Hello, my name is Peter Wilcox and I am a Doctor of Nursing Practice Student at Arizona State University and this is my Educational In-Service on Chronotherapeutic Scheduling of Anti-Hypertension Medications. This is an evidence-base practice project in partial fulfillment of the Doctor of Nursing Practice degree and I am conducting this in-service to evaluate if sharing information about chronotherapy has any affect on providers’ knowledge of chronotherapy, as well as their prescribing habits.
Management of hypertension, like everything in healthcare, is constantly evolving and is based upon the latest evidence-based information and recommendations. Although the recommendations for the initiation of therapy have changed over the years, the need to control blood pressure to reduce an individual's cardiovascular risk has not. Between 2003 and 2008 approximately 8.9% of the US adult population had uncontrolled hypertension despite utilizing at least three different anti-HTN drug classes within a one month time period (Persell, 2011). Recent literature has indicated that there is another strategy available that is effective in increasing the number of individuals with controlled blood pressure. This strategy is called chronotherapy, which simply put means managing an illness like hypertension by scheduling treatment around the body's natural circadian rhythm.
Objectives

- The importance and reasons for this educational in-service
- Chronobiology of blood pressure
- Barriers to management
- Current practice
- Chronotherapy of anti-hypertension medications

The objectives for this presentation are: To discuss the importance and reasons for this educational in-service, describe the chronobiology of blood pressure, identify the barriers to blood pressure management, discuss current practice, and conclude this presentation by discussing chronotherapeutic scheduling of anti-HTN medications.

To begin this in-service on chronotherapy I would like to discuss the chronobiology of blood pressure so that I may clearly depict how chronotherapeutic scheduling of anti-HTN medications impacts the body and ultimately approaches HTN management differently than current practice.
Chronobiology is the study of cyclic phenomena that occur within living organisms. One chronobiological phenomenon that researchers have identified is blood pressure. Although researchers have been able to explain many different components that contribute to the 24-hr blood pressure pattern, there is still a significant amount that is not well understood. What we do know is that blood pressure is an objective number that is directly associated with the amount of force applied to the vessels within the body when the heart pumps blood. The amount of force varies throughout the day relative to a number of external and internal factors. The National Institute of General Medical Sciences (2013) noted that the sleep-wake cycle, hormonal excretion, body temperature, as well as various other important biological processes displays an endogenous, entrainable oscillation of about 24 hours, also known as the circadian cycle. The culmination of these circadian cycles contributes to the blood pressure variability seen over a 24-hr period of time (Hermida, Ayala, & Portaluppi, 2007). A normotensive healthy individual will likely achieve their lowest BP in the early hours of the morning. This is then followed by the sharpest rise in the BP pattern occurring roughly between 6 -7 am. The rise is associated with changes in the autonomic systemic tone, vasoactive hormones, as well as hematological and renal variables (Hermida, Ayala, & Portaluppi, 2007). From this early morning spike, the BP fluctuates slightly with an overall gradual increase noted and peaking between 6 and 7 pm and then begins the gradual decline back to the lowest point.
The BP peak and trough is associated with natural fluctuations within the renin-angiotensin-aldosterone system (RAAS). This type of cycle where the BP drops during the nighttime is known as a “dipping” pattern and has been identified to reduce the workload on target organs, which is considered to be cardiovascular protective (Hermida, Ayala, Mojón, & Fernandez, 2010b). Unfortunately, when an individual has uncontrolled hypertension, their 24-hr blood pressure pattern becomes less consistent with higher degrees of fluctuations noted, in addition to placing the blood vessels under higher amounts of pressure. A systematic review by Zeng et al. (2011) identified that this 24-hr BP pattern was a significant indicator of cardiovascular health and recommended that it should be evaluated routinely, because uncontrolled HTN is commonly associated with the disappearance of the nocturnal BP decline creating what is known as a “non-dipping” BP pattern. When an individual’s BP does not decrease during the night, their target organs endure sustained amounts of high pressure, thus placing them at a greater risk for experiencing an adverse event such as a heart attack or stroke (Almirall, Comas, Martínez-Ocana, Roca, & Arnau, 2012). Therefore, when managing an individual’s hypertension, it is important to understand what their 24-hr BP pattern looks like.
Current Barriers to Management

- Out-of-date national guidelines such as those found in the Joint National Committee’s seventh publication (2003)
- The cost of treatment
- The medication and life-style modification compliance from the patient
- Healthcare provider practicing and prescribing habits.

There are many factors that directly impact the management of hypertension, which may include but not limited to: out-of-date national guidelines such as those found in the Joint National Committee’s seventh publication (2003); the cost of treatment; the medication and life-style modification compliance from the patient; and/or healthcare provider practicing and prescribing habits.
Several randomized control trials noted that the majority of individuals with HTN were instructed to administer their anti-HTN medications in the morning most likely due to convenience however, there were no definitive reasons identified for scheduling the medications in this manner (Smolensky, Hermida, Ayala, Tiseo, and Portalandi, 2010 & Hermida, Ayala, Mojon, & Fernandez, 2010b). Although the Joint National Committee's 7th publication does not give healthcare providers guidance on when to schedule anti-HTN medication, these findings are troublesome. When single dose early-generation anti-HTN medications are scheduled to be administered in the morning, they begin to lose efficacy by the time the BP is naturally at its highest point and then becomes even more ineffective by the time of the early morning BP spike due to a short half-life of the medication. This has led healthcare providers to either schedule these medications to be administered more frequently, which can contribute to unnatural fluctuations in the 24hr blood pressure pattern due to varying blood levels of the medication, especially if the patient isn't compliant with taking the medication on time. As another alternative, the healthcare provider could use later-generation anti-HTN medication that provide a longer acting more unified coverage of the blood pressure. Unfortunately, the later-generation medications have been integrated into the morning administration schedule with only minimal to no scientific evidence to support this decision (Smolensky, Hermida, Ayala, Tiseo, and Portalandi, 2010). Additionally, the PROFESS study by Yusuf et al. (2008a) found that administering a single dose later-generation medication in the morning did not significantly lower the rate of major adverse cardiovascular events, as compared to a placebo. Furthermore, a separate study conducted by Yusuf et al. (2008b) identified that administering the combination of two later-generation medications in the morning actually increased the risk for adverse events despite significantly lowering blood pressure values. These findings reveal that the key to cardiovascular health may not necessarily equate to a lower blood pressure value but rather administering anti-HTN medications at a time of day that would help mimic the body's natural 24-hour blood pressure pattern while maintaining blood pressure values within an acceptable range. So how can healthcare providers accomplish this?
What is Chronotherapy

- Treatment or management of an ailment by planning therapy around the body’s natural circadian rhythm.

Chronotherapy is the treatment or management of an ailment by planning therapy around the body’s natural circadian rhythm. When an individual is diagnosed with hypertension, it is indicative that their body has become less effective at lowering their blood pressure and therefore, is unable to maintain the natural 24-hour pattern. By scheduling anti-HTN medications to be administered at nighttime when the body is naturally attempting to lower the blood pressure, the body is better able to maintain the natural 24-hr blood pressure pattern while ensuring that an adequate level of the medication is present in the blood stream during the most crucial times of the day.
Chronotherapy of Anti-Hypertension Medications

- Administration time dependent effects have been studied in:
  - a-blockers, b-blockers, diuretics, angiotensin-converting enzyme inhibitors (ACEIs), angiotensin-receptor blockers (ARBs) and calcium channel blockers (CCBs).
  - Primarily focusing on the chronotherapeutic scheduling of single dose anti-hypertension medications.

The administration time dependent effects have been studied in a number of anti-HTN medication classes including: a-blockers, b-blockers, diuretics, angiotensin-converting enzyme inhibitors (ACEIs), angiotensin-receptor blockers (ARBs) and calcium channel blockers (CCBs). Hermida et al (2010b) stated that administering anti-HTN medications at nighttime rather than upon awakening positively affected the nighttime BP control and 24-hour circadian BP pattern regulation, which are both strongly associated with a lower CVD risk. For the purpose of this in-service I will be primarily focusing on the chronotherapeutic scheduling of single dose anti-hypertension medications. The pharmacokinetics and pharmacodynamics of these anti-HTN medications have resulted in differences in BP-lowering efficacy, duration of action, and effects on the 24-hr circadian BP pattern when medications are administered at nighttime compared to in the morning (Hermida & Ayala, 2009, Hermida, Ayala, Fernandez, & Calvo, 2008a, Hermida, Ayala, Fontao, Mojon, & Fernandez, 2010a). Labrecque & Beauchamp (2003) attributed the chronotherapeutic differences to varying rates of medication absorption, distribution, metabolism, and elimination changes based upon administration time of the medication (p. 103).
Benefits of Chronotherapy with Anti-Hypertension Medications

- A greater 24-hr blood pressure effect of the medication, which may potentially equate to fewer medications being needed to manage an individual's hypertension

- A significant decrease in the prevalence of individuals with a non-dipping pattern

- A greater blood pressure reduction however, this was not found to be unanimous within the literature because many of the research articles found the amount of blood pressure reduction to be equivalent.

These alterations in the body's ability to utilize the medications have led researchers to discover that chronotherapy of anti-HTN medication contributes to:
Benefits of Chronotherapy with Anti-Hypertension Medications (Cont.)

- Increase in sleep-time blood pressure control
- A reduction of cardiovascular disease (CVD) morbidity
- Less severe increase in the slope of the morning rise in the SBP and DBP
- 91% reduction in peripheral edema noted with calcium channel blockers when administered at nighttime

Additionally, several randomized control trials identified that chronotherapeutic scheduling of calcium channel blockers led to a significant reduction in peripheral edema with one trial noting a 91% reduction and thus, greatly improving patient tolerability (Hermida, R. C., Ayala, D. E., Fernandez, J. R., & Calvo, C., 2008b; Hermida, Ayala, Mojón, & Fernandez, 2010b; Smolensky, Hermida, Ayala, Tiseo, & Portaluppi, 2010).
Uncontrolled HTN is a major component in the development of heart disease and has been directly linked to an increased number of heart attacks and strokes (WHO, 2012). Chronotherapy of anti-HTN medications is a simple, cost-effective strategy that can significantly decrease the number of individuals suffering from uncontrolled HTN, as well as decreasing CVD risk.

This concludes my educational in-service please refer back to the main page to complete the post-intervention questionnaire. If you have any questions or thoughts on the in-service please feel free to contact Peter Wilcox at Pgwilcox@asu.edu
Reference:


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http://www.nigms.nih.gov/Education/Factsheet_CircadianRhythms.htm


