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The Pattern, Flow, Tempo of the Importance of Circadian Rhythm of Pain, And Analgesic Treatments

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ABSTRACT

The lower extremity specialist may have come to appreciate and respect that medical treatments that can be enhanced by an understanding of pharmacodynamics, pharmacogenomics, and pharmacokinetics of selected medications to include analgesics specifically opioids. Furthermore, these same foot and ankle specialist may fine-tune their prescribing abilities with analgesics by familiarizing himself or herself with the science of chronotherapy. The primary goal of chronotherapy is to determine times for drug delivery that allows for low toxicity and an increase in a medication's efficacy. Chrono pharmaceutics has been described as a branch of pharmaceutics devoted to the design of drug delivery system to ensure that a bioactive agent's release at a rhythm ideally matches the biological requirement of a given disease. The primary purpose of this narrative review is to describe, explore and present Chrono therapeutic concepts as they intersect with analgesics within the context of pain management and circadian rhythms. First, data and theories on the interaction of pain pathology and circadian rhythm will be introduced. Secondly, the science of pharmacogenomics and circadian rhythms as mediators of analgesic properties, specifically opioid drug-drug interactions grounded in the effects of pharmacokinetic metabolism will be presented. Lastly, relevant technology will be described to allow a lower extremity specialist to appreciate Chrono therapeutic drug delivery systems of a specific opioid analgesic.

Keywords
Medical treatments, Circadian Rhythm, Opioids, Pain management.

Introduction

The human body's functions are many and vary considerably during the day in a rhythmic fashion. Throughout the centuries, scientific investigations have been conducted to study both animals and plants processes behavioral and physiological rhythms known as "circadian rhythms". Sunil et al stated that the term "circadian" was devised by Halberg and Stephens in 1959 [1,2]. This autonomous and internal timing system is otherwise known as circadian clocks [3-6]. The Earth's rotation is the main environmental factor that promotes the formation of circadian clocks in different animal and plant species [2]. It comprises three components: 1) an input pathway comprising the photoreceptors and projections of the retinal ganglion cells, 2) circadian pacemakers that generate the circadian signal, and 3) an output pathway that combines the pacemakers with the effector systems [1,7,8]. Given this makeup, agitating this clock can trigger a series of diseases, such as metabolic syndrome (obesity, diabetes and cardiovascular diseases), neurological disorders, and the sleep deprivation caused by shift work [9]. Furthermore, the pain intensity of many diseases has been shown to also have a circadian rhythm [3]. Pain has been described as an unpleasant feeling that includes the emotional experience associated with actual or potential tissue damage. The International Association for the Study of Pain defines chronic pain as "pain that extends beyond the expected period of healing or progressive pain due to non-cancer disease" [10]. Chu et al takes this further by classifying different pain conditions as nociceptive pain, inflammatory pain, and neuropathic pain that may be affected by circadian rhythms [3]. Furthermore, Sunil et al assert that these rhythms not only affect the onset and severity of many diseases (including intractable pain), but also affect the medications for treating these diseases [1].

Lower extremity specialists may come to appreciate and respect that medical treatments that can be enhanced based on when they are given to a patient are collectively known as chronotherapy [1]. Furthermore, podiatric physicians can hold at a high value that the primary goal of chronotherapy is to determine times for drug delivery that allows for low toxicity and an increase in a medication's efficacy [1]. Chrono pharmaceutics has been described as a branch of pharmaceutics devoted to the design of drug delivery system to ensure that a bioactive agent's release at a rhythm ideally matches the biological requirement of a given disease [1]. The primary purpose of this narrative review is to present and describe chronotherapeutic concepts as they intersect with analgesics within the context of pain management and circadian rhythms. First, the data and theories on the interaction of pain pathology and circadian rhythm will be introduced. Secondly, the science of pharmacogenomics and circadian rhythms as mediators of analgesic, specifically opioid drug-drug interactions will be presented. Lastly, the relevant technology will be described to allow a lower extremity specialist to appreciate chronotherapeutic drug delivery systems.

Pain System and Circadian Rhythms

The pain system encodes and relays noxious sensory information from the periphery into the central nervous system to produce protective behavioral outcomes [11]. Clinical research has revealed that pain responsiveness varies across the day in both sexes of diurnal and nocturnal species (including humans) and that the pain system exhibits circadian rhythms when functioning [11-15]. In relation to this, the endogenous opioid system regulates the pain, emotional, and stress responses [16]. The circadian variations in the opioid levels and the binding activity throughout the day suggest that the opioid system plays a role in the circadian regulation of pain. This could potentially be through the modulation of the pain system. Several hormones that interact with the pain system exhibit circadian rhythms including cortisol, gonadal hormones, and melatonin. Cortisol modulates acute pain responsiveness and is thought to play a role in the development of chronic pain [17]. Its rhythms are phase-dependent and fluctuate across the day; the levels rise in the hours before waking and peak just after the onset of activity [18,19]. On the other hand, melatonin has a primarily analgesic effect, although the exact mechanism by which it produces analgesia is unknown [20,21]. Melatonin concentrations fluctuate in a phase-independent manner; its concentrations peak and persist in the dark phase and are almost entirely absent in the light phase [22].

Tanaka et al. attempted to identify the factors associated with the circadian rhythms of pain. They focused not on the diseases but the factors and mechanisms associated with pain, namely neuropathic pain and psychological factors [23]. This was because, in a study by Spar et al., patients with chronic low back pain—who were classified into two groups based on pain mechanism—and patients with neuropathic pain exhibited more intense pain and negative psychological states than those with nociceptive pain [23,24]. Therefore, Tanaka et al. chose to focus solely on the circadian factors and mechanisms associated with pain, namely neuropathic pain, and the psychological factors. They believed that neuropathic pain influenced the circadian rhythms of pain [23]. In addition to this, Wolf et al. reported that in patients with fibromyalgia, the severity of loneliness in the morning affected the intensity of pain in the evening [25]. Moreover, they surmised this is because the psychological factor of loneliness may be contributing to the circadian rhythm more than fibromyalgia itself [25]. Considering these findings, Tanaka et al. postulated that neuropathic pain and psychological factors affect circadian rhythms. This makes it necessary to understand and classify the circadian rhythms in terms of the disease and the pain itself [23]. In relation to this, they proposed two hypotheses: 1) Multiple patterns of pain circadian rhythms exist and are associated with neuropathic pain and psychological factors; 2) neuropathic pain influences the circadian rhythms of pain [23].

The study by Tanaka et al. investigated the relationship between the types of circadian pain rhythms and the factors associated with these rhythms among community-dwelling chronic pain patients. The most common site of pain was the lower extremity (46%). The total number of patients experiencing lower extremity and upper extremity pain accounted for less than 80% of the participants, with 35.7% of them experiencing neuropathic pain [23]. The study's results also indicated that it is appropriate to evaluate circadian rhythms through the lens of various diseases since these rhythms present in patterns that are difficult to explain based on a single disease's characteristics. Thus, in chronic pain patients, circadian rhythms need to be evaluated individually, as it may help in developing treatment strategies, such as adjusting their daily activities and physical activities [23].

Pharmacogenomics and Circadian Rhythms

Pharmacological methods center on melatonin, a rhythmically circulating hormone known to be important in the regulation of sleep and circadian rhythms. Melatonin directly affects the clock phase through the activation of melatonin type 2 receptors and is prescribed for numerous sleep disorders [26-28]. It is this author's hypothesis that supplemental Melatonin may assist patients with chronic pain by affecting these patient's clock phase and the further research is needed.

One of the more interesting areas in circadian treatment is chronotherapeutics. For example, chemotherapy treatments such as those related to cancer are applied in line the timing dictated by the molecular clock, allowing therapeutic actions to be maximized according to the transcriptional state of the target [29,30].

Early evidence suggested that a genetic mechanism lay at the core generator of self-sustained circadian rhythms. In 1961, Colin Pittendrigh noted that the clock mechanism could be contained in single cells and was considered unlikely to be simply a chemical reaction since it was relatively insensitive to the fluctuations caused by temperature variations [32]. Further evidence that gene transcription and translation was involved showed that the inhibition of protein synthesis could reset or temporarily stop the circadian clock [31-34].

Pharmacogenomics and circadian rhythms acts as mediators of cardiovascular drug-drug interactions. The rapidly incoming data from genomic and other panomic profiling research have revealed the existence of pharmacological "interactome" (pharmacointeractome) networks that function as regulators or determinants of multiple biological processes. These processes include drug absorption, distribution, metabolism, transportation, and excretion. They not only coordinate to maintain the optimal dosage and duration of drug exposure to therapeutic targets, but also give rise to drug-drug interactions [35-37]. Physiologically and pathophysiologically, the expression of biological clock genes results in the temporal dimension of the drug interactome. This allows for a more accurate administration time, allows for more proper use of circadian-time, and allows for the observation of dependent risk for drug-drug interactions [35,38,39].

A lower extremity specialist can recognize that the knowledge of opioid pharmacokinetics parameters is critical for a safe and effective administration. Absorption is the proportion of the active drug (whether given intravenously or absorbed from the gastrointestinal, respiratory, or cutaneous system) that enters the systemic circulation is defined as bioavailability. The wide bioavailability range amongst different opioids is partially attributable to differences in the first pass metabolism, i.e., when the drug is metabolized directly by the liver from the gastrointestinal tract before it reaches the systemic circulation. Distribution refers to the movement of the drug between the blood and various tissues in the body. The targeted tissue for opioids is the central nervous system (CNS). To activate the targeted receptors, the opioids must cross the blood-brain-barrier. The opioids with a higher volume and distribution are usually more lipophilic and more likely to distribute quickly and strongly in and out of the blood-brain-barrier. In clinical practice, these opioids also tend to have a quicker onset and a shorter duration of analgesic action. In this regard, metabolism is central to opioid pharmacokinetics. The metabolism process may involve the cytochrome (CYP) P-450 enzymes, particularly CYP 2D6 and 3A4, or other enzymes such as Uridine 5'-diphospho-glucuronosyltransferase (UDP-glucuronyltransferase). The spectrum of the interpatient analgesic variability and the clinically significant drug interactions of opioids are mostly due to the CYP enzymes. The interpatient analgesic variability of CYP 2D6 influences the metabolism of codeine, hydrocodone, oxycodone, and tramadol and has been found to have many genetic polymorphisms. Based on the phenotypic profiles, the patients can be poor, intermediate, or extensive metabolizers. Fentanyl and methadone are primarily metabolized by CYP 3A4. Although CYP 3A4 has many genetic polymorphisms, none have shown to be of major clinical relevance. UDP-glucuronyltransferase, the primary enzyme responsible for the metabolism of morphine, hydromorphone, oxymorphone, and tapentadol, does not possess significant interpatient variability either. However, three types of CYP P-450 enzyme subcategories are capable of clinically significant drug interactions: substrates, inhibitors, and inducers. Substrates require P-450 enzymes for metabolism. When enzyme inhibitors or inducers are concomitantly administered with the substrates, the serum levels of these substrates are altered. These enzyme inhibitors may increase the opioid serum levels and cause over-sedation, while the inducers may decrease the levels, leading to inadequate analgesia.

The constitutional clock genes and their complexes, through a predictable-in-time (circadian rhythmic) cycle, biologically activate or inactivate non-clock genes. These control and modulate a great number of biological processes, including those that play a role in drug metabolism and transport [40]. They include ones that give rise to administration-time differences in the pharmacokinetics of drugs, i.e., their absorption from the gastro-intestinal tract, distribution in free and protein-bound form, metabolism, and/or excretion. It has been well documented that CYPs may function in a circadian rhythm fashion during human diseases and affect drug metabolis [40-43]. Moreover, the drug metabolism can be affected by circadian variations in the 1) Phase I family of enzymes which, based on the laboratory animal models, collectively encompasses at least 28 CYP450 entities, 2) Phase II enzymes that modify Phase I-derived metabolites, and 3) the Phase III membrane transporters responsible for the elimination of the Phase II products. The study of drug-administration-time phenomena, with reference to the staging (peak and trough) of deterministic circadian rhythms, have formulated new perspectives on the relationship between the pharmacokinetics and pharmacodynamics of medications [44]. A lower extremity specialist can appreciate the research by Sunil et al., which presented several analgesics that are affected by circadian rhythms (Table 1) [1].

Table 1: Analgesics and Pharmacokinetic Process affected by Circadian Rhythms and Pharmacogenomics.

Analgesics		**Pharmacokinetic Processes**	
Acetylsalicylic Acid		**UGTs***	
Ibuprofen		**CYP2C8**	**CYP2C9**
Indomethacin		**CYP2C9**	
Ketoprofen		**CYP2C9**	
Paracetamol-Acetaminophen		**UGTs**	**SULT****
Piroxicam		**CYP2C9**	
Fentanyl		**CYP3A4**	
Morphine		**UGTs**	
Codiene	**Active metabolite is Morphine**	**CYP3A4**	**CY2D6**
Legend			
***UGTs**	**Uridine glucuronyl transferases**		
****SULT**	**sulfotransferases**		

Chronotherapeutic Drug Delivery Systems

Chronotherapeutic drug delivery systems tend to favor delayed or controlled-release formulations; however, advanced systems need to incorporate a real-time triggering biomarker to activate an on-demand release [45]. Examples of such constructs include chronoprogrammable electronic pumps that control drug infusion [46]. Other alternatives, in principle, involve the application of hydrogels with an appropriate response (such as swelling) onto the environmental rhythms of the surrounding fluids [47].

Chronotherapeutics has been seriously considered for several treatments: anti-inflammatory therapies using nonsteroidal anti-inflammatory drugs to match the drug with the expected cytokine peak; asthma, due to the immune system's variations in function; cardiovascular disease, due to the daily variation in blood pressure; dyslipidemia, due to the circadian nature of cholesterol metabolism; cancers, due to the circadian pattern of the adverse effects of chemotherapy [1]. It is hoped that pain management research will evolve to enhance the present chronotherapeutics by boosting the different techniques used in the preparation of its drug delivery systems, like the CONTIN® system.

CONTIN® technology (Purdue Pharma, Pickering, Ontario, Canada) combines a drug and hydrophilic polymer, followed by selective hydration with a polar solvent and fixation through a higher aliphatic alcohol.[1] CONTIN® technology functions as a conventional sustained release matrix system. Research has suggested that evening administration of Uniphyl® (theophylline) demonstrated that uses CONTIN® technology might improve lung function as compared to patients who oral ingested Uniphyl® throughout the day. However, investigations revealed that, when taken at night, Uniphyl® caused the theophylline blood levels to peak during the early hours of the morning [1,48,49].

Moreover, the first patients to use OxyContin® were women recuperating from abdominal and gynecological surgery at two hospitals in Puerto Rico in 1989 [50]. In the clinical study, designed and overseen by Purdue scientists and paid for by the company, 90 women were given a single dose of the drug while other patients were given short-acting painkillers or placebos [50]. None of the women in this observational investigation were regular users of painkillers, so it was concluded that they were more susceptible to the effects of narcotics.

It is found that more than a third of the women given OxyContin® started complaining about pain in the first eight hours and about half required more medication before the 12-hour mark, according to an FDA analysis of the study [50]. This study found that OxyContin® was safe, relieved pain and lasted longer than the short-acting painkillers. Purdue moved ahead on two paths: seeking patents for its new drug and running additional clinical trials to secure FDA approval [50]. In a 1992 submission to the Patent Office, the company portrayed OxyContin® as a medical breakthrough that controlled pain for 12 hours "in approximately 90% of patients." Applying for a separate patent a few years later, Purdue said that once a person was a regular user of OxyContin®, it "provides pain relief in said patient for at least 12 hours after administration."

This author postulates it if this delivery technology was less than stellar for treating acute and chronic pain with oxycodone. It is hoped that recent advancements in chronotherapeutics paved the way for developing **pulsatile drug-delivery systems** allowing the release of encapsulated drugs like opioids after the programmed lag phase to treat acute and chronic pain. It is hoped that the recent advancements in chronotherapeutics will pave the way for developing **pulsatile drug-delivery systems,** allowing the release of encapsulated drugs like opioids after the programmed lag phase to treat acute and chronic pain.

Conclusion

After reading this narrative, it is hoped that lower extremity specialists will understand the interplay between circadian rhythms, pain characteristics, and interindividual physiological differences. It is hoped that these specialists will understand that the existing oral dosage forms like tablets or capsules are developed with immediate, sustained, and controlled release formulations to cause the desired therapeutic effect. Lastly, empowered with the circadian rhythms and pharmacogenomics data from this review, lower extremity specialists may enhance their approach to treat their patients' pain syndromes with opioid analgesics.

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