Chapter

Ivan Illich, Iatrogenesis and Pharmacogenetics

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Abstract

In Medical Nemesis - The expropriation of health, IVAN ILLICH highlights several aspects of the medicalization of society, which was already observed in the mid-1970s. He addressed the various forms of iatrogenesis, classifying the new disease caused by the set of medical care as an epidemic that would not exist if there were no medical intervention. Of the various forms of iatrogenesis, he also addressed drug iatrogenesis, including the cause of hospital admissions. In this article, more than 40 years after Illich's seminal publication, we sought to revisit his thinking and assess the relevance of his narrative regarding the inconveniences resulting from the use of medicines, especially in their impacts on hospitalization, in addition to reflecting on the potential of pharmacogenetics to mitigate adverse events related to drugs that victimize people. After a brief presentation of Illich's trajectory, a digression is made on the association between the concepts of medicalization and iatrogenesis, to then make quick considerations about social iatrogenesis, considering the effects of this phenomenon on society. After presenting the consequences of iatrogenesis, from a fluent literature review, an update of the findings is made, showing that the problem is relevant today. A brief conceptual presentation of pharmacogenetics is followed by some examples of its clinical consequences. It is concluded that, despite the unequivocal importance of pharmacotherapy, iatrogenesis remains a problem of increasing relevance. Pharmacogenetics presents itself as a possibility to minimize the problem, making it possible to expand its use in the practice of medical services.

Keywords: Medicalization, iatrogenic disease, adverse effects, pharmacogenetics

1. Introduction

> *"Almost all men die from their drugs and not from their diseases"*
> *(Molière - 1622-1673, The Imaginary Invalid, Act III).*

In his work devoted to analyzing the theme of health, Ivan Illich addressed the medicalization of society, the harms caused by the medical apparatus, the so-called iatrogenesis, including drug iatrogenesis, which he also listed as the cause of hospital admissions [1].

Revisited more than 40 years after its publication, the work 'Medical Nemesis' still proves to be thought provoking and current. More than stimulating reflection, it has the strength to motivate the investigation of several of the aspects it addresses, so that one can know, for example, whether iatrogeneses related to hospital admissions are still a public health problem, a topic that has been extensively discussed. Extensive investigation [2–4].

Although adverse drug events (ADE) often include errors that occurred before and during hospitalization, even the correct prescriptions can present iatrogenesis, a situation that occurs when they cause more harm than good. In addition to the direct losses to patients, ADEs influence to increase the already unsustainable costs of health systems.

Therefore, iatrogenesis is not just a result of an error in the prescription. It is relatively common to have a correct diagnosis and prescription, but undesirable results due to several aspects. One of them has the explanation for the adverse effect in genetics. The literature also refers to writing iatrogenesis, when difficult to read writing causes potential or real problems to patients [5].

On the other hand, the contribution of drugs towards the cure or control of various diseases is undisputed, with a direct impact on prolongation and quality of life.

The association between drugs and different responses to treatments explained by individuals' genetic variants is an ancient discovery, confirmed by several scientists since the beginning of the last century [6]. The knowledge arising from the human genome project has led to advances in several fields of modern science, but it is in the field of Health, in particular, that its applicability has been growing in a promising way [7].

In Health, the discoveries of genomics have contributed to improve the assertiveness of diagnoses, prognoses and treatments, including those related to the ingestion of medications, which makes pharmacogenetics one of the main manifestations of the so-called precision medicine.

It may sound inconsistent to relate Ivan Illich - an iconoclast of health technologies and an opponent of everything that stimulates the medicalization of society - with pharmacogenetics, after all, one of the most advanced technologies. However, this new branch of science, which constitutes one of the most promising forms of the applicability of genomic findings, can respond to an important problem highlighted by the author (adverse drug reaction) that causes discomfort in people and increases the already unsustainable costs of the health system, especially when such effects result in hospital admissions [8].

The purpose of this article is to revisit Ivan Illich's thinking and discuss the currentness of his complaints regarding the inconveniences arising from the use of drugs, especially in their impact on hospitalization, and also reflect on the potential of pharmacogenetics to mitigate adverse events related to drugs that victimize people.

In the text that follows, it begins with a brief presentation of Illich's story. Thereafter, a digression is made on the association between the concepts of medicalization and iatrogenesis, to then make quick considerations about social iatrogenesis, considering the effects of this phenomenon on society. After presenting the consequences of iatrogenesis as proposed by Illich, from a fluent literature review, an update of the findings is made, providing evidence that the problem shows to be current and relevant nowadays. A quick conceptual presentation of pharmacogenetics is followed by examples of its clinical consequences in specific pharmacological groups.

2. About Ivan Illich and medicalization

Born in Austria in 1926, Ivan Illich is the owner of an extraordinary life trajectory. He resided in Florence, Italy, where he studied Natural Sciences with a specialization in inorganic chemistry and crystallography. In Rome, he graduated in Philosophy and Theology, and was ordained a priest. Subsequently, he completed a doctoral degree in Medieval History at the University of Salzburg [9], Austria, and

a post-doctoral degree at the Princeton University, USA. At the Vatican, he would be used in diplomatic functions, but in 1951 he preferred to be a parish priest in New York, USA. The parish served the Puerto Rican community, which led him to occupy, in 1956, the vice-rectory at the Catholic University of Puerto Rico [10]. He traveled alone through South America and in 1961 created, in Cuernavaca, in Mexico, a center for studies and preparation of missionaries for Latin America. Finally, in Bremen, Germany, he was a visiting professor - as, indeed, at several world-renowned universities - and died on December 2, 2002 [11]. Due to the plurality of themes that he studied, explained in greater detail and which he published on, he was considered a polymath - "an individual who knows a lot, who studies or who knows many sciences", in addition to polyglot, having mastered 10 different languages [9].

He was a controversial and polemical critic of the most diverse topics, such as education, transportation and health [12]. Due to disagreements with the Catholic Church, which also did not skimp on its critical approaches, he ended up leaving the priesthood in 1969 [11]. Most importantly, he wrote books and defended innovative and radical ideas in the field of education. In the health area, he used his restless and brilliant mind for a remarkable reflection, materialized in the publication, in 1974, of the work '*Medical Nemesis*' also known, in a 1975 reissue, as '*Limits to Medicine*', [1], where makes a forceful criticism, revealing original points of view at the time, to the phenomenon of "medicalization" that was beginning to become evident and that he qualified as "pernicious medicalization of health".

3. From medicalization to Iatrogenesis

The term "medicalization" (which has not yet been included in the main Brazilian dictionaries) can be considered a polysemic word, if not with different meanings, but certainly with different connotations. Some authors even associate the term with a positive attribute, as in the case of AIDS, when the entire health production chain mobilized, in an unusual way until then, to understand the etiology of the disease, learn to diagnose and develop treatments, first to avoid deaths and then to prolong life and to provide greater well-being to people affected by the referred disease [13].

In his approach, Illich made no concessions to the eventual positive aspect of what he called the "medicalization of life", which he called as unhealthy for producing a "morbid society".

Continuing in his critique on "medicalization", he found that epidemiologists were unable to prove, for example, that early intervention altered the survival rate of patients affected by breast cancer. Likewise, he questioned the treatments for lung cancer, whose medical interventions brought more expenses and more suffering, without changing the survival rate - constantly mentioning the studies and articles that supported his conclusions [1].

It was also worth using drug treatments as an example, stating that the evaluation of the advantages (benefits) and disadvantages (undesired effects) caused by the drugs could be null or even negative, an aspect that even today seems to remain unnoticed, if not neglected.

This preamble on "medicalization" was used by Illich in his book to make way towards the concept of iatrogenesis, formed by the Greek words iatros (doctor) and genesis (origin). He thus defined iatrogenic disease as one that characterizes all the clinical conditions of which physicians, drugs, laboratories or hospitals - any medical apparatus, anyways, are pathogenic agents.

4. Social Iatrogenesis

In the chapter he called Social Iatrogenesis, Illich dealt with issues that are still disturbing today and that are frequently addressed in the field of public health.

He affirmed, for example, that "the level of health did not improve even when medical expenses increased", and was supported by studies that showed that although the USA allocated a considerable percentage of its GDP in the health system (7.4%, in 1974), they were not able to obtain good indicators, because the life expectancy of adult men paradoxically declined in that country [1].

The percentage of GDP invested in health by the United States in health reached an incredible 17.1% in 2013 [14]. Although health expenditures in that country lead the world statistics by far, however, Americans, as Illich emphasized, are not able to obtain a counterpart in health indicators, as for example, the life expectancy at birth (79 years) where they appear in the 34th position [14].

It is worth mentioning, based on this evident American paradox,, a vernacular created by Illich, "counterproductivity" [15], which he defined as "the paradoxical effect of overproduction and overconsumption", to verify and exemplify that the global volume of vehicles, designed to allow greater speed in travel, ends up stopping circulation on the roads public; the global volume of education prevents children from expanding their curiosity, intellectual courage and sensitivity; and that the global volume of "medicalization" reduces the level of health (ILLICH, 1975, p. 70).

No less interesting, still to characterize the "medicalization" of society, it was the record that the author already made at that time about the wonder that technology caused in people, impelling them to believe that health increased as they had access to prostheses, drugs, hospitalizations and examinations for preventive controls.

A similar finding was recorded, more than twenty years later, by the American cardiologist Bernard Lown, who was discouraged after investing a lot of time in the collection of a detailed medical history, which gave him exactly the diagnosis, to see that the patient appears to be incredulous. But when he took him to an examination room, where he had an old-fashioned fluoroscope with an image intensifier, with an instrument panel similar to that of an airplane, he saw the patient impressed and saying with his buttons: "Ah, how nice it is to be in such a well-equipped medical office." Dr. Lown concludes, without hiding the nonconformity, that "the puerile faith in the magic of technology is one of the reasons why the public has been tolerating the dehumanization of medicine" [16].

In a recent publication, Atul Gawande, when dealing with aging and end-of-life care, also identifies the fetish that technology awakens in people, who are not encouraged to seek advice from a geriatrician, but who await with unquestionable expectation the invention of a device that doctors implant in them, for example, in the chest, hoping to reduce discomfort and prevent them from ending up, dependent on care, in a nursing home [17].

In general, it is common for people not to feel treated if the doctor does not request for an examination or does not prescribe a drug. On the contrary, they value the use of technologies, preferably the most up-to-date and sophisticated ones, without awareness of the iatrogenesis that tests and medications so often provoke.

"Medicalization" also reveals itself as a true outsourcing of care for one's own health, when people renounce the possibility of taking preventive care, eliminating bad habits, to surrender to the medical arsenals, the side effects of medicines and imaging tests, in addition to choosing hospitals as a safe place to obtain health, forgetting the risk of exposure to nosocomial infection, iatrogenesis of the most harmful.

Illich was radical and rebellious in renouncing "medicalization", so coherent and determined in his conviction, that he suffered for ten years from a brain tumor, the cause of his death, giving up the therapies available at the time, using only opiates to relieve the pain and accepting to live with a huge bulge on his right face that even startled his interlocutors [18].

5. Drug iatrogenesis and its consequences

Iatrogenesis caused by drugs is usually studied based on factors related to the prescription: whether it is foreign to the therapeutic relationship; if it is at odds with the clinical diagnosis; whether the doses or duration of treatment are inadequate; whether undesirable, harmful or unexpected effects occur; if there is morbidity or mortality and if interactions between drugs occur that are harmful to the patient [19]. In addition, iatrogenic episodes occur even when prescriptions follow clinical protocols and drug labels, for the simple reason that people do not react in the same way, even if they have the same diagnoses.

In addressing some causes of iatrogenesis caused by drugs, Illich highlighted some factors not directly linked to the doctor-patient relationship as described above, but to other external aspects, such as the role of the pharmaceutical industry, whether in spending on advertising and commercial promotion with doctors, but mainly in stimulating the overconsumption of medicines, which increases the potential for damage related to the intake of medicines.

These aspects are still a current phenomenon and have been echoed by several authors, who denounce even the manipulation of academic studies, the creation of diseases that no longer admit any healthy individual [20], treating as medical problems which are non-medical [13], inventing diseases to sell their drugs [21], even considering that "a healthy person is just an undiagnosed patient" [22].

The laboratories' obsession with increasing the consumption of medications seems to have no limit, as can be seen in the encouragement of prescription classified as off label, when manufacturers convince doctors to prescribe drugs for indications other than those approved regulatory agencies at the time of their registration. The pharmaceutical industry does this by preparing articles and paying researchers to put their names in these "studies", with the explicit aim of increasing sales, as Marcia Angell, a Harvard professor, reported in a hard-hitting publication [23].

In 'Medical Nemesis', Illich pointed out that 3 to 5% of all hospitalizations in the United States of America (USA) had as a main reason, bad drug reaction. And that, once hospitalized, 18 to 30% of patients experienced an adverse reaction caused by a drug substance, doubling the length of hospital stay (ILLICH, 1975, p. 25).

The consultation of more recent studies confirms the relevance of this relationship, as was verified in the assessment of patient admissions in the Department of Cardiology and Pulmonology, in a large hospital in the Netherlands [24]. The authors conclude, after evaluating 2,000 hospitalizations by pharmacists and epidemiologists, that 19% of hospital admissions were motivated by adverse drug reactions (using the World Health Organization definition for this type of occurrence) and this percentage may reach 29% if hospitalizations classified as possibly iatrogenic are also considered.

An observational study carried out at a University Hospital in Spain sought to estimate the prevalence of negative results associated with drugs as a cause of hospitalization, by means of a random choice carried out by lot, which resulted in the analysis of 163 patients [25]. In 16.6% of the studied cases (27 patients) admission

to the hospital was caused mainly by an adverse reaction due to use of the drug, of which 88.9% were considered preventable. The study concluded that hospitalizations motivated by an adverse reaction to medications had a high prevalence and most would be preventable through pharmacotherapeutic follow-up.

Another cross-sectional study, also conducted in Spain, evaluated patients who were hospitalized from the emergency services of a hospital. We sought to assess the negative results associated with the use of drugs that motivated hospitalization, to know the drugs that appeared more frequently and to assess the economic impact of these occurrences [26]. The conclusion was that 19.4% of hospitalizations occurred as a direct consequence of negative clinical results associated with the use of drugs, 65% of which were considered preventable. In addition, it was observed that the antineoplastic and immunosuppressive therapy groups motivated 38% of these adverse reactions. It was also found that 20.4% of the patients needed to be treated in an intensive care unit. Finally, it was found that the expense incurred was 237,377 euros (estimated annualized cost of 15,568,952 euros).

In the case of illnesses caused by Adverse Drug Events (ADE), in a meta-analysis 39 studies were selected (out of a total of 153) that evaluated the incidence of severe or even fatal ADE in American hospitals [27]. The conclusion was that the incidence of serious (6.7%) and fatal events (0.32%) was considered expressively high. Although the authors of the study noted the caveat that the results should be viewed with caution, because of the heterogeneity between the studies and possible bias in the samples, they warn that these data suggest that the adverse reaction to drugs represents an important health problem public in the United States of America (USA).

In a review article on adverse events (AE) in medical and hospital care, it was noted that ADEs are the most frequently identified, in addition to being also the most underreported [28]. In another evaluation carried out in a teaching hospital, which sought to estimate the frequency of this occurrence, it was observed that 14.6% of the 240 hospitalizations evaluated were motivated by ADE [29].

In England, a prospective observational study conducted in two large general hospitals sought to assess the cause of hospitalization in 18,820 patients hospitalized over a six-month period, seeking to identify which of these admissions were due to ADE, in addition to other aspects related to them. The prevalence obtained was 6.5% (1,225 cases), with 80% of this total directly related to an adverse drug reaction. The study concludes that this is an important problem considering morbidity, mortality and extra costs attributed to the studied events [30].

In Brazil, an original study focused on hospital admissions related to intoxication and adverse effects of drugs in children under one year of age. The retrospective analysis of the Authorizations for Hospital Admissions (AHA) of the Unified Health System (SUS), from 2003 to 2005, identified that a total of 1,063 children under one year of age were hospitalized as a direct or indirect consequence of drug-related intoxications or adverse effects [31].

Elderly patients are more susceptible to this type of occurrence due to the overuse and concomitant use of various drugs, administration errors and changes in the organism that interfere with pharmacodynamics and pharmacokinetics [32]. Although more vulnerable, the occurrence of iatrogenic disease in the elderly has not been studied in the dimension that the problem represents, since the population considered elderly is characterized by having multiple chronic diseases, is usually treated by many doctors and ends up being more subject to hospitalization and medical or surgical procedures [33].

Studies that analyze the relationship between pharmacotherapy and hospitalization of the elderly population also confirm that the occurrence rates are significantly high and are largely preventable [34]. Many of these hospital admissions for

elderly patients are attributed to known drugs and occur because of drug interactions, which can also be prevented [35].

In the analysis of emergency hospitalizations for ADE in older adults, it was also found that they resulted from commonly used drugs and relatively few occurred due to the use of drugs considered to be high risk or inappropriate, which allows us to infer that such occurrences would also be preventable [36].

There are numerous studies that list hospital admissions due ADE and invariably conclude that we are facing an important public health problem, which not only reduces the patient's quality of life but generates unnecessary expenses for hospitals [37] and, consequently, for the health system. Although the hospitalizations that are attributed to ADE vary in relation to the percentage, the findings are always significant when studying the causes of hospitalizations [38].

Adverse reactions to medications, even in cases of diagnosis, prescriptions and correct administration, can be explained by the trial-and-error methodology, which is still decisive in medical practice.

It should be emphasized that the search for the definition of the most appropriate drug and dosage makes use of experimenting with people's reactions, and while pursuing the patient's benefit, it often produces harmful effects. In the next topic, the potential contributions of knowledge of genomics to mitigate the harmful effects of iatrogenesis caused by drugs and their possible repercussions on people and health systems will be discussed.

6. Pharmacogenetics

The sequencing of the human genome has revolutionized biology in several fields of study. Until 2012, 67% of global investments in genome sequencing technologies were directed to pure research and 11% to field of health. The projection for 2017 pointed out that investments in health would channel 39% of resources, mainly due to the reduction in the cost of exams and the applicability in medical practice, diagnosis and treatment [7]. That is, the field of health is the one that increasingly uses the potential of next generation sequencing.

The influence of genetics on how people react differently to drugs has been observed for at least five decades. Recent knowledge brought by genomics has an invaluable support potential to medicine, for doctors, geneticists and for the pharmaceutical industry, in the use of personalized treatments [39].

In the case of drugs, therapeutic inefficacy or pharmacological toxicity has frequently been observed due to the presence of some metabolizing enzymes in drugs, in which drugs can interfere as inhibitors or inducers of these enzymes, an activity that varies between individuals and that can be determined by DNA analysis [40]. Genetic variability, therefore, can affect how a drug can be absorbed, activated, metabolized or excreted from the organism [41].

The reaction to the same drug varies from person to person depending on weight, age, gender, liver and kidney function, interactions between drugs, type of disease and genetic factors. The drug goes through two major processes in the organism, called pharmacokinetics and pharmacodynamics. Pharmacogenetics seeks to study how the drug passes through these processes, establishing the link between metabolism and individual differences in people's DNA [42].

This metabolization can occur in different ways. In addition to the normal metabolizers, which respond as expected to the dosage of the package insert leaflet, there are slow metabolizers, which, due to reduced enzyme activity, are at risk of accumulating toxic levels and are more exposed to adverse reactions. Ultra-rapid metabolizers tend to require higher doses and are subject to the inefficacy of

pharmacological therapy [41]. In addition, there is the intermediate metabolizer, which can benefit from the dose of the package insert leaflet but which can also be subject to the inefficacy of drug therapy.

The inclusion of genetic tests in the routine of medical practice is one of the main objectives of the *Clinical Pharmacogenetis Implementation Consortium (CPIC)*, a non-profit entity created to disseminate knowledge and issue guidelines on the use of genomic findings in drug prescriptions [43], which brings together the *PharmaGKB and Pharmacogenomics Research Network* [44].

CPIC defines the terms pharmacogenetics and pharmacogenomics, which are sometimes used interchangeably by some authors. Pharmacogenetics is the study of the genetic influence on the response to the drug, normally considering one or only a few genes involved. Pharmacogenomics is the study of the variation of how genomics influences the response to the drug, considering the sequencing of the entire human genome[1].

Pharmacogenetics emerged as a diagnostic tool that uses genetic information to guide pharmacotherapy decisions, improving the clinical outcome, giving rise to personalized clinical decisions [45].

These terms also differ according to their origin. Pharmacogenetic expression was coined by Friedrich Vogel in 1959 [46]. The word pharmacogenomics appears logically after the Human Genome Project.

Pharmacogenetics associates variability to drug response to hereditary aspects after the identification of some pharmacogenes [47]. Pharmacogenomics is one of the first clinical applications of the post-genomic era and expands this dimension to even point to the development of personalized drugs [48].

The following are some examples of the applicability of the use of pharmacogenetics in drug treatments widely used in psychiatry, cardiology and oncology.

7. Pharmacogenetics in psychiatry

The main causes of individual variability in response to the same dose of a drug are: age, biological factors, immunological factors, interactions between drugs and genetic factors [49]. Pharmacogenetics studies the role of genetics in variability of drug response.

This response can vary from potentially lethal adverse reactions to the equally serious lack of therapeutic efficacy.

Genetic variability plays an important role in pharmacokinetics (absorption, distribution, metabolism and excretion) and in pharmacodynamics, that is, in the interaction of the drug with the target and in the relationship between its concentration and its effect [50].

Currently, many studies are published that relate drugs to individuals' genetic variants. In psychiatry, in the case of initial treatment for depression, about 30 to 40% of patients do not respond adequately to the prescribed medication, and it can take up to six weeks to characterize that it is not effective [51], exposing the patient to a long period therapy based on trial and error, with a high chance of adverse reactions.

The use of knowledge of the presence of variants in the genes involved in the metabolism of antidepressants such as CYP2D6 can provide the physician with an important subsidy in the choice of medications and in the definition of the dosages used in the treatment of depression [52].

[1] PGKB – PharmGKB – The Pharmacogenomics Knowledgebase, available at https://www.pharmgkb.org/page/overview

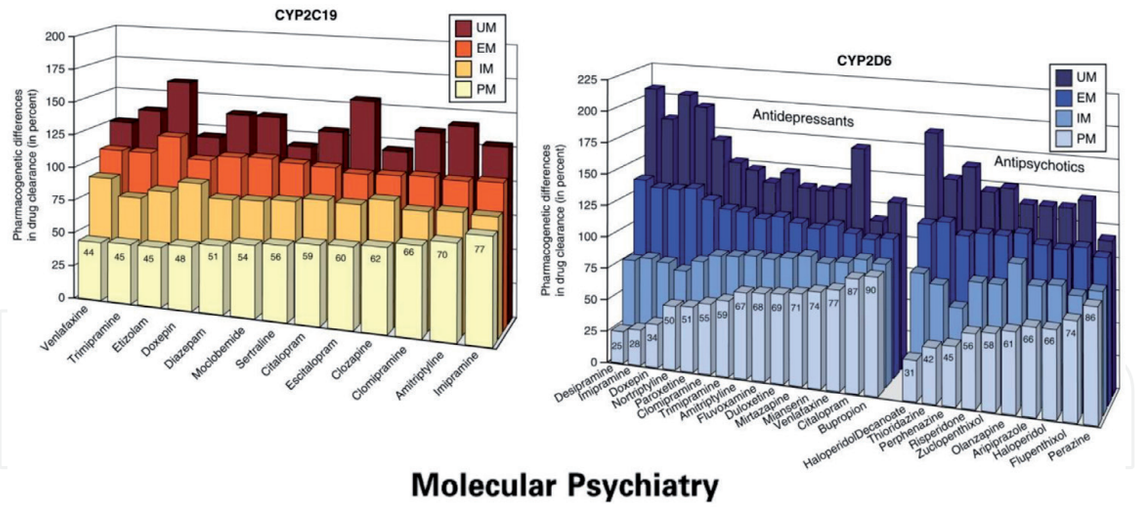

Figure 1.
Genetic variability of enzymes that metabolize drugs. Source: Molecular Psychiatry *(2013)* ***18****, 273–287; doi:10.1038/mp.2012.42.*

The genetic variability of the drug response, depending on the type of metabolizer, is very high, as shown in **Figure 1**, which shows the demonstration of the main marker genes (CYP2D6 and CYP2C19) for antidepressants and anxiolytics [53].

Considering the Extensive Metabolizer (MS) as one that obtains an adequate response with the dose of the package insert, the window of variability is very large in relation to the Ultra-Rapid Metabolizer (UM) and the Poor Metabolizer (PM), especially, as shown in **Figure 1** in the cases of the psychotherapeutic drugs, Escitalopram and Desipramine.

8. Pharmacogenetics in cardiology

Several important drugs used in the treatment of heart disease are already the subject of studies on pharmacogenetics, especially in anticoagulants, antihypertensive agents, antiarrhythmics and statins.

Warfarin is the most commonly used oral anticoagulant in the world and aims to prevent thromboembolism. Warfarin therapy is often associated with a high risk of increased bleeding, especially during the initial phase of treatment. The CYP2C9 gene is responsible for the metabolic degradation of the activity of this drug and the VKORC1 gene is responsible for the activation of vitamin K-dependent coagulation factors. When inhibiting VKORC1, Warfarin produces the anticoagulant effect [54].

Although the consequences of undue dosages are always serious, the dose of Warfarin is usually adjusted by the trial-and-error method, or by considering other clinical parameters obtained in conventional laboratory tests. The optimal dose of warfarin varies greatly between patients. If the dose is too strong, the risk of serious bleedings increases, and if it is too weak, the risk of stroke increases. It is estimated that two million Americans start treatment with warfarin annually [55].

A study that sought to describe the frequency and characteristics of ADEs, which led people to seek emergency care in the USA, concluded, among other findings, that the second drug that motivated the occurrence was warfarin, just behind the insulins [56].

Another study that evaluated the bleeding complications caused by the use of anticoagulants concluded that the drug has been used in an increasing proportion and that bleeding has been a predominant reaction, in addition to being an important cause of mortality [57].

From what we tried to describe, there is no doubt that we are dealing with a class of drugs (anticoagulants) of special relevance, which deserves all possible care in the prescription process, mainly due to the high potential for harm to patients and the cost it entails for the health system, as ADE almost always require hospital admissions.

In another case–control study in the USA, we sought to assess whether the genotyping test for patients starting warfarin treatment could reduce the incidence of hospitalizations due to bleeding or thromboembolism. Compared with the control group over a six-month period, one of the main conclusions was that genotyped patients had a 43% lower risk of hospitalization for bleeding or thromboembolism. The authors conclude that genotyping for the anticoagulant reduces the risk of hospitalization for hemorrhage or thromboembolism in patients who start outpatient treatment with warfarin, with great statistical and clinical significance. They further defend that doctors should seriously consider the use of pharmacogenetic tests for patients who are starting treatment with the referred drug [58].

It should also be noted that oral anticoagulants are among the most sensitive to drug interactions, especially when taken simultaneously with antidepressants [59]. In these cases, the influence of metabolization between drugs must be observed by clinicians and pharmacists, without obviously disregarding the adverse events arising from these interactions.

More recent studies seek to evaluate new algorithms that increase assertiveness in warfarin prescription. Such algorithms associate genetic variables with age, gender, body mass, vitamin K levels and thyroid function. At the current stage, studies should also be developed that also consider geographic areas and ethnic groups, in order to guarantee greater therapeutic efficacy, mitigate adverse reactions to the drug and reduce hospitalizations motivated by it [60].

In the case of statins, used in the control of cholesterol and in the prevention of cardiovascular diseases. Its use is widespread today, but the prescriptions ignore the effects of the presence of polymorphisms in the SLCO1B1 gene, in charge of synthesizing a family of proteins inside the cells for their metabolism and therapeutic action.

Several studies have been and are being carried out to verify how patients metabolize the different types of statins, some more or less indicated according to the phenotype of each individual, in order to avoid the side effects that in the case of statins are manifested mainly in myopathies that can worsen patients' living conditions.

Currently, at least 7 types of statins can be prescribed: atorvastatin, fluvastatin, lovastatin, pravastatin, pitavastatin, rosuvastatin and simvastatin. Although these different types share the same mechanism of action, they have differences in their chemical structures and pharmacokinetic profiles. Chemical structures end their solubility in water and influence the way they are absorbed, distributed, metabolized and excreted [61]. The patient can metabolize each of these different types of statins differently, an aspect that can be revealed by the pharmacogenetic test.

As an area responsible for the main cause of death in the world, drug therapy for Cardiovascular Diseases is the focus of attention in pharmacogenetic studies also for other drugs related to it. In addition to those already mentioned, there are plenty of studies relating genetic variants to the way we process antiplatelet drugs such as Clopidogrel, aspirins and antihypertensive drug [62].

9. Pharmacogenetics in oncology

Minimizing toxicity while maximizing efficacy is a common goal for the treatment of any condition, but its importance is even more evident in the case

of oncology, due to the severe nature of the disorders and the aggressive toxicity caused by chemotherapeutic agents, in addition to the risk of relapse cancer or disease progression. The challenge of achieving an optimal therapeutic index is especially relevant for the elderly population, due to age-related changes in metabolism and the interaction with concomitant medications [63].

Over the past decade, advances in pharmacogenetics and pharmacogenomics have revealed the relationship between genetic variables and individual differences in drug responses. A large part of these advances has been made in the field of antineoplastic therapy.

Periodically, the American agency U. S. Food and Drug Administration (FDA) updates drug labels and edits table with related pharmacogenomic biomarkers. In 2016, 166 drugs (55 of them for cancer treatments) made up the table in which the FDA defines it as mandatory or in which it at least recommends the pharmacogenetic test, before the first prescription [64]. The variable reaction to drugs in the forms of unresponsiveness and adverse effect, and the motivation to use them better are the basis for one of the main objectives of the so-called personalized medicine, more recently disseminated as precision medicine.

10. Final considerations

Currently, iatrogenesis classified as adverse events, including those caused by drugs, are still an important public health problem, as has been demonstrated.

In response to the effects of these events, which are almost always harmful to people and those who offend the cost of assistance, pharmacogenetics, which emerged to improve the assertiveness of treatments to the point of being able to personalize them, may also contribute to minimize iatrogenesis, including the most serious ones requiring hospital admissions.

Although this goal is promising, there are still many challenges in implementing pharmacogenetic tests in clinical practice. First, concomitant factors such as diet, age and drug interactions affect pharmacokinetics and pharmacodynamics, increasing the complexity of assessing biomarkers in each patient. Second, the nature of the heterogeneity of clinical conditions presents a considerable therapeutic challenge. For example, in the case of cancer, treatment choices based on a biomarker present in a single biopsy sample may not be sufficient. Third, the definition of gene panels for each case is another area that needs to be developed, in order to facilitate the interpretation of clinicians [65].

The adoption of pharmacogenetic tests in routine clinical practice has been very scarce, particularly in Brazil. The main barriers to its implementation in the medical clinic are the lack of doctors' knowledge about the applicability in prescriptions, in addition to the provision of clear and accessible recommendations, based on proven evidence, as CPIC has been trying to do [66].

It is noteworthy that another difficulty of great relevance has been the lack of studies that demonstrate the positive cost-effectiveness of its application [67].

However, the continuous fall in the costs of sequencing allows us to project a not-too-distant future in which the realization of the exome (mapping the approximately 20,500 genes currently known), in early life, will allow a continuous revisit to the genetic results, which will be available and applicable in medical clinic for life [43], including the specificity of drug reaction.

The use of the findings of pharmacogenetics may not be a redeeming strategy in the solution of all drug iatrogeneses, reported more than forty years ago by Ivan Illich, because other factors, as mentioned here, interfere in the metabolism of drugs. But their adoption may significantly mitigate the deaths and suffering caused

by them, in addition to replacing the practice of trial and error in prescriptions and dosimetry - a notable imperfection in medical practice and the health system.

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