



## Chronotherapeutics

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Coordinating biological rhythms with medical treatment is called chronotherapy. It considers a person's biological rhythms in determining the timing and sometimes the amount of medication to optimize a drug's desired effects and minimize the undesired ones (1). Study of influences of biological rhythm on the effects of medication is known as chronopharmacology (2) while the science of study of biological rhythms is known as chronobiology (3).

Now the pivotal question arises; what are biologic rhythms?. In essence, they are the rhythms of life. All forms of life on earth, including our bodies, respond rhythmically to the regular cycles of the sun, moon and seasons (3). Some of the rhythms that affect our bodies include *ultradian* (cycles shorter than a day like firing of neurons take milliseconds), *circadian* (cycles lasting 24 hours such as sleeping and waking pattern), *infradian* (cycles longer than a day like menstrual cycles) and *seasonal rhythms* (such as seasonal affective disorders causing more depression in susceptible individuals in winter) (1). Medical chronobiologists have found that circadian rhythm affect the timing of body secretions (1) and this rhythm can also affect the severity of disease symptoms, diagnostic test results and even the body's response to drug therapy (3). Many hormones like cortisol, catecholamines, plasma renin, aldosterone and angiotensin are secreted in the morning. In contrast, gastric acid, growth hormone, prolactin, melatonin, follicle-stimulating hormone, luteinizing hormone and adreno-corticotrophic hormone peak in the evening or during sleep (1).

Likewise, in allergic rhinitis; symptoms of sneezing, runny nose and stuffy nose are typically worse in the early waking hours than later during the day. In most of the asthmatic patients, symptoms are 100 times more likely to occur in the few hours prior to awakening than during the day. In stable angina chest pain and electrocardiographic (ECG) abnormalities are most common during the first 4 to 6 hours after awakening. In Prinzmetal's angina ECG abnormalities are most common during sleep; chest pain can occur even at rest. Heart attacks and strokes most commonly occur in the early waking hours. The highest blood pressure readings typically occur from late morning to middle afternoon;

lowest occur during early sleep. Rheumatoid arthritis symptoms are most intense upon awakening while symptoms of osteoarthritis worsen in the afternoon and evening. Ulcer pain typically occurs after stomach emptying, following daytime meals and in the very early morning, disrupting sleep. Epileptic Seizures often occur only at particular times of the day or night; individual patterns differ among patients (3).

Although, the presence of circadian rhythms in human health and illness has been alluded to since the time of Hippocrates (4) but chronotherapy has a way to go, considering that only 5 percent of the doctors are very familiar with the subject (1). That's because most doctors are not taught about chronobiology - in fact, they are taught something that seems to contradict it. Homeostasis - the concept that body functions are in a constant steady state throughout the day and night; and that the goal of treatment is restoring or maintaining this "steady state". Even the treatment itself may have this goal, for example, a prescribed drug is given in a way ("every 4 hours") that theoretically will ensure a steady level of it in the patient's bloodstream. Obviously, this view contrasts sharply with diagnosing and treating illness chronobiologically - "by the clock." (3).

Fortunately, although chronobiology is not yet taught in medical schools, doctors are increasingly taking biologic rhythms into account in diagnosing and treating illness (3). Classical example of disruption of body clock is jet lag; which is treated with melatonin. Melatonin is the principal indoleamine in the pineal gland and it also serves a role in the regulation of biological rhythms (5). Equally important is the finding that cholesterol synthesis peaks in the evening, so statins are more efficacious if used in the evening (2). Recent studies linking circadian rhythms with blood pressure control (6) and type-2 diabetes (7) have forced the scientists to look for the ways to set the clock right. The risk of myocardial infarction, cardiac death and stroke is higher by 40%, 29% and 49% respectively, between 06:00 am and noon, than that expected to occur by chance (8). In these patients, the paradigm has shifted towards chronotherapeutics i.e. the dosing of medications at 10 pm with novel drug delivery systems to provide

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additional blood pressure control and lower heart rate during the vulnerable period of 6 am to noon (2). It has been documented that with verapamil monotherapy at night, reduction in morning blood pressure was significant in African-Americans; the patients with highest prevalence of high blood pressure as a group (2 out of every 5 African-Americans) (9). A recent study showed that the proportion of patients with controlled ambulatory blood pressure increased from 43% to 65% ( $P=0.019$ ) with single bedtime dose of angiotensin converting enzyme inhibitor, ramipril (10). Currently, there are few antihypertensive medications that are chronotherapeutic medications using verapamil, diltiazem & propranolol (2).

Another study suggests that melatonin has direct stimulatory effects at human islet-cells and that it stimulates insulin secretion as a consequence of elevated glucagon release (11). A follow up study suggests a possible link between circadian rhythm regulation and glucose homeostasis through the melatonin signaling pathway. In this genome-wide association (GWA) data from 2,151 non-diabetic French subjects, rs1387153 was identified near MTNR1B (which encodes the melatonin receptor 2), as a modulator of fasting plasma glucose (FPG). The rs1387153 T allele was associated with increased FPG, type 2 diabetes risk and risk of developing hyperglycemia or diabetes over a 9-year period & incident cases (12). This melatonin based pathway may prove to be a novel one for the development of a new drug for type 2 diabetes, based on chronotherapy.

While studying the metabolism of migratory birds, it was observed that they develop seasonal insulin resistance and dopamine plays a role in it (13). This novel observation lead to the development of new drug, bromocriptine mesylate which has been approved by FDA on May 5, 2009 to be used as an adjunct to diet and exercise to improve glycemic control in adults with type-2 diabetes mellitus, as a single morning dose. This drug acts by causing resetting of abnormally elevated hypothalamic drive for increased plasma glucose, triglyceride, and free fatty acid levels in fasting and postprandial states in insulin-resistant patients (14). Considering the fact that combined burden of type 2 diabetes and hypertension is very high, (15) novel chronobiology based drugs/treatment plans which have started to flow in, will definitely improve patient's well being.

In conclusion, there is growing evidence that circadian rhythmicity influences disease symptoms, diagnostic test results and even the body's response to drug therapy, but the concept is yet to be fully understood and adopted in the clinical practise.

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