.	At the end the effective and compared effect of morning and evening dosage was realized. The total duration of the study will be approximately 13 to18 weeks for each subject.
2	Boehringer Ingelheim (2014)	Japan	285	46.5	Evaluation of Tiotropium 2.5 and 5 µg once daily delivered via the	It was a randomized, double, parallel assignment.	Initial outcome was the response obtained from	In this trial, no preliminary endpoints of efficacy were

					respimat inhaler compared to placebo in patients with moderate to severe persistent asthma.		the FEV1 after certain time duration.	defined.
3	GlaxoSmithKline (2018)	France and Germany	423	46.5	Compare the efficacy of Fluticason Furoate/Vilanterol inhalation powder with usual inhaled corticosteroids.	Allocation: Randomized Intervention Model: Parallel Assignment Masking: None (Open Label)	Primarily a self-administered questionnaire utilizing 5 questions to assess asthma control during the past 4 weeks on a 5-point categorical scale was set.	At the end of the trials the percentage of participants an almost even conclusion was drawn for both cases.
4	AstraZeneca (2019).	Chile,	233	46.5	Evaluate the onset	Allocation:	Ascertain the	A final result was

		Germany, Hungary, Korea, Philippines, United States			of effect and time course of change in lung function with benralizumab.	Randomized Intervention Model: Parallel Assignment Masking: Double (Participant, Investigator)	effect of benralizumab on the time course of change on lung function.	obtained on the evaluation of patient impression of overall asthma severity, as well as, overall change from baseline as reported by the patient.
5	Milton S. Hershey (2018)	United States	144	39	This study will evaluate the effectiveness of clarithromycin at controlling asthma symptoms.	Allocation: Randomized Intervention Model: Parallel Assignment Masking: Quadruple.	Asthma reduction by monitoring and controlling medication use.	An adequate AM and PM time was arrived at.

6	Boehringer Ingelheim (2015)	Argentina, Austria, Croatia, Estonia, Guatemala, Hungary, India, Italy, Korea, Poland.	465	46.5	The aim of this trial is to evaluate the efficacy of 2.5 and 5 mcg tiotropium compared to placebo over 12 week treatment period.	Allocation: Randomized Intervention Model: Parallel Assignment Masking: Double	Peak FEV1 0-3h response was defined as the difference between the maximum FEV1 measured within the first 3 hours post dosing after a treatment.	At the end of the trial the change from baseline at the end of 12 week was achieved.
7	Milton S. Hershey (2018)	United States	224	25	This study will examine the effectiveness of the medication tiotropium bromide combined with a low dose of ICS at maintaining asthma	Allocation: Randomized Intervention Model: Crossover Assignment Masking: Quadruple	Asthma reduction by monitoring and controlling medication use.	An adequate AM and PM time was arrived at.

					control in people with moderately severe asthma.			
8	Milton S. Hershey (2018)	United States	342	25	The clinical trial examined the benefits (if it was more beneficial) to adjust corticosteroid treatment based on asthma symptoms and/or biomarkers of lung function versus standard medical guidelines.	Allocation: Randomized Intervention Model: Parallel Assignment Masking: Quadruple	The initial time of treatment was set.	At the end of the trial the total amount of oral prednisone required and total amount of inhaled steroids was achieved.
9	GlaxoSmithKline (2017)	United States	48	36.5	This study is intended to	Allocation: Randomized	Determination of adequate	FEV1 was documented in

					determine the dose response and duration of action.	Intervention Model: Crossover Assignment Masking: Double	dosage response.	triplicate, having patients advised to inhale full breaths regardless of the likelihood of chest tightness or not. With consideration to FEV1, a pre-challenge baseline was defined test was conducted for each challenge time point as maximum of triplicate measurements performed prior to the commencement of the challenge.

10	Boehringer Ingelheim (2014)	Brazil, China, Colombia, Germany, India, Japan, Mexico, Poland, Romania, United States	1032	46.5	The aim of this trial is to evaluate the efficacy and safety of 2.5 and 5mcg tiotropium over a 24-week treatment period as compared to placebo and salmeterol (50 mcg twice daily).	Allocation: Randomized Intervention Model: Parallel Assignment Masking: Double	Control medication in patients with moderate persistent asthma.	Efficacy and safety was be assessed by measuring effects on lung function, effects on quality of life, effects on asthma control was also measured

4.1 Discussion

Our search revealed a total of 591 published articles, of which 10 articles were selected based on the inclusion and exclusion criteria. The most common study design utilized in these studies was the Randomized Control Trial (RCT). The findings of one of the journals were inconclusive, however initial results with regards to the outcome of FEV1 was obtained after certain time duration. Nevertheless, the other articles demonstrated a positive outcome that is, made substantial finding on the use of chronotherapy in asthma treatment.

This review sought and evaluated current published literature (2010–Aug 2019) which evaluated the time and intervals for the administration of drugs with regards to asthma patients. The presentation of the results was based on the use of meta analysis and the definition of different terminologies as they relate to the field of chronotherapy. We discovered from our research that there are several emerging studies and investigations supporting the application of chronotherapeutic principles. This is the case for drugs utilized in conditions where there is a clear circadian influence on disease pathophysiology, for which asthma has been found to be one of those types of drugs.

In one of the studies examined, out of the 1169 asthma patients admitted in the hospital, a total number of 10 deaths were experienced. Nevertheless, all the ten deaths experienced happened between the hours of 12 am and 6 am. This implies an increased possibility for considerable worsening of asthma in the nocturnal hours. Nocturnal worsening of the symptoms have been directly linked to increased death rate in asthma patients.

From another clinical trial study performed over a period of 24 months the authors examined markers for disease severity and the use of drugs. They discovered that those who had died were frequently reported for awakening at night. Additional, other symptoms and disease such as airway caliber, measured by peak expiratory flow rates (PEFRs) or forced expiratory volume in 1 second (FEV1), and bronchial hyperresponsiveness to irritants all go along with the circadian rhythm and for which they are highly dysfunctional at night.

Furthermore, it has noticed that airway hyperresponsiveness to aeroallergens fluctuates significantly worsens at night. This can be based on the time in which the aeroallergen was inhaled. From one of the trials conducted, the changes in FEV1 was studied. As a marker of bronchial patency, after breathing in dust at four time marks (8 am, 3 pm, 7 pm, and 11 pm) the entire day, it was found that the drop in FEV1 was greatest when the exposure occurs at 11 pm (20% decrease) and much smaller when the exposure occurred at 3 pm (5% decrease).

The use of inhaled corticosteroids in chronotherapy as a means to the management and treatment of asthma was brought about by the knowledge of oral corticosteroid. In one of the clinical trials, a once daily dosing at 3 pm of an oral corticosteroid was found to be much more effective than the traditional 8 am or 8 pm dosing. When prednisone was administered at 3 pm, the patients experienced decreased reduction in FEV1 over- night as at when compared to placebo. On the other hand, the 8 am and 8 pm dosage revealed no difference in FEV1 compared to placebo. Furthermore, in cases where prednisone was given at 3 pm, the patients displayed substantial improvement in morning FEV1 the next day.

Another study showed that the optimal once daily dosing of an ICS (triamcinolone acetonide) is actually between 3 pm and 5:30 pm. The administration of the inhaled ICS once a day within this timeframe indicated equal efficacy to the four times daily dose arm in improving PEFRs. In addition, both the afternoon dosing and QID dosing were much more effective when compared to the once a day morning dosage of 8 am. Prior to this, traditional dosing of ICS was actually four times daily.

Studies also suggest that the once a day or twice a day dosage, when administered at appropriate times could not only improve symptoms but also improve medication adherence. Also beclomethasone dipropionate, was considered in order to determine its effectiveness with regards to once daily dosing as opposed to twice daily. From the study it was found that beclomethasone had as much efficacy of maintaining mean morning and evening PEFRs, if it was either administered twice daily (500 μg) or as a single dose (1000 μg) towards evening at 5 pm or at night by 10 pm.

The trial concluded that a single daily dosing between the late afternoon hours or evening hours was also a befitting alternative to twice a day dosage. Mometasone

furoate also displayed an equal value and efficacy with once a day dosage in the evening as compared to twice a day treatment. Further studies also revealed that inhaled mometasone 200 μg, given in the evening, was as efficient in maintaining FEV1 readings and morning PEFRs as 400 μg daily dosage in the morning and was much better to 200 μg administered in the morning.

In another clinical trial examined, short-acting beta-agonists (SABAs) provide bronchodilation and symptom relief. Usually, the time interval for SABAs to effectively act is approximately between 4 to 6 hours. Therefore, when taken long before bedtime, this unfortunately subjects most asthmatic patients to severe worsening during the early morning hours. It was also seen that inhaled long-acting beta-agonists (LABAs) can aid in minimizing nocturnal symptoms.

In other clinical trial theophylline was used on the patients. Theophylline is a phosphodiesterase inhibitor and mild respiratory stimulant. It was shown to have the capacity to achieve higher theophylline serum strength at night resulting in higher awakening FEV1 measurements. A once daily (long acting) preparation of theophylline given at approximately 7 pm, hence producing a highest serum dosage during the early hours of the morning was shown to be more effective than traditional twice daily dosing of the drug.

For the last few years the field of chronotherapy has been of great interest to the medical field. From the reviews conducted it would be necessary to pay more attention to chronotherapeutic principles. On the other hand, it was also discovered that the amount of research of asthma management using chronotherapy was limited. Our analyses also indicated that in cases in which publications noted that the drugs being tested or administered were done at a particular time, for example morning, evening, night time or bed- time, the actual time for the administration of the drugs were not clearly stipulated. In addition, drug administration times such as evening or night are sometimes used interchangeably.

Taking into consideration the numerous mechanisms that govern the use of chronotherapy for asthma patients, our review suggests that futures researches should be concentrated chronoeffectiveness trials. This suggestion is made due to the fact that chronoeffectiveness can be considered as being relatively easier to conduct.

Chronoeffectiveness studies can easily be incorporated within a regular clinical trial, as they usually only require an additional arm where in the drugs are administered at a time conflicting with the circadian clock as compared to the time in which the drug is being administered in the actual trial.

Chapter 5

5.1 Conclusion

This thesis work presented the scope of chronotherapy with regards to asthma treatment. It is believed that the knowledge and science of chronotherapy is increasing becoming an effective and recognized technique for asthma treatment and management. The current and ongoing studies on the use of chronotherapy is promising.

This statistical review has highlighted several concepts and definitions within the field of chronotherapy. Using these definitions, a scope of the utilization of chronotherapy was done. It has shown that there is considerable evidence for the effect of time on the administration of drugs with regards to asthma patients. In such conditions, it may be prudent for professional practice guidelines to make due reference to chronotherapeutic principles. We believe that the knowledge of chronotherapy is growing and current researches within this are promisingly.

5.2 Impact of findings on practice

- Firstly, based on our finding from the research carried out, it was discovered that there are other drugs and diseases in which research have suggested an optimal circadian time for the administration of the drugs. It is important that medical practitioners absorb this knowledge to relevant drugs and conditions in order to increase the effectiveness of clinical effects.
- Secondly, it was also discovered that it is important that when medical practitioners are counseling patients on the time duration and interval for medications should be administered, pharmacy practitioners must pay more attention to the circadian influence on drugs and the disease condition being treated.

5.3 Recommendation

- In any future clinical trials carried out, studies should also endeavor to explore gender, genetic and age related differences. Preliminary assessment of new drugs for chronotherapeutic usage can serve as a effective way to improving the quality of drugs utilized and the management of asthma patients.
- Clinical curricula should incorporate a certain level of exposure towards the concept of chronotherapy.
- It was noted that most of the studies were performed within Europe. This therefore makes it difficult to generalize the results obtained to the entire worlds population.
- Furthermore, it was discovered that most of the chronotherapeutic research works have been performed with conventional or already marketed drugs. It is my opinion that all new drugs should be checked for chronotherapeutic potential. This can be done using a preliminary screen of checklist and questions.
- I also found that most reviewed studies examined and described mostly main clinical effects but did not actually make any reports and the outcomes such as adherence. The time in which a drug is administered is a key element of adherence because administration at times that are skewed against the optimal circadian time may negate the therapeutic effect and sometimes even the patient's safety. Therefore, it is important that chronotherapeutic experts and researchers alike factor in adherence or the effects of chronotherapeutic administration on adherence in future studies.
- Chronotherapy is now accepted by biologists and researchers; however, it still somewhat of an under explored area. In my opinion efforts should be made to bring chronotherapy within mainstream of clinical practices incorporating clinical practitioners such as nurses, pharmacists and physicians, who have a major role in bringing the benefits of chronotherapy to their patients. Pharmacists in particular are in the best position to aid in the education of patients regarding differences between conventional and chronotherapy drug administration, the rationale behind it as well as its advantages.

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