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Lifestyle Biopharmaceutics and Mechanistic Basis of Drug Clinical Outcomes: A Review

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ABSTRACT

Background and objectives: Biopharmaceutics explores the physicochemical properties of actives alongside their excipients in that complex and projects at adjusting the delivery of drugs in a manner that gives optimal therapeutic activity for safety and efficacy. Prescribing considerations, therefore, involve careful evaluation of the potential risks and benefits to every user. This review was aimed at highlighting the various mechanisms where lifestyle practices modulate physiologic changes impinging on the pharmacokinetic and pharmacodynamics vis-a-vis biopharmaceutics of drugs as it affects the pathophysiological/biochemical events in pharmacotherapy. **Methods:** Publications emanating on issues in this regard from 2000 to 2023 (137 articles) were examined and reviewed by searching the literature manually from Google Scholar and other scientific databases (e.g., PubMed, Web of Science, Embase and Scopus). Words and phrases such as "physicochemical", "lifestyle" "pharmacokinetics", "biopharmaceutical implications", "pharmacodynamics of medications", "biochemical changes", "pathophysiological changes" and "dosage adjustment". **Results:** Every individual is a physiological and biochemical complex defined by lifestyle preferences. Lifestyle research has demonstrated significant physiological changes that may influence the prescribing style and drug disposition. Consistent lifestyle practices present a platform for a pathophysiologic framework upon which the physiochemical and pharmacological basis of drugs interface. **Conclusion:** Alterations in the human physiology due to lifestyle practices require concerted and progressive biopharmaceutical research efforts to reflect the pharmacokinetic disposition cum pharmacodynamic responses of different chemical entities. Lifestyle practices vary widely, so also the expected physiological changes and consequent pharmacokinetic effects cum pharmacodynamic outcomes. This will be the research direction in the future.

Keywords: Lifestyle practices, Biopharmaceutics, Pharmacokinetics, Pharmacodynamics, Physiologic changes

INTRODUCTION

The physiologic changes occasioned by the lifestyle of an individual on various classes of medicines can influence the safety and efficacy outcomes [1]. These changes may affect the drug's pharmacokinetics and pharmacodynamics which are the predictors of drug clinical outcomes [2]. The pharmacologic plasticity may not extend to all drugs but will play vital roles when considering drugs with a narrow therapeutic index[3]. Behavioural and lifestyle research is fast developing especially in describing the biopharmaceutics of major prescribed medications. There is scarce literature detailing the salient mechanistic protocols of various lifestyle practices that affect the pharmacokinetics and pharmacodynamics of medicines via physiological reorganization. This review was therefore aimed at highlighting certain lifestyle practices and how they may influence selected biopharmaceutics and clinical outcomes of specific medications.

Drug development research

Upon the discovery and approval of an investigational new drug (IND), clinical research is performed on healthy volunteers usually with no special reference to already known lifestyle practices across communities [4]. The available pharmacokinetic profiles of drugs are therefore premised on healthy individuals' physiological characteristics [5]. Pharmacokinetic parameters such as drug half-life (t½), and plasma or serum maximum concentration (Cmax or Smax), are known to vary with different environmental and genetic factors. The maximum concentration (Cmax), and the onset of action time are functions of the physiological expression of an individual. The clinical trials and research that culminated in those parameters may therefore not give realistic values in altered physiologic conditions based on adjusted or preferred lifestyles. The dose administered determines the optimal effectiveness or toxicity or sub-therapeutic effect. It is therefore important to prioritize drug-lifestyle preferences that can lead to pharmacokinetic and pharmacodynamic parameter variabilities. Drugs play an essential role in human health and understanding each patient factor remains an ever-present challenge in optimizing therapy[6].

Lifestyle preferences

Individuals' lives vary widely due to cultural, environmental and personal preferences. In some settings or communities, individuals with similar living preferences are summed together to form a population based on their lifestyle [7]. Following this, there are individuals that smoke, eat much and tend towards heavy weights. Similarly, some persons consume alcohol as a binge or on a spree. Another class of persons exercises or does not at all. There are persons that sleep or rest well while another category of persons steadily observe stressful life. There are habitual or occasional coffee consumers and water intake levels may describe some people's way of life. The types of diet (e.g. plant-based and whole grains) are lifestyle dispositions that may be characteristic of a population. Finally, the socio-economic circumstances may lead to a sustained or perturbed emotional status affecting a population with respect to living a balanced life. Isolated cases of these lifestyle presentations or their combination may present some group populations with their characteristic physiological presentations [8, 9].

An unhealthy lifestyle has been associated with the aetiology of many disease conditions. The ensuing pathologies may produce characteristic pharmacokinetic dispositions. The consideration of patient-specific factors will require that dosage of drugs be designed to capture deviations from the normal and idealistic populations. A multidisciplinary approach toward considering of pharmacokinetic effects of different physiological presentations emanating from lifestyle preferences in categorical populations is an essential guarantor of the safe and efficacious use of medicines. Physicochemical determinants of drugs such as partition coefficients, molecular weight, size of molecule, solubility, ionization constant, and hydrogen bonding all influence drug-membrane permeability and are considered in the light of drug dispositions at physiological platforms. These physicochemical properties of drugs matched with cellular/molecular conformational descriptors and their role in quantitative structure permeability relationships (QSPR) [10].

Alcohol consumption

Alcohol consumption is a well-known and socially accepted lifestyle. In many communities, it is a routine part of the social norm of the population [11]. It has influence socially, nationally, and internationally. It is therefore simple to overlook the health and social influence this lifestyle causes because of its widespread acceptance [12]. Alcohol causes gastritis by irritating the lining of the stomach. It is also a slow stimulant of gastric acid and gastrin at low concentrations [13]. On the contrary, chronic alcoholics may have normal, enhanced, or diminished acid-secreting capacity [14]. Alcohol consumption may cause variabilities in drug pharmacokinetic profiles.

In drug biotransformation, excessive use of alcohol leads to organ damage with the liver as the target pathological environment. In alcohol-induced fatty liver, the metabolism of drugs may be impaired through the activities of enzyme production inhibition [15].

Chronic and acute administration of drugs

Use of medications that are not prescribed on an acute, intermittent or chronic basis appears to be a lifestyle [16]. Drug-induced liver injuries happen for both

acute and chronic use of medications. This event can be caused by almost all medications especially the over-the-counter medications that are common features in households [17]. In acute intake of medicines, the benign infirmity caused improves after the offending drug is withdrawn, only to appear again on another exposure. Whereas, chronic drug use may cause the injury to progress to an established liver disease depending on user's genetic susceptibility and other risk factors, with the attendant physiologic and biochemical changes [17]. Worthy of note are the effect of these indulged drugs on Cytochrome P450 enzymes that metabolizes the wide range of prescribed medications [18]. More common causes of elevated liver enzymes are over-the-counter medications (e.g., paracetamol) and certain prescription medications (e.g., the statins) with alanine transaminase (ALT) and aspartate transaminase (AST) being majorly and prominently observed. The physicochemical properties of administered drugs and their effect on affected enzymes, when taken as acute or chronic exposures, will be required for individualized dosing [19] Co-morbidities and multiple dosing regimens for chronic conditions

Co-morbidities make patients take a line-up of medications, most oftentimes for long period of time. The interaction of the medications with the biological system presents a biochemical platform akin to a lifestyle presentation [20]. Dosing is therefore considered in view of the expected biochemical alterations from the line-up of drugs in employed in the chronic care protocols. Individualized dosing therefore becomes intriguing and also challenging requiring some mathematical models that can simplify the arduous task in precision medicine.

Physical exercise

Many metabolic diseases including those associated with joint and skeletal problems, obesity, hypertension, etc., have been severally linked to patients' lifestyle [21]. It is therefore pertinent to look at drug disposition in cases involving some described lifestyle practices such as physical activity. In recent times, widespread changes in living and lifestyle dispositions occur while adjusting to socioeconomic and political changes [22]. Emerging new technologies such as domestic appliances or public utilities are noted to threaten previously observed physical/mental activities and alertness. Similarly, technology is brazing up to amend the produced inactivity it caused by introducing devices or instruments such as pedometers, accelerometers used in fitness technology.

Lifestyle preferences affect hormone production and consequently many physiological processes. Performing moderate aerobic exercise has been reported to increase the production of nighttime melatonin [23]. Melatonin and other hormones contribute to human reproduction, growth, and body tissue development. Furthermore, this hormone plays a role in fluid and electrolyte balance thereby regulating the body's cellular functions. Drug movement responds to the affected cellular protocols; therefore, the ultimate response to drugs relates extensively to individual lifestyle, especially their physical activity. As physical activities affect hormone release, cellular changes occur in response to an increase or decrease in hormonal activities.

Physical activities markedly influence the physics and overall dynamics of blood flow. Looking at haemodynamics and physiologic blood flow as fluid flowing through pipes or cylinders, lifestyle practices have been related to the narrowing or opening of blood vessels [24]. Atheromatous deposits in arteries hinder effective or physiological blood flow to different organs or tissues and indeed target organs [25, 26]. Factors affecting haemodynamics are quite extensive. They include circulatory fluid volume, respiration, vascular diameter, membrane receptors and blood viscosity. All of these are affected by some lifestyle preferences. The concept of laminar flow which is characterized by a gradient of flow lines representing varying velocities at different locations in the tube can give a literal translation to the pharmacokinetics of drugs. Variables affecting blood viscosity, both within and external factors may contribute to turbulent flow within the system. Plasma concentration of drugs relates well with systemic blood volume and the volume of distribution follows from here based on drugs' physiochemical properties and of course physiological presentation much influenced by lifestyle preferences alongside genetic factors [27-29].

Tobacco use

The number of cigarette smokers has increased despite the extensive scope of the hazards to health [30]. Smoking is a well-established lifestyle that has been thought to cause alterations in the pharmacokinetic variation of drugs. Cigarette smoke-induced alteration on drug absorption, distribution, metabolism, excretion, and effectiveness may be due to the polyaromatic hydrocarbon and nicotine present in cigarettes. The effect of smoking on the pharmacokinetics of drugs has been extensively reported [31, 32]. Drugs including pentazocine, phenylbutazone, warfarin, and furosemide have been reported to show significant alteration in pharmacokinetic disposition between smokers and non-smokers. Non-smokers show more pain relief on propoxyphene compared to smokers. The clearance of warfarin is increased and a recorded reduction in prothrombin time in smokers compared to non-smokers [33, 34]. It has also been reported that smoking causes a reduction in the diuretic effect of furosemide. Smoking influences strongly the diuretic treatment of hypertensive smokers via its effect on blood pressure lowering from nicotine action [35]. In drug distribution, smoking affects

the protein-binding features of lidocaine [36]. Smoking affects the gut microbiota and modifies the activity of transporter protein thereby altering the pharmacokinetic properties of drugs [37]. Smoking increases the metabolic activities of CYP 450enzymes especially CYP 1A2, an enzyme that is known to metabolize a wide range of commonly prescribed drugs (e.g., caffeine, dozapine, olanzepine, theophylline, fluoroxamine etc.) [38].

This lifestyle preference induces nicotine-mediated sympathetic activation. This activation influences many physiologic targets thereby influencing pharmacokinetic drug disposition. Nicotine is the direct constituent of cigarettes, alongside other components which include polyaromatic hydrocarbons (PAHs). The PAHs are also potent inducers of CYP450 enzymes. Aryl hydrocarbon hydroxylase (Primarily CYP4501A2) has been reported to cause many pharmacokinetic interactions [30, 31, 32].

Caffeine and coffee intake

People of different societies have characteristic and enduring differences in fundamental attitudes, values, and beliefs that form their culture. This may require research into drug disposition in the circumstance[39]. Coffee is the most traded and widely consumed stimulant beverage across the globe. The bioactive component, caffeine, has been reported to cause clinically significant pharmacokinetic interactions with drugs. A high amount of caffeine is consumed in some geographic settings. The circulating stress hormones produced by the adrenal glands in these individuals may influence the ensuing physiological changes. Some of these are sleep loss, appetite change, digestive issues and ultimate decrease in energy levels. Concomitant or lifestyle caffeine use has been reported to significantly affect the absorption, distribution, metabolism and excretion of drugs in fundamental ways. Caffeine stimulates the central nervous system as it antagonizes adenosine receptors [40].

One of the main side effects of consuming too much coffee is frequent urination. The mechanism of caffeine to increase urination is by increasing the glomerular blood pressure within the capillaries in the kidney. Due to this mechanism, coffee increases blood filtration which leads to an increase in urine formation [41]. Renal excretion of drugs may be increased by the intake of coffee.

From the standpoint of biotransformation, coffee inhibits the activities of enzymes. The key role of coffee intake in the metabolism of several clinically important medications is underestimated. When caffeine and drugs (that are metabolized by CYP1A2) are administered together, competing for the same enzyme is common. Consequently, the availability of enzymes to metabolize drugs is decreased as it is saturated by caffeine. In other words, caffeine and drugs act as a metabolic inhibitor to each other which lead to a decreased rate of elimination of drugs [42]. Prescribing in such areas where coffee intake is high will require clinically-based dosage adjustment for therapeutic results.

Fluid intake and Hydration status

By preference or as a culture, water intake is limited, adequate, or excessive in some climes [43]. Water is the most essential nutrient and the amount in the body defines the hydration status. Hydration status is determined by water balance (the relativity between water input and output). Hypohydration or negative water balance is affected by numerous factors, either internal (i.e., a lack of thirst sensation) or external (e.g., polypharmacy or chronic consumption of certain drugs). Research on the pattern of lifestyle influence on hydration status alongside interaction between hydration status and drugs/excipients has been scarce. Lifestyle preferences may trigger the physiologic status of hypohydration using the increase of water elimination through either diarrhoea, urine, or sweat [44]. Similarly, alterations in hydration status by cultural practices decrease gastrointestinal transit time or increase the gastrointestinal tract rate or intestinal permeability. These studies support the aim of monitoring the hydration status in patients, mainly in those population segments with a higher risk, to avoid complications and associated pathologies, which are key axes in both pharmaceutical care and the field of nutrition. Taking non-steroidal anti-inflammatory drugs (NSAIDs) while in a dehydrated state may lead to decreased kidney function. An individual's hydration status may be affected by drugs that have the potentials to alter thirst sensation leading to decreased fluid intake. Similarly, the use of diuretics causes increased urine output which may worsen the clinical outcome in scenario of a lifestyle of low flood volume intake [45].

Diet types

Currently a number of persons have widespread interest in varieties of foods. The New Atkins diet in the USA; Dukan diet in France; Cambridge diet in the UK, and the embraced Noakes diet in South Africa are gaining increasing popularity. Ketone diets for the epileptic patients and keto diets for losing weight [46]. Most of these diets are premised on the reasons of longevity or weight loss plans. Diet is one of the 5 components of a healthy lifestyle. This is partly responsible for the choice of food that many embrace [47]. There are many diet types to choose from based on personal convictions of efficacy and interest. There are studies that highlight the physiological and biochemical influences that different food types and their composition (i.e., individually or combination) exert in humans.

Table1. Some Selected Dietary Models, Food Types and Physiological Features of Users

Diet	Food types	Chemical feature	Physiological feature	Basis of choice	Popular location
Ketogenic	Seafood, meat, poultry, non-starchy vegetables	High fat low-carbohydrate	Low blood glucose feedback and reduced stimulus for insulin secretion	Treatment options for epilepsy and weight loss [65]	Not specific
Mediterranean	Vegetable-rich diet, whole grains, dairy products	Phytochemicals e.gcatotenoids, vitamins and flavonoids	Antioxidant properties and anti-weight gain plan [66]	Proper eating plan and health-awareness	Southern Europe featuring the Mediterranean basin and Iberian Peninsula
Intermittent fasting	Any food type during eating period and abstinence from food during fasting period	Improves blood pressure and resting heart rates. Fat losses and retained muscle mass	Boost working memory in adults, improve blood pressure and resting heart rates [67, 68]	Losing weight and improving health [67]	Not specific
Paleolithic	Lean meat, fish, fruits, vegetables, nuts, seed etc	Low glycaemic fruits and vegetables	Improves blood pressure and glucose tolerance	Avoiding processed food and weight loss plan [69]	Not specific
Vegetarianism	High dietary fibre, low calorie, saturated fat, cholesterol, antioxidants E and C, increased collagen	Absence of animal sourced protein	Lower risk of developing coronary heart disease, high blood pressure, diabetes and projected increased longevity	Health, religious convictions and concerns about animal welfare	Not specific. Worldwide prevalence is not uniform
High fat	High calorie per gram, Cookies, cake, French fries and greasy food	30% of calories or les from fat	Possible weight gain propensity	Perception of need for high calories and some health-related concerns such as improving immunity levels	Not specific

Table 2. Drugs and biomarkers for drug effectiveness monitor

Drug	Drug class	Therapeutic area	Biomarkers	Warnings
Atorvastatin	HMG-CoA Reductase inhibitor	Metabolic and endocrinology	LDL receptor	May interact with other medications (e.g., warfarin, digoxin, certain BP medications). May cause stomach or intestinal bleeding especially in the elderly [94]
Carbamazepine	Anticonvulsant	Neurology	HLA-B	Dose-dependent side effects; May interact with warfarin, apixaban, rivaroxaban and other blood thinners; antibiotics e.g., erythromycin or antifungal e.g., fluconazole [93]
Carvedilol	Beta-blocker	Cardiovascular	CYP2D6	Not indicated in asthma, bronchitis, emphysema and severe liver disease. Drug-alcohol interaction on concomitant use [95]
Citalopram	SSRI	Psychiatry	CYP2D6	Need to monitor heartbeat, watch out for shortness of breath, dizziness or fainting. Drug interactions with drugs e.g., buspirone, tramadol, fentanyl, tryptophan etc [96]
Clopidogrel	Antiplatelet	Cardiovascular	CYP2C19	Drug and food/supplement interactions with grapefruit, garlic and other blood thinners [97]
Diazepam	Benzodiazepine	Neurology	CYP2C19	Drug-drug interaction with a wide range of medications may increase the activity of diazepam. This is also present with herbal supplements [98]

*HLA- Human Leukocyte Antigen; LDL- Low Density Lipoprotein; HMG-CoA - Hydroxyl-methylglutaryl coenzyme A; CYP- cytochrome P; SSRI- Selective serotonin reuptake inhibitor; COX-2 – cyclooxygenase -2.

Nutritional transition includes the change from the intake of traditional to modern diets featuring high-energy density alongside low-nutrient diversity [48]. The diets taken are comprised of diverse components with nutrients supplying the raw materials that drive the cellular metabolic processes.

The walls of the alimentary canal contain a number of sensors namely mechanoreceptors, chemoreceptors and osmoreceptors. These receptors sense the presence of food, breakdown products of ingested food and the level of breakdown. Furthermore, the amount of fluid present, types of nutrients in the food (e.g., lipid, carbohydrates and /or proteins) are detected and responded to accordingly. Stimulation of receptors lead to production of digestive juices into the luminal side and subsequent stimulation of gastric muscles to propel content along the passage [49]. The level of gastric motility corresponds to the nature of the luminal content and is affected by the activity of the nerve plexuses innervated from the central nervous system. Foods that distend the stomach cause short reflex initiation. Short reflexes are orchestrated by intrinsic nerve plexuses within the alimentary system wall and this regulates the activation of peristalsis. In the same light, extrinsic nerve plexus orchestrates long reflexes which involve the central and autonomic nervous system. These responds to sensory detections of sight, smell and taste of food and delivered to the medulla oblongata [50-52]. Dietary models, composition, chemical feature and their physiological importance are spelt out in **Table 1**.

a. Ketogenic diet

Lifestyle modification premised on behaviour has been reported as the most effective strategy to manage metabolic syndromes. The protocols for recommendation on diet and exercise, alongside behavioural and cognitive strategies, have been regarded to be pivotal to therapeutic success. The addition of these protocols with pharmacotherapy and actual implementation of necessary adjustment in every individual is a hope to raise optimistic expectations of a safe and effective treatment [53].

The intake of food increases blood flow to the gastrointestinal (GI) system and thus has been documented to affect heart rate, blood pressure, and cardiac output, though the mechanism has not been spelled out [54]. Presence of food in the GI will cause the secretion of gastrin, which causes distention of epithelial wall and production of gastric acid by the parietal cells of the GI mucosa. The intestine secretes at the duodenum which stimulates the production of cholecytokinin (CCK). CCK in turn stimulates the production of pancreatic enzymes and bile in the liver [49, 55]. Several studies have revealed the effect of different types of food on drug absorption [56]. Drug dosages, therefore, have recourse to types of diet and the timing of drug intake

(i.e., before or after food). Nutritional and biopharmaceutics studies accounted for the variability introduced by the physicochemical properties of co-ingested food as it influences drug disposition [57]. Metabolic food-drug interactions have been reported [58, 59]. This occurs when the consumption of a particular food modulates the functionality of a drug-metabolizing enzyme system. This results in an alteration of the pharmacokinetics of the affected drugs [58, 60].

Intake of food, beverages, and dietary supplements has been reported to influence certain interactions as one co-administered beverage or drink may indirectly affect the pharmacokinetics of the drug via a physiological alteration. This may cause potential harm to users [58, 61]. Many dietary components may influence the functionality of some cell types relating to their physiological signal transduction mechanisms. It is in light of this that research proposes to study the reliability of a drastic alteration of the efficacy of drugs based on lifestyle meal types. Some individuals or indeed a community bound by cultural preferences stick to some particular food types and may respond to some drugs in a programmed fashion. The amount, composition, and time of meals as a lifestyle can therefore potentially affect the pharmacokinetic processes through the alteration of gastric pH, motility, and biliary acid secretion [62, 63].

Gastric sensory-motor functions and hormone profiles in normal-weight, overweight and obese people have relayed the possible drug disposition in the realms of drug absorption and distribution. Furthermore, peptide YY (PYY) levels have been reported to be decreased in overweight and obese individuals [64]. The relationship of these hormones to gastric functions including satiety in food consumption is components of lifestyle practices. Physiological parameters such as gastric volume, gastric emptying rates, food maximum tolerated volume, and any resulting overweight or obesity have been related to drug disposition from the level of absorption through distribution, metabolism, and excretion. The pharmacokinetic profile of each named drug, therefore, is premised on these fundamentals.

b. Mediterranean

Mediterranean diet refers to a traditional eating habit common in area bothering the Mediterranean Sea. The components vary widely, hence no standard Mediterranean diet. The component differs in these countries based on the respective culture, religion, ethnic follow, geography, economy and agricultural production in the area. The common features are copious amount of fruits, vegetables, potatoes, bread, bean, nuts and seeds. It also includes dairy products, fish, eggs and other poultry products in low amounts. As research into the benefits of this type of diet progresses, there will be certain foods that are found to have greater significance

for health and may influence the disposition of drugs[70-72].

c. Intermittent fasting

It has been reported that variation in drug response exists among patients who practice intermittent fasting. This lifestyle may cause alteration in the expression of drug-metabolizing enzymes (DMEs) and may affect the pharmacokinetics/drug response. In a study on intermittent fasting on mice, gene expressions that bother on drug disposition were correlated with the pathohistological alterations, in which case, livers of diabetic mice showed dilatation in the blood sinusoids. Intermittent fasting has some benefits such as protecting the liver against diabetes-induced hepatotoxicity. It has also been shown to be useful in down-regulation of DME genes in the diabetic liver. Dosing in this lifestyle practice is therefore modified to give optimum drug levels for therapeutic activity. Intermittent fasting appears an equivalent alternative to calorie restriction (CR) to improve health in humans. However, few trials have considered applying meal timing during the 'fasting' day, which may be a limitation. We developed a novel intermittent fasting plus early time-restricted eating (iTRE) approach. [73, 74, 75].

4. Pathophysiological and pharmacokinetic factors

The mechanistic protocols of pharmacokinetics spanning over absorption, distribution, metabolism, and excretion are based on a balanced and ideal physiologic system[76],[77]. Pathophysiologic alterations and their indicators may affect all the protocols of pharmacokinetics. The physicochemical properties of drugs align with the physiologic presentations giving an ultimate integrated outcome. This review examines in part the lifestyle preferences and the physiologic and biochemical basis for the alterations of drug kinetics and the ultimate response to drugs.

Diseases

In humans, diseases broadly refer to conditions that cause dysfunction, distress or death. In broader sense, disease includes injuries, disabilities, disorders, syndromes and infections. The presence of certain diseases has been reported to affect the disposition of medications thereby requiring fundamental protocols and adjustments to ensure safety of drug use [78, 79].

Obesity

Obesity and morbid obesity-associated physiological changes have been reported to cause pharmacokinetic alterations. The physiological parameters affected are increased blood volume, cardiac output, splanchnic blood flow, and hepatic blood flow [80]. In obesity, pharmacokinetic parameters such as drug absorption and volume of distribution vary largely, based on total body weight. Changes in clearance may be smaller than in distribution; whereas there is growing evidence that the influence of obesity on clearance can be predicted based on reported changes in the metabolic or elimination pathways involved [81]. Furthermore, overweight and obesity are associated with low postprandial gastric volume and normal PYY levels.

At present, lifestyle modification has been recommended as the foundation upon which other additional therapies rest. The peculiar lifestyle and the disposition of the drug both agree with the ultimate effect of therapeutics. More research is therefore expected on physiological studies, clinical experience, observational studies, and randomized controlled trials on lifestyle and drug disposition [62, 82].

Acute physiological Stress

Physiological effects caused by acute physiological stress include blood pressure alteration, heart rate, and cardiac output, release of stress hormones including catecholamines, noradrenaline, adrenaline and cortisol. Physiological stress leads to challenges on the homeostasis of a cell /organism. Acute physiological stress has been reported to cause increase in heart rate and redirection of blood to large muscles. The protocols in physiological stress may influence the disposition of medications [83]. A stress response is caused by an interplay of endocrine, nervous and immune mechanisms. This also involves the activation of sympathetic –adreno-medullar (SAM), hypothalamus-pituitary-adrenal (HPA) axes alongside the immune system. In today's worlds, some environmental demands (e.g., looming work deadline), and psychological challenges (e.g., anxiety of losing a job) can trigger a cascade of reactions involving stress hormones; orchestrating a number of physiological changes. Stressful incidents have been typified by pounding heart, faster breathing, tense muscles and appearance of beads of sweat [84].

Over the years researchers have looked at the effects of physical and psychological stress on physical and psychological health. The conclusion of these studies has repeatedly indicated that continuous activation of the stress response takes a toll on the body. Through its contribution to raised blood pressure, promotion of artery clogging deposits, contribution to obesity directly (causing people to eat more) or indirectly (decreasing sleep and exercise). However, there is scarce information on the disposition of drugs, both in terms of rate and extent. The entire world is presently undergoing some level of stress every day [85].

Lifestyle and precision medicine

Precision medicine has been projected as the future of medicine. The concept is not entirely new but the tools are robust and complex, including the consideration of cardinal issues of lifestyle

biopharmaceutics. As vast as the individualized drug delivery-based design for personalized medicine can be, it is suggested that the differences and peculiarity of lifestyle practices and its consequential physiological alterations form a basis for drug selection and prescribing. In drug development, the protocols ought to accommodate the delivery of precision dosing [86, 87]. This approach may appear herculean but the methods of individually tailoring the dose of drugs, especially in the extremes of population (e.g., in the elderly), highlight great benefits and least risk. In conventional terms, adjusting doses based on age, sex, ethnicity, organ failure or co-administered drugs are directed at achieving a single dose that will be employed for a generalized group of persons. This further corroborates that a kind of "one dose fits all" approach is not an idealistic concept for this present age.

The influence of lifestyle as emphasized in this review is a set of co-presenting lifestyle preferences that will further create a platform for a fine-tuned precision dosing. Warfarin is a narrow therapeutic window medication that presents a scenario where some persons take more or less than the actual required dose causing toxicities or sub-therapeutic levels in plasma. Precision dosing is therefore appropriately premised on lifestyle preferences of users for the utmost approach to safe use of drugs. Drugs have been categorized as one of these, those possessing wide-population-level therapeutic window, no population level therapeutic window or narrow population level therapeutic window, based on the effective dose in segments or subset of a wide population. It suffices to state that from the drug development level to the consulting rooms and bedside of patients, precision dosing may present some form of complexity [88, 89].

After the initial dose for clinical use of drug is developed, subsequent testing and additional hospital visits for dosing consideration and re-adjustments based on follow up significantly contribute to cost. The cost of ensuring this protocol holds may be prohibitive and the commercial value of precision dosing during drug development research, if considering all set of lifestyle preferences may be commercially unattractive despite the increased benefits to the users. Notwithstanding, the consequences of using a sub-therapeutic dose and indeed a toxic dose may make regulatory authorities insist on precision dosing protocols highlighting lifestyle preferences [87].

The size of the population or individual therapeutic window, the variability between patient and the consequences of using sub-optimal dose are key considerations for safe and efficacious use of drugs. An approach to design a mathematical protocol to describe the relativity of lifestyle preferences to portray this uses utility functions demonstrating the variation of optimal individual dose compared with the optimal population

dose is therefore a research direction. From the industry today, everyone (prescribers and payers) is exploring ways to reduce cost by individualizing dosing. For example, omalizumab was developed with a dosing algorithm considering disease variability, immunoglobulin E levels and some core factors for precision dosing [90, 91]. Though this may not be advocated for all drugs but it is proposed that an assemblage of lifestyle preferences can form the basis of forming populations upon which drug development and precision dosing protocols can be founded. This is believed to be able to open the frontiers of research in this dimension.

Precision dosing is therefore advocated for narrow therapeutic window drugs for improved utility. Furthermore, drugs for diseases with serious or irreversible consequences for under treatment (e.g., anticancer or neurodegenerative drugs are also sure candidates. Similarly, drugs with serious or irreversible adverse events from too high a dose and lastly drugs with invasive route of administration (e.g., intravitreous, intrathecal) will also benefit from precision dosing stemming from the influence of lifestyle preferences.

Biomarkers of drug effects

These will be required to integrate with drug dosing as precision is a watchword. It will be researched for different population of lifestyle preferences. In cases of insulin therapy, glucose levels and HbA1c are useful parameters instead of insulin concentrations in blood. The role of pharmacogenomics biomarkers with integrated lifestyle influences in predicting and improving drug responses in line of therapy optimization is the way to go in the future [92]. Many adverse drug reactions may be avoided if clinicians have biomarkers on drug effect as treatment progresses. Developing biomarkers with biopharmaceutics principles will optimize therapeutics. Markers of pharmacological effects or disease activity or a co-variate of disease variability are object of research for the future in line with evidence based medicine and therapy optimization.

The primary focus in the study of hypersensitivity in response to carbamazepine is the human leukocyte antigen. These are genes that codes for proteins that play major roles in disease and immune defense. They are found on the cell membranes of almost all nucleated cells and have played a diagnostic role in drug-induced severe cutaneous adverse reactions [93.]

Artificial intelligence

The application of artificial intelligence (AI) to many sectors and fields have been increasing. The primary aim of AI in health-related matters has been to analyze relationships between prevention or treatment profiles and the ensuing patient outcomes. In light of the applications of AI to personalized medicine and patient monitoring/care, the extensive lifestyle practices can be

captured for a more definitive healthcare service [99, 100]. This includes the pharmaceutical sector involving drug repurposing and clinical trials among others [101].

There are multidimensional data and modern techniques for data analysis and postulation of mathematical variables developed based on lifestyle preferences [102]. These are aimed to bring to fore the benefits of drug users' behaviour to their prescribed drugs. Data science is a novel approach to the collection, aggregation, and analysis of data towards characterizing drug-response variability at the individual level. These scientific endeavours will enable clinical pharmacology and biopharmaceutics to become critical contributors to personalized healthcare via precision dosing [103, 104]. Currently the concept of artificial intelligence technique as is employed for handling life-threatening diseases can be extended to cover other pharmacotherapy areas. It is in the interest of establishing a robust biopharmaceutics and therapeutics system that the interplay of such techniques with conventional pharmacokinetic/ pharmacodynamic approaches is recommended in drug research and early development [105].

CONCLUSION

The lifestyle preferences in any setting and the individuals in that environment can form the basis of the design of studies leading to pharmacokinetic profiling of drugs for safety and efficacy. The advancement in science and technology is matching up with the challenges posed by individual variations and presentations so much that biopharmaceutics and drug selection alongside therapeutics will make healthcare smooth and handleable.

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REFERENCES

1. Pi-Sunyer A. How effective are lifestyle changes in the prevention of type 2 diabetes mellitus. Nutr Rev. **2007**; 65(3):101-110. Doi:10.1111/j.1753-4887.2007.tb00287.x.

2. Davies M, Jones RDO, Grime K, Jansson-Lofmark K, Fretland AJ, Winimarter S, Morgan P, McGinnity GF. Improving the accuracy of predicted human pharmacokinetics AstraZenica drug pipeline over two decades. *Trends Pharmacol Sci.* **2020;** 4(6):390-408. Doi:10.1016/j.tips.2020.03.004.

3. Parnham MJ, Geisslinger G. Pharmacological plasticity-How do you hit a moving target. *Pharmacol Res Perspectl* **2019**; (7): e00532. Doi.org/10.1002/prp2.532

4. Ndejjo R, Musinguzi G, Nuwaha F, Bastiaens H, Wanyenze RK. Understanding factors influencing uptake of healthy lifestyle practices among adults following a community cardiovascular disease prevention programme in Mukono and Buikwe districts in Uganda: A qualitative study. *PLoS One,* **2022**; 17(2):e0263867. Doi: 10.1371/journal.pone.0263867.

5. Høye S, Kvigne K, Aiyub I, Gillund MV, Hermansyah H, Nordström G, Rystedt I, Suwarni A, Trollvik A, Wilde-Larsson B, Hov R. A Healthy Person: The Perceptions of Indonesian and Scandinavian Nursing Students. *Glob Qual Nurs Res.* **2016**; 3:2333393616651766. Doi: 10.1177/2333393616651766.

6. Lesko LJ, Schmidt S. Individualization of drug therapy: History, present state and opportunities for the future. *Clin Pharmacol Ther*. **2012**; 92: 458-466. Doi. 10.1038/clpt.2012.113

7. Pruitt JN, Riechert SE, Iturralde G, Vega M, Fitzpatrick BM, Avilés L. Population differences in behaviour are explained by shared within-population trait correlations. *J Evol Biol.* **2010**; 23(4):748-56. Doi:10.1111/j.1420-9101.2010.01940.x.

8. Banerjee A, Chaudhury S. Statistics without tears: Populations and samples. *Ind Psychiatry J.* **2010;** 19(1):60-5. Doi:10.4103/0972-6748.77642

9. Farhud DD. Impact of lifestyle on health. *Iran J Public Health.* **2015**; 44(11): 1442-1444. PMID: 26744700

10. Avdeef A . Physicochemical profiling (solubility, permeability and charge state). **2001**;1(4):277-351. Doi: 10.2174/1568026013395100.

11. Glasson JC, Sawyer WT, Lindley CM, Ginsberg B. Patient specific factors affecting patient-controlled analgesic dosing. *J Pain Palliat Care Pharmacother.* **2002**; 16(2): 5-21.Doi:10.1080/j354v16n02_02

12. Gureje O, Lasebinan VO. Alcohol beverage types; problem drinking and self-reported health status. *Niger J Psychiatric.* **2006**; 4(1): 4 – 8.Doi: 10.4314/njpsyc.v4i39883

13. Matsuno K, Tomita K, Okabe S, Wine stimulates gastric acid secretion in isolated rabbit gastric glands via two different pathways. *Ailment Pharmacol*

Ther. **2002**; 16; Suppl 2(2002) 107-114. Doi:10.1046/j.1365-2036.16.s.1.9,x

14. Bujanda L, The effects of alcohol consumption on the gastrointestinal tract. *Am J Gastroenterol,* **2000**; 95;12: 3374-82. Doi: 10.1111/j.1572-0241.2000.03347.x.

15. Osna NA, Donohue TM, Kharbanda KK, Alcoholic Liver Disease: Pathogenesis and Current *Manag Alcohol Res*. **2017**; 38(2): 147-161. PMID: 28988570; PMCID: PMC5513682.

16. Cameron A, Roubos I, Ewen M, Mantel-Teeuwisse AK, Leufkens HGM, Laing RO. Differences in the availability of medicines for chronic and acute conditions in the public and private sectors of developing countries. *Bull World Health Organ.* **2011**; 89: 412–421 Doi:10.2471/BLT.10.084327

17. Bibi Z. Role of Cytochrome P450 in drug interactions. *Nutr Metab.* **2008**; 5(27). Doi: 10.1186/1743-7075-5-27.

18. McDonnell AM and Dang CH. Basic review of the Cytochrome P450 system. *J Adv Pract Oncol.* **2013**; 4(40: 263-268. Doi: 10.6004/jadpro.2013.4.4.7

19. Zanger UM, Schwab M. Cytochrome P450 enzymes in drug metabolism: Regulation of gene expression, enzyme activities, and impact of genetic variation. **2013**;138(1): 103-141. Doi: 10.1016/*j.pharmthera.*2012.12.007

20. Somvanshi PR, Venkatesh KV. A conceptual review on systems biology in health and diseases: from biological networks to modern therapeutics. *Syst Synth Biol.* **2014**; 8(1): 99-116. Doi: 10.1007/s11693-013-9125-3.

21. Kerkaki A, Sadig AA, Bawadi H, Al Thiami AM, Al Chetachi N, Akram H, Al Hazzaa HM, Musaigner AO. The relationship between lifestyle factors and obesity indices among adolescents in Qatar. *Int J Environ Res Public Health.* **2019**; 16(22): 4428. Doi: 10.3390/ijerph16224428.

22. Woessner MN, Tacey A, Levinger-Limor A, Parker AG, Levinger P, Levinger I. The evolution of technology and physical inactivity. The good, the bad, and the way forward. *Front Pub Health.* **2021**; 9. Doi: 10.3389/fpubh2021.655491.

23. Escames G, Ozturk G, Bano-Otalora B, Pozo MJ, Madrid JA, Reiter RJ, Serrano E, Concepcion M, Acuna-Castrovejo C. Exercise and melatonin in humans: reciprocal benefits. *J Pineal Res.* **2012**; 52: 1-11. Doi:10.1111/j.1600-079x.2011.00924.x.

24. Nicolás FR, Natalia H, Roberto MM. Pathophysiology of Vascular Remodeling in Hypertension. *Int J Hypertens.* **2013**; Article ID 808353, 7 pages, 2013. Doi.org/10.1155/2013/808353

25. Al-Namari A. Atherosclerosis and Physical Activity, *Oman Med J.* **2014**; 24(3): 173-178. Doi:10.5001/omj.2009.34

26. Aengevaeren VL, Mosterd A, Braber TL, Prakken HJ, Doevendans PA, Grobbee DE, Thompson PD, Eijsvogels MH, Velthuis BK. Relationship between lifelong exercise volume and coronary atherosclerosis in Athletes, Circulation. **2017**; 136: 138-148. Doi: 10.1161/CIRCULATIONAHA.117.027834

27. Rudwwicz RJ. Turbulent flow Bioanalysis in drug metabolism and pharmacokinetics. Bioanalysis. **2011**; 3(11). Doi.org/10.4155/bio.11.137

28. Zhang D, Hop CECA, Patilea-Vrana G, Gampa G, Seneviratne HK, Unadkat JD, Kenny JR, Nagapudi K, Di L, Zhou L, Zak M, Wright MR, Bumpus NN, Zang R, Liu X, Lai Y and Khojasteh SC. Drug Concentration Asymmetry in Tissues and Plasma for Small Molecule–Related Therapeutic Modalities. *Drug Metab Disposition.* **2019**; 47(10): 1122-1135. Doi: 10.1124/dmd.119.086744

29. McCullough E, Zhen C, Shin S, Lu M, Arsenault J. The role of food preferences in determining diet quality for Tanzanian consumers. *J Dev Econ.* **2022**; 155: 102789. Doi: 10.1016/j.jdeveco.2021

30. CPHI. Committee on the Public Health Implications of Raising the Minimum Age for Purchasing Tobacco Products; Board on Population Health and Public Health Practice; Institute of Medicine; Bonnie RJ, Stratton K, Kwan LY, editors. Public Health Implications of Raising the Minimum Age of Legal Access to Tobacco Products. Washington (DC): *National Academies Press (US);* **2014.** The Effects of Tobacco Use on Health. Available from: https://www.ncbi.nlm.nih.gov/books/NBK310413/ (Accessed 20/09/22).

31. Gagne JJ, Bykov K, Choudhry NK, Toomey TJ, Connolly, JG , Avorn J. Effect of smoking on comparative efficacy of antiplatelet agents: systematic review, meta-analysis, and indirect comparison. *BMJ.* **2013**; 347: f5307. Doi:10.1136/bmj.f5307

32. Diab O, Arafat T, Yousef A. Effect of Smoking on Pharmacokinetics of Clopidogrel, an Antiplatelet Drug. *Trop J Pharm Res.* **2015**; 14(4): 693-700. Doi:10.6314/tjpr.vi4.19

33. Fidler JA, West R. Enjoyment of smoking and urges to smoke as predictors of attempts to stop smoking. A longitudinal study. *Drug Alcohol Depend.* **2011**; 115(1-2); 30-4. Doi: 10.1016/j.drugalcdep.2010.10.009

34. Erickson M, Mackay J, Ross H. The tobacco atlas New York', NY. American Cancer Society,**2013.** https://www.afro.who.int/sites/default/files/2017-09/Front%20Matter.pdf

35. Leone A. Biochemical markers of cardiovascular damage from tobacco smoke. *Current Pharm Design.* **2005**; 11(17): 2199-2208. Doi: 10.2174/1381612054367391.

36. Leone A, Landin L, Biadi O, Balbarini A. Smoking and cardiovascular system: cellular features of the damage. *Curr Pharm Design.* **2008**; 14918: 1771-1777. Doi. 10.2174/138161208784746699

37. Gui X, Yang Z, Li MD. Effect of Cigarette Smoke on Gut Microbiota: State of Knowledge. *Front Physiol.* **2021**; 12: 673341. Doi: 10.3389/fphys.2021.673341. PMID: 34220536; PMCID: PMC8245763.

38. Hukkanen J, Jacob P, Peng M, Dempsey D, Benowitz NL. Effect of nicotine on cytochrome P450 1A2 activity. *Br J Clin Pharmacol.* **2011**; 72(5): 836-8. Doi. 10.1111/j.1365-2125.2011.04023x.

39. Blunsdon B, Reed K, Bliston P, Dastmalchian A. Social change and ways of living. An Introduction in ways of living. **2010**; ISBN: 978-1-349-30039-6.oi:10.1057/9780230273993_1

40. Carillo JA, Benitez J. Clinically significant pharmacokinetic interactions between dietary caffeine and medications. *Clin Pharmacokinet.* **2000**; 39(2): 127-153. Doi. 10. 2165/00003088-200039020-0004.

41. Chen H, He C, You Z, Zhang S, He H, Chen XN, Wang S, Lin K, Guo Y. Association between urine pH and risk of contrast-associated acute kidney injury among patients after emergency percutaneous coronary intervention: a V-shape relationship? *Clin Exp Nephrol.* **2021**; 25(5):554-561. Doi: 10.1007/s10157-020-02015-2

42. Belayneh A, Molla F. The effect of coffee on pharmacokinetics properties of drugs view. *Biomedical Res Int.* **2020**; 24 7909703. Doi.10.1155/2020/7909703

43. Manz F, Wentz A. Hydration status in the United States and Germany. *Nutr Rev.***2005;** 63:S55–62 (2005). Doi: 10.1111/j.1753-4887.2005.tb00154.x.

44. Popkin BM, D'Anci KE, Rosenberg IH. Water, hydration and health. *Nutr Rev.* **2010;** 6(8): 439-58. Doi:10.1111/j.1753-4887.2010.00304.

45. Walter AN, Lenz T. Hydration and medication use. *American J Lifestyle Med.* **2011**; 5(4): 332-335. Doi. Org/10.1177/1559827611401203.

46. Guzek D, Skolmowska, Głąbska D. Associations between Food Preferences, Food Approach, and Food Avoidance in a Polish Adolescents' COVID-19 Experience (PLACE-19) Study Population. *Nutrients.* **2022**; 13(7): 2427. Doi: 10.3390/nu13072427

47. Boyles TM, Wasserman S, Noakes' low – carbohydrate, high-fat diet: call for evidence: correspondence. *South African Med J.* **2013**; 103(12): 882-883. DOI: 107196/SAMJ.7674

48. Cheng Y, Michalak M, Agellon LB. Importance of Nutrients and Nutrient Metabolism on Human Health. *Yale J Biol Med.* **2018**; 91(2): 95-103. PMID: 29955217

49. Chandrashekar J, Hoon MA, Ryba NJ, Zuker CS. The receptors and cells for mammalian taste. *Nature.* **2006**; 444(7117): 288-94. Doi: 10.1038/nature05401.

50. Roudaut Y, Lonigro A, Coste B, Hao J, Delmas P, Crest M. Touch sense: functional organization and molecular determinants of mechanosensitive receptors. *Channels (Austin).* **2012**; 6(4): 234-45. Doi: 10.4161/chan.

51. Abraira VE, Ginty DD. The sensory neurons of touch. *Neuron.* **2013**;79(4): 618-39. Doi: 10.1016/j.neuron.2013.07.051.

52. Acosta A , Camilleri M, Shin A, Vazquez-Roque MI, Iturrino J, Burton D, O'Neill J , Eckert D , Zinsmeister AR. Quantitative Gastrointestinal and Psychological Traits Associated With Obesity and Response to Weight-Loss Therapy Andres Acosta Alimentary Canal, **2014**; 148(3): 537-546. Doi: 10.1053/j.gastro.2014.11.020

53. Tyson RJ, Park CC, Powell JR, Herbert J. Precision dosing priority criteria: Drug Disease and Patient population variables. *Front Pharmacol.* **2012**; Vol 11. Article 420.doi:10.388/fphar.2020.00420.YEAR

54. Abdel-Salam OM**,** Czimmer J, Debreceni A, Szolcsanyi J, Mozsik G. Gastric mucosal integrity: gastric mucosal blood flow and microcirculation. An overview. *J Physiol Paris.* **2001**; 95: 105–127, 2001.doi:10.1016/50028-425(02)00015-8

55. Lee AA, Owyang C. Sugars, Sweet Taste Receptors, and Brain Responses. *Nutrients.* **2017**; 9(7): 653. Doi: 10.3390/nu9070653

56. Cheng L, Wong H. Food Effects on Oral Drug Absorption: Application of Physiologically-Based Pharmacokinetic Modeling as a Predictive Tool. *Pharmaceutics.* **2020**; 12(7): 672. Doi:10.3390/pharmaceutics

57. Barbour NP, Lipper RA. Introduction to Biopharmaceutics and its Role in Drug Development. In: Krishna, R., Yu, L. (eds) Biopharmaceutics Applications in Drug

Development. *Springer,Boston, MA.* **2008**. Doi.org/10.1007/978-0-387-72379-2_1

58. Bushra R, Aslam N, Khan AY. Food-drug interactions. *Oman Med J.* 2011; 26(2): 77-83. Doi: 10.5001/omj.2011.21. PMID: 22043389; PMCID: PMC3191675.

59. Awofisayo SO, Okhamafe AO. The effect of co-administered drugs and food on the absorption of artemether-lumefantrine tablet, *J Advances Med Pharm Sci.* **2015**; 2(4): 126-134. Doi: 10.9734/JAMPS?2015/15333

60. Awofisayo SO, Arhewoh MI, Okhamafe AO. Effect of Food/Beverages and Selected Drugs on the Oral Absorption of Artemether-Lumefantrine Tablet: an in situ and in vivo Study, *BFOPCU*, **2019**; 57; 2: Doi: 10.21608/bfpc.2019.101872.

61. Cheng Y, Michalak M, Agellon LB. Importance of Nutrients and Nutrient Metabolism on Human Health. *Yale J Biol Med.* **2018**; 91(2): 95-103. PMID: 29955217

62. Hanley MJ, Abernethy DR, Grenblatt AJ. Effect of obesity on the pharmacokinetics of drugs in humans. *Clin Pharmacokinet.* **2010**; 49: 71-87. Doi:10.2165/11218100-000000000-00000

63. Ticho AL, Malhotra P, Dudeja PK,Gill RK, Alrefai WA. Bile Acid Receptors and Gastrointestinal Functions. *Liver Res.* **2019**; 3(1): 31-39. Doi:10.1016/j.livres.2019.01.001

64. Karra E, Chandarana K, Batterham RL. The role of peptide YY in appetite regulation and obesity. *J Physiol,* **2009**; 587: (1):19-25. Doi.10.1113/jphysiol.2008.164269

65. Williams MS, Turos E, The chemistry of ketogenic diet: updates and opportunities in organic synthesis, *Int J Mol Sci.* 2021; 22(10): 5230. Doi. 10.3390/ijms22105230.

66. Biesalski HK. Diabetes preventive components in the Mediterranean diet. *Eur J Nutr.* 2004; 43Suppl 1: 26-30. Doi: 10.1007/s00394-004-1106-6.

67. Collier R. Intermittent fasting: the science of going without. *CMAJ.* 2013; 185(9): E363-E364. Doi: 10.1503/cmaj.109-4451.

68. Patterson RE, Sears DD. Metabolic effects of intermittent fasting. *Annual Rev Nutr.* 2017; 37(1): 371-393. Doi:10.1146/annurev-nutr-071816-064634

69. LM Kowalski LM, J Bujko J. Evaluation of biological and clinical potentials of Paleolithic diet. *Rocz Panstw Zaki Hig.* **2012**; 63(1): 9-15. PMID: 22642064

70. Patikorn C, Roubal K, Sajesh K Veettil SK, Chandran V, Pham T, Lee YY, Giovannucci EL, Varady KA, Chaiyakunapruk N. Intermittent Fasting and Obesity-Related Health Outcomes: An Umbrella Review of Meta-analyses of Randomized Clinical Trials. Doi:10.1001/jamanetworkopen.2021.39558.

71. Harris L, Hamilton S, Azevedo LB, Olajide J, De Brún C, Waller G, Whittaker V, Sharp T, Lean M, Hankey C, Ells L. Harris L, et al. JBI Database System Rev Implement Rep. **2018**;16(2):507-547. Doi: 10.11124/JBISRIR-2016-003248.

72. Naous E, Achkar A, Mitri J. Naous E, et al; Intermittent Fasting and Its Effects on Weight, Glycemia, Lipids, and Blood Pressure: A Narrative Review. *Nutrients.* **2023** Aug 21; 15(16): 3661. Doi: 10.3390/nu15163661.

73. Lammers LA, Achterbergh R , Ron AA, Mathôt RAA, Johannes A, Romijn JA. The effects of fasting on drug metabolism **2020**; 16(1): 79-85. Doi: 10.1080/17425255.2020.1706728

74. Al-Kazimi N, Jarrar Y, Abdul-Wahab G, Alsayed AR, Madani A, Abulebdah D, Musleh RS, Jarrar Q, Al-Ameer HJ, Al-Awaida W, Abdullah E. Effects of intermittent fasting on the histology and mRNA expression of major drug-metabolizing cyp450s in the liver of diabetic mice. *Libyan Journal of Medicine,* 18:1. Doi: 10.1080/19932820.2023.2270188

75. American Diabetes Association; Bantle, JP; Wylie-Rosett, J.; Albright AL, Apovian CM, Clark NG, Franz MJ, Hoogwerf BJ, Lichtenstein AH, Mayer-Davis E. Nutrition recommendations and interventions for diabetes: A position statement of the American Diabetes Association. *Diabetes Care.* **2008**; 31 (Suppl. 1): S61–S78. Doi: 10.2337/dc08-S061.

76. MS Roberts, BM Magnusson, FJ Burczynski, M Weiss, Enterohepatic circulation: physiological, pharmacokinetic and clinical implications. *Clin Pharmacokinet.* 2002; 41: 751–790. Doi:10. 2165/00003088-200241100-00005

77. Mehrotra N, Gupta M, A Kovar A, Meibohm B. The role of pharmacokinetics and pharmacodynamics in phosphodiesterase-5 inhibitor therapy. *Int J Impot Res.* 2007; 19: 253-264. Doi:10.1038/sy.ijir.3901522

78. Wakefield JC. The concept of mental disorder: diagnostic implications of the harmful dysfunction analysis. *World Psychiatry.* **2007**; 6(3):149-56. PMID: 18188432; PMCID: PMC2174594.

79. Gandhi A, Moorthy B, Ghose R. Drug disposition in pathophysiological conditions. *Curr Drug Metab.*

2012; 13(9):1327-44. Doi: 10.2174/138920012803341302. PMID: 22746301; PMCID: PMC3937312.

80. Magder S. An approach to hemodynamic monitoring: Guyton at the bedside. *Crit Care.***2012**; 16: 236–43. Doi: 10.1186/cc11395.

81. Knibbe CAJ , Brill MJE, Rongen A, Diepstraten J, van der Graaf PH , Danhof M. Drug Disposition in Obesity: Toward Evidence-Based Dosing. *Ann Rev Pharmacol Toxicol.* **2015**; 55(1): 149-167. Doi: 10.1146/annurev-pharmatox-010814-124354.

82. Vazquez-Roque MS, Camilleri M, Stephens DA, Jensen MD, Burlon DD, Bader KL, Meishe ZAR. Gastric sensory molar function and hormone profile in normal weight, overweight and obese people. *Gastroenterol.* **2006**; 131(6): 1717 – 24.Doi:10. 1055/j.gastro.2006.10.025

83. Campbell J, Ehlert U. Acute psychosocial stress: Does the emotional stress response correspond with psychological responses? *Psychoneuroendocrinol.* **2012**; 37(8): 1111-1134. Doi: 10.1016/j.psynuen.2011.12010.

84. Schubert C, Lambert M, Neleser RA, Bardwell W, Choi JB, Dimsdal JE. Effect of stress on heart rate complexity-A comparison between short-term and chronic stress. *Biol Psychol.* **2009**; 80(3): 325-332. Doi.10.1016/j.biopsycho.2008.11.005

85. Ryan KK, Grayson BE, Jones KR, Schneider AL, Woods SC, Seeley RJ, Herman JP, Ulrich-Lai YM. Physiological Responses to Acute Psychological Stress are Reduced by the PPAR gamma Agonist Rosiglitazone. *Endocrinol*. **2012**; 153(2): 1279-1287. Doi:10.1270/en.2011-1689

86. Perk RW, Precision medicine is not just genomics: the right dose for every patient. *Annu Rev Pharmacol Toxicol.* **2018**; 58: 105-122. Doi:10.1146/annurev-pharmtax-010617-052446

87. Schuck RN, Pacanowski M, Kim S, Madabushi R, Zineh I. Use of titration as a therapeutic individualization strategy: an analysis of Food and Drug Administration-approved drugs. *Clin Transl Sci.* 12, **2019**; 12: 236–239. Doi:10.1111/cts.12626

88. Bica I, Alaa AA, Lambert C, van der Schaar M. From real-world patient data to individualized treatment effects using machine leaSrning: current and future methods to address underlying treatment challenges. *Clin Pharmacol Ther.* **2021**; 09: 87–100. Doi: 10.1002/cpt.1907

89. Perk RW. Precision Dosing: An Industry Perspective. *Clin Pharmacol Ther.* **2021**; 109(1): 47-50.Doi:10.1002/cpt.2064

90. Cildag S, Senturk T. The effect of omalizumab treatment on IgE and other immunoglobulin levels in patients with chronic spontaneous urticaria and its association with treatment response. *Postepy Dermatol Alergol.* **2018**; 35(5): 516-519. Doi: 10.5114/ada.2017.71422

91. Menzella F, Just J, Sauerbeck IS, Mailaender C, Saccheri F, Thonnelier C, Jaumont X, Mala L. Omalizumab for the treatment of patients with severe allergic asthma with immunoglobulin E levels above>1500IU/mL. *World Allergy Organ J.* **2023**; 16(6): 100787. Doi: 10.1016/j.waojou.2023.100787

92. Ventola CL. The role of pharmacogenomics biomarkers in predicting and improving drug response. *Pharm Ther.* **2013**; 38(9): 545—551. PMID: 24273401; PMCID: PMC3828931.

93. Rashid M, Rajan AK, Chabra M, Kashyap A, Chandran VP, Venkataraman R, Nair S, Thunga G. Role of human leukocyte antigen in anti-epileptic drug-induced Stevens-Johnson syndrome/toxic epidemiological necrolysis: meta-analysis. *Seizure.* **2022**; 102: 36-50. Doi: 10. 1016/j. Seizure. 2022.09.011.

94. Ji Y, Schaid DJ, Desta ZK, Kubo M, Batzler AJ, Synder K, Mushiroda T, Kamantani N, Ogburn E, Hall-Flavin D, Nakamura Y, Mrazek DA, Weinshilboum RM. Citalopram and escitalopram pharma drug and metabolite concentrations: genome-wide associations. *Br J of Clin Pharmacol.* **2014**; 78(2): 373-383. Do:10.111/b cp.12348.

95. A Raskovic A, V Cvejic V, Stilinovic N, Golocorbin-kon S, Vulnirovic N, Mimicov M, Interaction between different extracts of hypericum perforatum L from Serbia and pentobarbital and paracetamol. *Molecules.* **2014**; 9(4): 3869-82. Doi: 10.3390/molecules19043869.

96. Dilsizian SE, Siegel EL. Artificial intelligence in medicine and cardiac imaging: harnessing big data and advanced computing to provide personalized medical diagnosis and treatment. *Current Cardiol Report.* **2014**; 16(1): 441. Doi: 10.1007/511886-013-0441-8.

97. D Paul, S Guarav, S Snehal, K Dnyaneshwar, K Kiran, KT Rakesh, *Drug Discov Today*. **2021**; 26(1); 80-93. Doi:10.1016/j.drudis.2020.10.010

98. Johnson KB, Wei-Qui W, Weeraratne D, Frissae ME, Misulis K, Rhee K, Zhao J, Snowdon JL. Precision Medicine, AI, and the Future of Personalized Health Care. *Clin Transl Sci.* **2021**; 14(1): 86-93. Doi:10.1111/cts.12884

99. Maloney A. A new paradigm. " learn- learn more"; Dose-exposure-response at the centre of drug development and regulatory approval. *Clin Pharmacol Therap.* **2017**; 102: 942-950. Doi: 10.1002/cpt.710.Epub.2017May 30

100. Ribba B, Dudal S, Lavé T, Peck RW. Model-informed artificial intelligence: reinforcement learning for precision dosing. *Clin Pharmacol Ther.* **2020**; 107: 853–857. Doi:10.1002/cpt.1777

101. Landmark CJ, Patsalos PN. Interactions between antiepileptic drugs and herbal medicines. *Boletin Latinoamericano y del Caribe de Plantas Medicinales Aromaticas.* **2008**; 7(2): 109-118. Http://www.redalyyc.org/articulo.oa?id=85670209

102. Vinks AA, Peck RW, Neely M, Mould DR. Development and implementation of electronic health record-integrated model-informed clinical decision support tools for the precision dosing of drugs. *Clin Pharmacol Ther.* **2020**; 107:129–135.Doi:10.1002/cpt.1679

103. Jones HM, Parrott N, Jorga K, Lave T. A Novel Strategy for Physiologically Based Predictions of Human Pharmacokinetics. *Clin. Pharmacokinet.* **2006**; 45; 511–542. Doi. 10.2165/00003088-2006.

104. Li LR, Du B, Liu HQ, Chen C. Artificial intelligence for personalized medicine in thyroid cancer. Current Status and future perspectives. ***Front Oncol.*** **2021**; 10.604051. Doi. 10.3389/fonc.2020.604051.

105. Teuscher N. The history and future of population pharmacokinetic analysis in drug development. *Xenobiotica.* **2023.** Doi: 10.1080/00498254.2023.2291792