

DOWNLOAD PDF CIRCADIAN VARIATION IN CARDIOVASCULAR DISEASE: THE NEED FOR COMPLIANCE

Chapter 1 : Recent advances in circadian rhythms in cardiovascular system

The importance of circulation variations in cardiovascular diseases has led to a growing acceptance among clinicians that effective therapy should provide complete protection over the full hour period.

Four hundred years later, this statement has been repeatedly supported by mounting basic and clinical research and is widely understood to be true. Light-dark cycles synchronize biological functions with the environment in a periodic pattern that takes about 24 h, which is known as the circadian rhythm. Despite growing evidence of the impact that circadian dysfunction has on morbidity and mortality rates for numerous common medical illnesses, topics such as human circadian biology, circadian disorders, and chronobiology have received limited consideration in the medical school curriculum. Today, the few health care professionals who gain adequate competency in these areas do so mostly as a result of postgraduate specialty training. This leaves a large body of professionals unaware of how to i evaluate the clinical relevance of circadian cycle disruption in disease onset, ii optimize therapeutic strategies to include times of the day at which treatment efficacy is most favorable, and iii gauge the relevance of chronotherapies for disease outcome. According to the Bureau of Labor Statistics, in the U. Disruption of circadian rhythms because of long-term shift work has been implicated in many different illnesses including the top two causes of death among Americans - cardiovascular disease and cancer, most prominently breast and prostate cancers [3 , 4]. Even short-term health effects e. As a result, there is a sense of urgency in having medical students understand the relative contribution of the environment to diverse aspects of human physiology early in their careers. These subjects are typically only taught for a short time period and are restricted to a number of specific sleep topics e. A recent survey of medical schools across different countries, which had a Although structured teaching on the topic of circadian-related disorders and chronobiology would be difficult to incorporate in an already demanding curriculum, alternatives include developing core competencies that focus on: The authors propose to integrate these competencies using a longitudinal teaching format within three different levels in the medical curriculum and without the need for developing additional lectures Table 1. Table 1 Strategies for incorporating circadian rhythm concepts in the medical curriculum. Patient education regarding shift work and sleep disorders â€” Continuing educational opportunités as available First, we envision an approach in which circadian biology becomes part of the conversation early on in medical school by adding the topic to existing blocks of lectures allocated to, for example, metabolism, endocrine regulation, and gene expression; all of which are processes that have been proven to be linked to circadian rhythms on a molecular level [12 , 13 , 14 , 15]. Application of circadian rhythms to clinical medicine is of relevance as the time of day is an important variable when running medical tests [e. In addition, conceptualization of biological rhythms in laboratory medicine is certainly relevant to health professionals as it represents a challenge, helps improve diagnostic accuracy, and is an opportunity to better assess the therapeutic efficiency of a given drug. Figure 1 Circadian acrophase chart for various parameters in plasma. It is certainly clear that concepts such as chronokinetics, dose-time dependent differences in absorption, distribution, metabolism, and elimination of drugs from the body [23 , 24], and chronodynamics, dose-time dependent differences in drug effects [25], may challenge some long held concepts in pharmacology. Making students aware of the current status of knowledge in these areas will provide them with a more holistic view of what constitutes the best therapeutic strategy. Accordingly, circadian variations in blood pressure, heart rate, and other mediators have been shown to increase the risk of stroke and myocardial ischemic events in the morning [26], which led to the examination of cardiovascular medications and the impact of their timing. For example, many studies found a benefit in dosing amlodipine and other cardiovascular medications at bedtime [27 , 28 , 29]. Others examined how chronotherapy affects subsets of patients with chronic conditions and risk factors for hypertension or cardiac disease. Remarkably, hypertensive patients with type 2 diabetes that are given medication for hypertension at night exhibited significant decreases in both nocturnal and 24 h systolic blood pressure values [30]. Other prospective studies

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for chronotherapy regarding antihypertensive medications, demonstrated that bedtime dosing was more effective in controlling the 24 h blood pressure pattern while concurrently reducing adverse effects and cardiovascular disease risk, particularly for those medications targeting the renin-angiotensin-aldosterone system [31 , 32]. The need for chronocontrol of blood pressure is of relevance to reducing vascular risk associated with chronic kidney diseases, as bedtime ingestion of angiotensin-converting-enzyme inhibitors as well as angiotensin-receptor blockers have proven to be more effective in reducing blood pressure during sleep, as well as, overall than morning intake [33]. Consequently, careful timing of medication dosing provides clinicians with a means to effectively treat hypertension-associated disease severity. Other disparate examples involve the optimization of chrono-based formulation for the treatment of rheumatoid arthritis using low doses of prednisone clinical trial NCT, [34] as well as the development of chronopharmacotherapy adjunctive approaches to enhance cognitive-behavioral therapies for treating a resistant form of obsessive-compulsive disorders [35]. Chemotherapy is another area of medicine where including time-of-day-dependent administration of treatments in the form of chronotherapeutic protocols has shown promising results [36]. For example, a recent clinical study established a relationship between circadian rhythms and the variable pharmacokinetics and toxicity of cisplatin for patients with advanced non-small cell lung cancer [37]. Similarly, chronomodulated chemotherapy of platinum-based drugs and 5-fluorouracil can significantly improve efficacy and reduce adverse events in patients with metastatic colorectal cancer; however, these results must be taken with caution as its effect may be different for the treatment of other solid tumors [38]. Nevertheless, what started as a growing understanding of the importance of biological timing for normal physiology and the pathophysiology of diseases like cancer is now a more comprehensive field that revolves around cancer-associated clock disruptions, clock-dependent mechanisms of cancer, and chronotherapeutic approaches. Areas of study such as neurology and psychiatry would also benefit from incorporating concepts related to circadian behavior in their lectures, as several lines of evidence show a direct, albeit complex, relationship between sleep and circadian abnormalities and cognitive performance and even neurodegenerative disorders [39 , 40 , 41]. Delay, advances, or desynchronizations of circadian rhythms are important pathophysiological factors that influence psychiatric disorders and are, by far, the most widely reported disturbances associated with depression [42]. Changes in daily and seasonal mood variations [43 , 44 , 45], brain activity [46 , 47], core body temperature e. Because circadian alterations may represent a core component of depression, at least for some patients, they are worth clinical and therapeutic consideration. Consequently, programs need to be organized in a manner in which pre-clinical instruction incorporates knowledge about the connections between biological clock functions and behavior. This could be accomplished through individual combinations of lectures, problem-based learning, tutorials, small-group seminars, and even as part of the early contact with patients. Thus, concepts are incorporated at all levels from passive information absorption through didactically-delivered lectures to an active learning system when interacting with patients. Second, since almost every physiological variable that is taken into consideration as a diagnostic indicator in the clinic has been shown to exhibit circadian rhythmicity [52], it should be fairly straightforward to incorporate concepts related to circadian rhythms as additional material in patient clinical case discussions, particularly during the first two years of medical school. Clinical rotations during the last two years of medical school present additional opportunities for the introduction of circadian knowledge. Core disciplines may incorporate the subject topic in a variety of formats; for example, pediatric medicine can take into consideration concepts that relate to circadian markers in pediatric obstructive sleep apnea, circadian-linked metabolic deregulation in early childhood, changes in rhythms during puberty, the clinical use of melatonin in pediatrics, along with topics linked to sleep disordered breathing and bipolar disorder in infants [53 , 54 , 55]. Furthermore, the clinical discipline of internal medicine provides a unique scenario for developing concepts in, for example, the circadian-immune connection and in cardiovascular health and disease prevention in a system whose functional organization has clear links to circadian rhythmicity [56 , 57]. Lastly, elective rotations, often placed predominantly during the fourth year in the medical curriculum

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structure, may provide an excellent opportunity for developing the subject area of circadian rhythms and associated diseases, particularly if offered by institutions that have affiliated sleep centers. These electives would allow students additional exposure to the specialty and additional instruction, particularly for students that do not anticipate completing a sleep fellowship but may desire additional knowledge for their future practice. The flexibility that many medical schools have regarding travel for elective rotations would also allow fourth year students from schools that do not have sleep centers to travel to schools that do. In these ways, the last two years of medical school present a unique opportunity for students to develop these skills before entering a diverse range of specialties. Beyond the Classroom Curriculum The recommendations to the medical school curriculum summarized in Table 1 would likely fall within the fellowship training programs rather than influencing changes at the residency level, at least, in the short term. One of the early approaches to introduce the concept of circadian disruption and its physiological implications was led by Stanford University through the creation of the Accreditation Council for Graduate Medical Education ACGME sleep disorder medicine fellowship training program at the Stanford Center for Sleep Sciences and Medicine <http://> Here, professionals are trained in multiple aspects of sleep medicine including pharmacology of sleep, disordered breathing, neuro-degenerative disorders, insomnia, narcolepsy, and orthodontics in children and adults, among other relevant topics. Although the aforementioned program, and other outstanding fellowship programs taught at various Sleep Centers nationwide, focuses on one aspect of circadian deregulation, sleep, their efforts constitute a valuable first step towards understanding and strategically incorporating specialized topics related to rhythms at the upper level of education. A long-term goal might include the establishment of an alternate research-based fellowship program to promote career development of clinician researchers in the area of circadian disorders that would consider incorporating research aspects of circadian biology into the clinical practice, a relevant topic to both ACGME and the Center for Sleep and Wake Disorders, National Institutes of Health. Creating a residency area that specifically advocates for gene-environment interaction and their deregulation in various diseases and for treatment would likely take time to implement but would be worth pursuing in the long-term. Lastly, an additional topic that deserves to be mentioned for further discussion, although it is beyond the scope of the present article, refers to disruptions that the hospital environment itself poses to medical students, nurses, physicians, technical personnel, and patients as they are exposed to relatively constant levels of noise, light, and activity around the clock, especially in intensive-care units and in patients that have remained admitted to the hospital for several days. Although a subject of considerable controversy in both Europe and America, there have been steps already taken to evaluate, set, and enforce standards for effective medical residency that considers circadian disruption as a factor that influences occupational stress, fatigue, and, ultimately, performance in medical residents and hospital personnel in general [62 , 63 , 64 , 65 , 66]. Not only does it represent the last opportunity to address the relevance of circadian rhythms in disease onset and progression to health professionals in their final stage of training but it also is a topic that affects medical students as they are among the professionals that are most heavily exposed to circadian disruption during their training years. In a landmark study, Landrigan et al. Of note is that, whereas the Landrigan et al. Thus, there is value in emphasizing the many physiological consequences, other than cognitive, that circadian disruption might also have on providers and the long-term impact of these consequences on their health and that of their patients. Competing interests The authors declare that they have no competing interests. All authors edited the essay, provided intellectual contributions, and supported the conclusions. Acknowledgements The authors thank Dr. Hausman for comments and manuscript edition. 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