Mathematical Simulation of Aspirin and Valsartan's Circadian-Dependent Antihypertensive Effects

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Received: 07-04-2025; Revised: 07-05-2025; Accepted: 29-05-2025; Published: 03-06-2025

Abstract

Tailoring when drugs are given what's called chronotherapy has become essential for making antihypertensive treatments more effective. Valsartan, an ARB, as well as aspirin, often taken for cardiovascular prevention, show changed effects over time because of the daily rhythms of blood pressure and platelet stickiness. The investigation explores just how valsartan and aspirin affect blood pressure at each time of day through a detailed model that combines body rhythms, drug absorption and action on the body. The model uses ODEs and simulates populations to follow the changing effects of drugs on endogenous rhythms in the renin-angiotensin system and blood vessels. Published results from clinical trials and in vivo studies were applied to set up and check the model. Results from simulations show that giving valsartan in the evening reduces blood pressure overnight, in harmony with the body's natural clock, while on the other hand, aspirin achieves its strongest impact on platelets and weakest on blood pressure when taken in the early morning. Following chronobiology rules, mosquitocides used simultaneously demonstrate advantages over their single use. The findings of this research show that the right administration timing plays a vital role and gives doctors tips on forming regimens to better help people with hypertension and reduce heart risk. It allows clinicians to predict the best way to schedule treatment for individual patients.

Keywords: ***Chronotherapy, Circadian rhythm, Valsartan, Aspirin, Antihypertensive modeling, Pharmacokinetics, Pharmacodynamics, Blood pressure regulation, Mathematical modeling, Cardiovascular pharmacology, Dosing-time dependency, Renin-angiotensin system.***

1.Introduction

In the past few years, studies at the intersection of circadian biology and drugs have contributed a new and important idea in medicine: chronotherapy. Essentially, chronotherapy acknowledges that the body's internal clock helps decide when drugs work best and are safest. This is especially clear in cardiovascular medicine, since blood pressure, heart rate and hormone release follow structured rhythms throughout the day. With hypertension and related heart diseases increasing around the world, managing treatment timing can make treatment more successful, cause fewer side effects and encourage patients to stick to their therapies.

Chronotherapy was originally inspired in the 1950s by observations that most incidences of heart attacks and strokes took place in the early morning. As a result, a key question was formed: Could adjusting the timing of actions change the odds of cardiovascular issues? If these patterns are present, how do we make sure therapy fits with them? The need for time-sensitive medicine led to the creation of chronopharmacology which deals with the way our body clock affects medicine(1).

The results are especially significant in cardiovascular health. Just like many other factors, blood pressure is not fixed and changes throughout your day. Close to midnight, those who have healthy circadian rhythms will usually see their blood pressure drop by about 10–20%. In contrast, "non-dippers" do not fall in blood pressure when sleeping which puts them at greater risk of heart damage and heart disease. Chronotherapy strives to help hypertensive patients by timing their medications to improve or restore normal physiological patterns.

Among several trials, MAPEC (Monitorización Ambulatoria para Predicción de Eventos Cardiovasculares) demonstrated that late evening dosing of antihypertensives reduced both cardiovascular trouble and deaths more than accepting identical medication in the morning. Because of these findings, the idea of always taking medicine in the morning was questioned and (so) guidelines in different countries had to be reconsidered. Ongoing meta-analyses have confirmed that medicines from the ACE inhibitor, ARB and calcium channel blocker groups work better when given at night.

Yet, the initial findings are not leading to its use in every-day medical practice. Some issues cause these situations. It is common for clinical trials using traditional methods to concentrate only on the amount and frequency of a drug, but not when it works best. Findings suggest that there is no wide agreement on which times of day doctors should recommend for taking medicines. Thirdly, ensuring patients stick to the treatment and fit well into their daily lives can create big challenges. It is common for physicians to doubt that the benefits of chronotherapy are greater than the challenges involved, in patients who require various medicines.

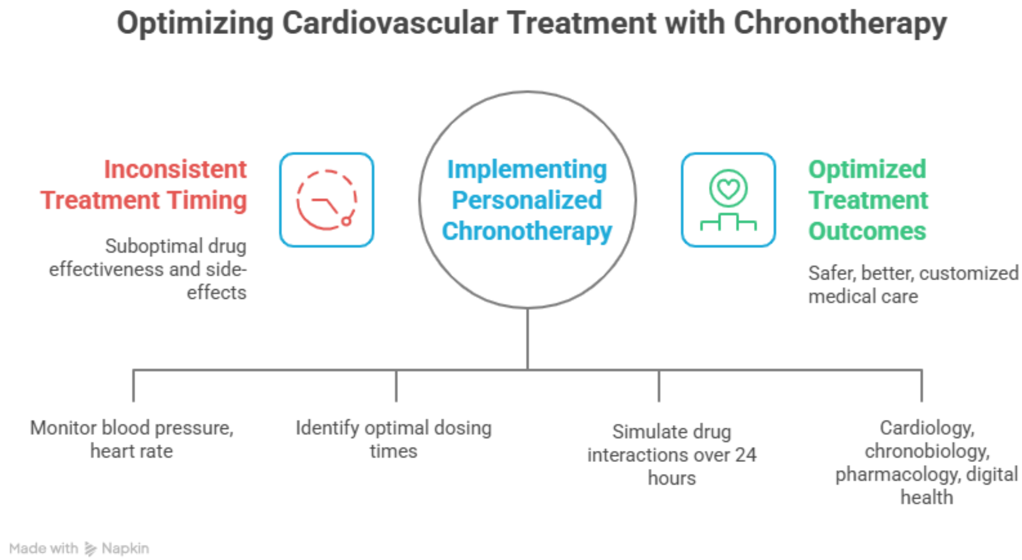

FIGURE 1 Optimizing Cardiovascular Treatment with Chronotherapy

There is an extra difficulty in this area since circadian phenotypes show great variation between individuals. Every person's body operates on internal rhythms differently. The actions and intensity of physiological responses to medications can be affected by different genetic versions of clock genes. Besides, anything that interferes with your sleep or changes what you eat can disrupt your body's natural rhythms and may reduce the results you hope to see from using these drugs at the right time. As a result, it is important to give every patient personalized chronotherapy, where drugs are scheduled according to their own circadian rhythm(2).

Wearable technology and digital health tools are now ready to help fill this gap. Real-time circadian data can be created by systems that constantly track blood pressure, heart rate variance and activity levels. These understandings can inform machine learning models used to identify the ideal time for a patient's dose. At the same time, models and simulation frameworks for circadian PK-PD help shape the use of drugs that follow daily rhythms. They consider essential physiological information and simulate its interactions with the drugs for 24 hours, allowing the prediction of results using different dosing strategies.

Drug development is now exploring approaches based on our body's circadian rhythm. Conventionally, evaluating pharmacological agents is done by examining how their effects change with various doses without considering when the effects happen. But if we include chronobiology in early research, we could find new paths for treatment and avoid harmful side effects. By micronizing certain antihypertensive agents, their properties can be improved to allow them to act smoothly with the body's own rhythms.

We should still be careful about using them. For instance, the TIME trial didn't find morning dosing to be significantly better for those with high blood pressure(3). Because their results are so different, these studies highlight how essential trial design, patient selection and their context are. They also point out that it is important to conduct further large and organized trials that study both the timing of medicine and how it fits with a patient's health and personal habits.

In the future, getting chronotherapy into regular cardiovascular care will depend on experts working together from cardiology, chronobiology, systems pharmacology and digital health. Emerging evidence should be treated in policy frameworks and practitioners should be trained to be able to use these insights. Harmful insects respond to treatment at particular times and people need to appreciate this.

Chronotherapy brings about a major change in the way cardiovascular diseases are managed. By managing medicines according to the body's internal rhythms, people may receive safer, better and more customized medical care. Nevertheless, its achievement depends on solving methodological, infrastructure and educational problems. Updating and improving chronotherapy could make it a well-known method in the field of cardiovascular medicine, helping launch temporal precision medicine.

2.Data-Driven Personalization in Hypertension Therapy: A Computational Framework

A traditional approach to hypertension management has mostly used common protocols influenced by research done on groups rather than individuals. Even though this method has helped many people lower their BP, it usually struggles to consider differences in drug response, BP changes over a day and other related metabolic health conditions. With the help of new data and computational methods, we can now move from a common approach to treat hypertension to one that is unique to each person, using their unique bodily, behavioral and clock-following traits.

What drives this change is the integration of data from everyday life such as ABPM, sensor signals, EHRs and genomics. Because of this extensive set of data, machines can predict what each person will require in treatments and the right time to start intervention. Such models are able to grow and improve thanks to their ability to respond to any new data they receive.

This personalized concept relies on accurately recording the body's circadian blood pressure fluctuations. In contrast, ABPM permits finer observation of systolic and diastolic changes throughout the course of a day and night. This makes it possible to determine dipper compared to non-dipper status, the height of morning surge and the level of variability all vital for cardiovascular risk prediction. When timing of the treatment matches with timing of the data, it becomes possible to see when a drug works best or when its action may bed impaired due to changes in the body.

Effective use of these data streams is made possible by advanced modeling strategies. ODE-based modeling is commonly used to chart how the levels of SVR, HR, secretion of norepinephrine and drugs within the system all change with time. With these models, clinicians can see how the body may react to various doses and then use this information offline(4).

A good example is using personal models to see the BP response to taking antihypertensive drugs at different times of the day. Examples of inputs are daily activity recorded by accelerometers, using apps to track dietary salt, sleep and wake times and taking medications. Live data is used by the computational engine to customize important parameters in each person, including rates of drug uptake and removal, blood pressure sensitivity and overall kinetics. As a result, we have a digital map of the patient's blood vessels and we accurately predict how controlling blood pressure will be affected by interventions.

These frameworks are seeing more implementations of machine learning (ML) algorithms. Unlike systems that are just rules-based, ML tools can detect patterns in big, confusing datasets. As an illustration, supervised learning models can be trained using thousands of patient records to predict those people who are most likely to react well to bedtime ACE inhibitor doses. In addition, using unsupervised clustering, it's possible to identify additional types of hypertensive patients for example, those with different patterns of glycemic variation, sleep or variations in their clocks genes. As a result, the insights inform better and more precise treatment methods.

One best thing about data-driven frameworks is that simulations can be performed without real experiments. Rather than letting patients receive many different doses, computational models can single out the most likely effective options, lowering the risk and costs involved. As an example, a virtual trial could find that the best result for reducing nighttime BP for a specific patient comes from giving a calcium channel blocker at 10 PM information that is not easy to spot without a simulation.

But there are still some issues with these systems. It is very challenging to bring together and standardize various different types of data. The information gathered by sensors may not always be accurate, medical records are stored in EHRs without structure and can contain gaps and patient-entered material may be biased. Resolving These Problems Demands That Users Have Strong Preprocessing Workflows and Data Audit Requirements. It is essential to ensue that data privacy and transparency in algorithms are prioritized as these models begin to affect doctor and patient actions.

It is often difficult to understand the meaning behind advanced models. ML models deliver powerful predictions, but experts often view them as hard to explain because of their mystery. Many clinicians find it hard to use treatments guided by systems they do not understand completely. Researchers are contributing to XAI which helps physicians trust machine learning results and easily see how different factors impact prediction outcomes(5).

We should consider a computational framework for personalized hypertension therapy as just one element in a clinical decision support system (CDSS). The purpose is to add to, not take away from, how physicians practice. As an illustration, the model may recommend that a patient with uncontrolled morning blood pressure take their medication at night, but the physician also considers the patient's job, mental state and overall medicine routine in making a decision.

In addition, patient feedback should be included in these systems. When patients can use apps to log their symptoms, side effects and levels of following the treatment regimen, this improves the model's accuracy. With time, using this approach leads to a strong relationship where both data and the patient are valued.

The future relies on technology merging wearables, mobile applications for health, genetics and cloud systems which builds up a real model of a patient. Scientists are now using these systems in real environments, hoping to compare the results they give to standard procedures. In the initial results, patients report better blood pressure control, fewer bad effects and better satisfaction with their treatment.

Altogether, using data-driven computational techniques in hypertension therapy changes the medical approach to rely on real-time measures. Using real-time, individualized modeling, we are able to customize treatment for each person as well as the point in the individual's biology when the treatment will work best. Now, decisions in cardiovascular care are made using proven evidence along with scientific and rhythm guidance.

3.Dynamic Systems in Biomedical Engineering: Modeling Autonomic Control of Blood Pressure

The cardiovascular system in humans is controlled by interactions between automatic, chemical and environmental factors. At the center of this regulation is the autonomic nervous system (ANS) which plays a major role in controlling heart rate, blood vessels and balanced blood flow. Biomedical engineers have begun using dynamic system modeling to study, test and adjust therapeutic treatments for hypertension. The models help understand the ways in which physiological variables change in relation to time and also make useful predictions(6).

A dynamic system consists of interrelated components and the condition of each component changes through time. Such models try to describe how things such as a person's activity, emotional state, drugs or the time of day can change key outputs such as SBP, DBP, SVR and HR. The fact that these systems adapt, do not stay constant and are nonlinear suits the way the cardiovascular system really functions.

Early modeling work began with LTI models which showed how the BP system responded to steady perturbations. Soon afterward, the fact that both the baroreceptor reflex, major feedback systems and circadian cycles were nonlinear showed that the basic approaches were not enough. As a result, biomedical engineers recently depend on advanced methods, including nonlinear ODEs and sometimes partial differential equations, for vascular system models.

For a representative model, it is possible to add variables like CO, R, C and S. A basic SVR equation may connect sympathetic activity and endothelial vasodilator release, whereas the HR equation features vagal tone and catecholamine levels. Moreover, these models may consist of a baroreflex arc which helps balance HR and vascular changes when BP changes.

The use of external cues such as details from patient actions and the environment, is needed to accurately model the body's behavior. One example of these is:

- In most cases, the level of physical activity is collected by using wearable accelerometers.
- Some stress markers for the brain and emotions can be identified by reviewing heart rate variability data.
- Rises and falls in blood sugar, especially in people with diabetes, that can disturb the function of the autonomic system.
- The way the plasma concentration of an antihypertensive drug changes as treatment proceeds.
- A useful way to put the model into practice is to develop a system of equations in which BP components react to the body's circadian rhythms as well as outside factors such as medication or activity. Here's what a simple dynamic model could look like:
- Both sympathetic signals and the role of the endothelium affect SVR
- The HR response depends on physical exercise and the baroreflex gain.
- Measures of systolic and diastolic BP are the result of interactions between SVR and HR and are modified for both cardiac contraction and vascular structure.

To make these models more accurate, circadian modulation is added by earning sinusoidal or cosinusoidal terms to indicate 24-hour rhythms. Because the most sympathetic tone often appears in the early morning, it can explain the rise in blood pressure known as the morning surge which is linked to a number of cardiovascular problems. Using time-sensitive parameters in the model allows for predictions of how a drug will work earlier or later in the day because of changes in the activity of the autonomic nervous system.

Dynamic system modeling is valuable because it makes “what-if” scenarios easy to carry out. As an illustration, you can see what happens to sleep BP, morning BP and the full BP load if a beta-blocker is taken in the morning versus late evening. Building such simulations is important for designing chronotherapeutic approaches and can also benefit clinical decision support systems.

Good data is necessary for these models to be validated. It is important to have time-series data from ABPM, HR monitors and medicine logs on hand. A more in-depth approach can include testing hormones (such as cortisol and aldosterone) which rise and fall with the day and can change blood pressure. After being validated, these models allow us to learn how certain treatments fared previously and help plan future treatment strategies that are customized to an individual(7).

An illustration of dynamic modeling is in clinical research with non-dipper and dipper hypertensive patients. Such adults do not experience the usual decline in blood pressure at night, increasing their danger of organ damage. Through mathematical modeling of the autonomic system and the vascular system, both engineers and clinicians can spot dysfunctions, including less effective baroreflex gain or different sympathetic thresholds and estimate the effect of treatments on keeping the rhythms normal.

As well as looking at each patient, these systems are being applied to studying clusters of people to find groups with different hemodynamic patterns. With the help of machine learning, dynamic models provide a base for bigger platforms that adjust treatment strategies. They are updated immediately using input from the patient and any data from their wearable, making the system easier to optimize.

Besides, biomedical modeling helps in education and training by offering medical devices that replicate many bodily functions. Even so, a number of issues still need to be addressed. Sometimes, having a complicated model leads to trouble since there are too many parameters and it’s hard to uniquely define their values with the data that’s available. For this reason, we must perform careful sensitivity analysis and use regularization methods whenever we are estimating parameters. Being able to understand and use the predictions from models is very important in translating results into practice which is especially true in medical fields.

Overall, dynamic systems modeling gives a clear way to observe, replicate and enhance autonomic regulation of BP. Because they show how cardiovascular control changes and depends on various factors such models form the basis for designing future precision therapies that take account of each patient’s health situation. Because biomedical engineering advances, these concepts will be key in leading the future progress of caring for the heartbeat.

4.Adaptive Optimization Techniques for Pharmacological Models in Chronomedicine

Because chronomedicine uses timing to affect drug treatment, old static ways of arranging medicine often miss the complexity of time-related changes in the body. The fact that at what time a drug is taken can strongly affect treatment outcomes has made it necessary to create techniques that manage both individual and environmental changes effectively and quickly. For such models, adaptive optimization techniques now act as the primary design methodology for handling circadian-aware intervention. The approaches enhance the ability to fit and manage PK/PD models, allowing better use of models in calculating treatment schedules(8).

They are different from classical optimization methods since they are designed to improve and develop when new information appears. The influence of circadian patterns makes this type of dynamics very important in pharmacological modeling. How drugs are absorbed, spread through the body, processed and eliminated all depend on circadian rhythms, making their effects on targets more or less sensitive. The medications ACE inhibitors and ARBs are shown to work differently depending on the time of day they are given. In order to show how these effects change over time, we need various parameters such as the half-life and bioavailability of the drug, along with the heart rate variability, systemic vascular resistance and baroreflex sensitivity of each patient. Because these factors interact in a complex, often unclear way, trying different dosages in hopes of finding out what works can be both ineffective and risky. Here, adaptive optimization stands out by adjusting the model step by step, to allow more treatment benefit and help lower possible side effects.

Genetic algorithms, simulated annealing and scatter search are considered leading forms of metaheuristic algorithms for tackling the challenging, multi-peaked search spaces found in biology. Genetic algorithms use a model of evolution, where recommendations change and dogs of different breeds combine which makes the best solutions produce even better ones; simulated annealing is like metal cooling, making it possible for the system to break out of simple solutions and find others in the wider search space. When it comes to chronopharmacology, these practices allow experts to set the perfect quantity of medication, time of dosing (Ta), variation in the drug’s rhythm (amplitude) and phase shift factors which can be included in a model describing changes in drug effectiveness over a day. These methods are important because they avoid making assumptions about how the solution space is organized and therefore suit complex biological systems about which we may not know everything(9).

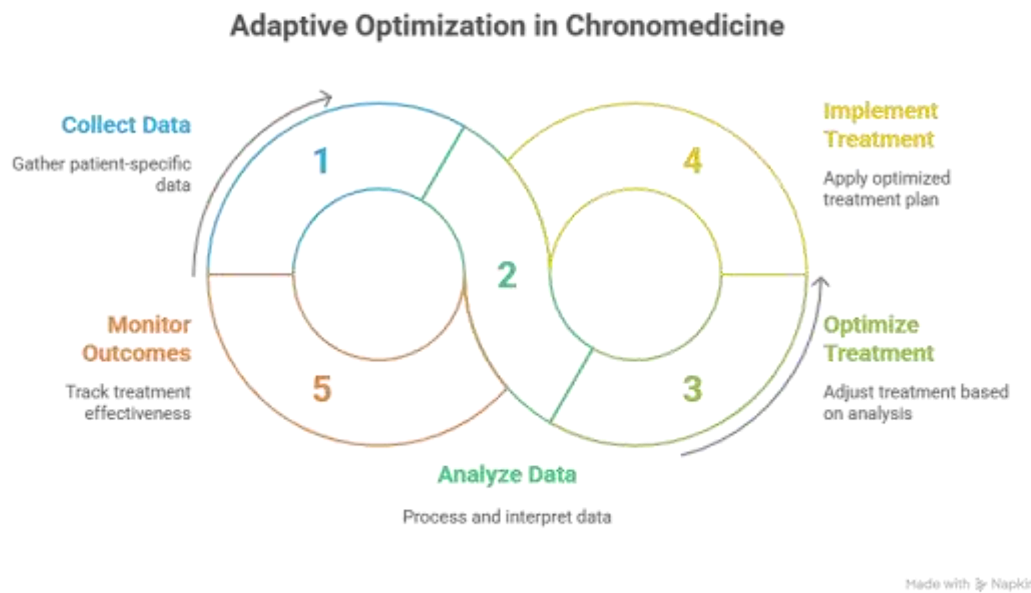

FIGURE 2 Adaptive Optimization in Chronomedicine

Gradient-based tools such as steepest descent or Levenberg-Marquardt algorithms, are useful when the landscape makes sense mathematically. The two groups of methods are often mixed, so that metaheuristics search the entire solution space and gradient-based methods adjust the local solution. In pharmacological modeling, the hybrid method helps choose a potential area for therapy and then makes it possible to decide on the perfect time and dose. This process makes optimization results both more accurate and easier to make sense of for clinicians.

Because adaptive optimization is developing fast, researchers are turning to reinforcement learning (RL) as a new technique. Contrary to standard optimization methods, RL algorithms obtain experience from a computer model of the cardiovascular system and are directed by feedback generated by the reward. Should altered blood pressure and no morning hypotension result from sticking with a certain dosing regimen, the agent improves its policy. With time, the RL agent is able to learn strategies that remain effective in different physiological situations. This feature helps the most for people whose body rhythms are unpredictable or who suffer from many chronic diseases, as fixed models may not meet the need. For these reasons, people with chronic illnesses like hypertension can rely on reinforcement learning to regularly tune their treatment to the changing state of their condition.

It is the existence of detailed, multiple imaging datasets that enables these improvement strategies. The optimization engine can get feedback from 24-hour blood pressure, HRV via wearables, data on physical activity and the biomarkers melatonin and cortisol found in saliva. Thanks to the dynamic datasets, the model is able to often adjust itself and improve predictions by using updated information. Further, using cloud computing and edge processing, researchers can implement adaptive models in real patient care, where they work seamlessly in system-based decision support. The systems can use fresh data to update their models, give health advice to doctors and in some cases, offer treatment plans to patients using mobile apps.

On the other side, using adaptive optimization strategies can be a real challenge. With a large number of parameters, high-dimensional models are more likely to overfit when data are either scarce or noisy. To solve this, regularization and Bayesian inference are added, as they restrain complex models and provide a figure for parameter uncertainty. Clinicians also need to understand not just the model's advice, but also the reasons behind that decision. As a result, recent studies in explainable AI have tried to make it easier to show how different parameters matter and how decisions are reached in complex algorithms.

In the end, adaptive optimization changes pharmacological modeling from a descriptive activity to one that guides what happens in patient care. By considering how human physiology naturally changes and repeats, these methods make it possible to develop dynamic treatment strategies that match the time of the patient's body clock. As chronomedicine improves, ensuring that treatments are the right time and fit a patient will rely on adaptive optimization, preparing smart healthcare systems that respond well to natural life patterns.

5.Conclusion and Future work

Chronomedicine has caused us to rethink the way we approach treatments of chronic diseases such as hypertension. Although traditional treatment focused only on the amount of medication, new approaches now pay attention to how medication is given at the right moment each day. Because of our use of dynamic physiological models, adaptive optimization and real-time patient data, we can now mimic and anticipate drug reactions in individuals. Consequently, doctors can now provide tailored treatments that reduce side effects, increase how well patients respond and improve their compliance.

This change is driven by mathematical models becoming more advanced to describe the processes of autonomic control, the body's resistance to blood circulation and heart rate, all within day and night periods. Combining these models with various optimization approaches leads to dosing schedules that can change with changes in the patients' bodies and actions. Additionally, new wearable gadgets and healthcare technology platforms make it possible for these models to include high-quality data that is tracked precisely in time. All of these developments form a significant leap forward in giving care that is on time and focused on patients.

Still, despite good progress, a lot of issues must be overcome. Still, there aren't many doctors or hospitals aware of, trained in or allowed by regulations to use these medical tools. As patient circadian profiles vary a lot because of their genes, habits, health issues and environment, models must be both highly adjustable and useful for different populations. While simulation and preliminary studies indicate that tailored chronotherapy is effective, large random studies by different centers are needed to prove its benefits and cost-efficiency in normal care settings. Their use can be supported in healthcare policy and guidelines only if there is such evidence(10).

As we move ahead, more research should aim to fuse mechanistic and data-driven models, using their special feature of being both clear and strong in handling patterns. Fusing physiological rules into machine learning systems could lead to systems that are both accurate, reliable and easier to explain to doctors. In addition, applying chronotherapeutic modeling to other conditions including metabolic disorders, cancer and mental health could widely increase its benefits, as circadian rhythms play an important role in all our bodily functions. For this vision to become a reality, clinicians, biomedical engineers, data scientists and behavioral researchers must cooperate.

We must make sure not to overlook the ethical issues when it comes to personalized products and services. Because some decisions are being made by automated systems, guaranteeing transparency, accountability and getting patient consent will play a crucial role. Similarly, we should make sure innovative technologies in this field reach everyone, not just people in rich countries.

Ultimately, instead of only being person centered, pharmacological intervention will also consider the time factor. We are ready to transform how medicine is given because of the strong combination of science, technology and experts' knowledge in healthcare. Chronomedicine based on adaptive modeling and optimization does more than provide a tool; it introduces a new concept by working with the human body's natural cycles to encourage better health.

Acknowledgement: Nil

Conflicts of interest

The authors have no conflicts of interest to declare

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