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What's the importance of portable tele-monitoring devices in patient therapeutic adherence?

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Dissertação para obtenção do Grau de Mestre em
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Dedicatória

Quero dedicar esta tese aos meus pais, Orlando e Fernanda, que sempre estiveram presentes durante o meu desenvolvimento, me proporcionaram uma excelente educação, me amaram incondicionalmente e tentaram estar sempre disponíveis para mim.

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Abstract

In the United Kingdom, it's estimated that the National Health System spends every year almost $121 million in unused drugs. The hospital admission costs attributed to patients not taking their prescribed medicine properly was estimated to be between $44m and $240m per year. In the United States of America, medication non-adherence is estimated in $100 to $300 billions of avoidable healthcare costs annually, representing 3–10% of total United States healthcare costs.

Studies show that improving medication adherence may have a greater influence on the health of the population than the discovery of any new therapy. Effective medicines are available for many conditions. Yet patients are non-adherent 50% of the time, reaching its critical point in certain disease states, such as asymptomatic conditions like hypertension, in which the incidence may approach 80%. Each disease has its special challenges. To answer the non-adherence problem, we must understand that people under certain disease states, are not aware of the danger when they unconsciously neglect the treatment and stop taking the prescribed medication. With the technological boom over the recent years, we were flooded with gadgets and devices that allow us to do practically everything in our everyday life, and the rise of tele-monitoring devices is going to be a reality, not only to monitor bio-signals but to help us with medication compliance. The objective of this dissertation is to gather information to establish what are the main strengths of nowadays technology to assemble the best integrated monitoring and control device, for therapeutic adherence.

Our proposal is to create a therapeutic adherence monitoring device that consists in a smart blister coupled to a device which has the capacity to collect (from other medical devices) and send data (medicine taking time, blood pressure and oximetry) to a cloud every day. This allows the clinician to know, with high certain, if the patient is taking his medicine exactly how it has prescribed as well as the schedule of the same.

Concluding, therapeutic non-adherence is a public health problem that leads to high economical and health losses. Nevertheless, we find that the technological devices fit within the lifestyle of the average person and present themselves as a solution.

Keywords

Non-adherence; Portable Devices; Compliance; Internet of Things; Tele-monitoring; Patient Friendly.

Índice

Lista de Figuras

Lista de Tabelas

Lista de Acrónimos

AP – Arterial Pressure

BD – Bipolar Disorder

COPD – Chronic Obstructive Pulmonary Disease

DALY's – Disability-Adjusted Life Years

EMBLEM – European Mania in Bipolar Longitudinal Evaluation of Medication

EMP – Electronic Monitoring Packaging

ER – Emergency Room

GDP – Gross Domestic Product

IoT's – Internet of Thing's

LDL – Low Density Lipoprotein

MCA - Multi-Compartment Compliance Aids

MPR – Medication Possession Ratio

NHS – National Health System

NIHCM – National Institute for Health Care Management

OptumHealth HRA – OptumHealth Health Reimbursement Accounts

PDC – Proportion of Days Cover

QALY's – Quality-Adjusted Life Years

SMS – Short Message Service

SOHO – Schizophrenia Health Outcomes

WHO – World Health Organization

1. Introduction

According to the World Health Organization (WHO) it has been calculated that, in 2001, chronic diseases contributed approximately 60% of the 56.5 million total reported deaths in the world and approximately 46% of the global burden of disease. In 2020, it is expected to increase to 57%[1], and contrarily to what may be predicted it will affect not only the developed countries but also the developing countries (Fig. 1).

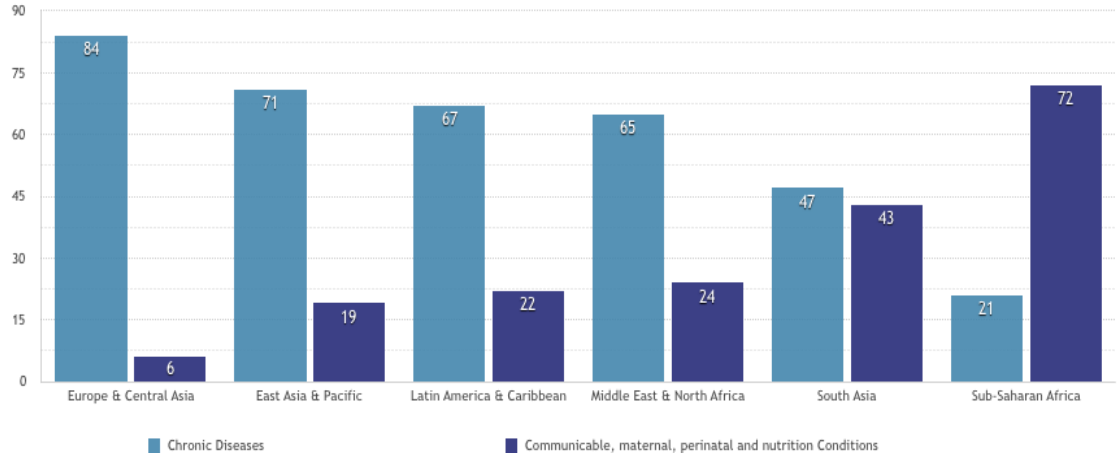


Figure 1 – Worldwide share of deaths, by cause [2].

Nowadays, 117 million Americans live with at least one or more chronic diseases, often requiring multiple lifelong medications for control. In Portugal, 5.4 million people live with one or more chronic conditions. Additionally, Portuguese women with more than 65 years only have plus 6.6 years of a healthy life. On the other hand, Norwegian women have, on average, plus 15.4 years (Fig. 2) of healthy life. Other countries share the Portuguese trend, and the increased incidence of long-term chronic diseases must be a wake-up call to health services worldwide [3]. Improving medication adherence may have greater influence on the health of the population than the discovery of any new therapy. Effective medicines are available for many conditions and yet patients are non-adherent to their medicine 50% of the time [4]. Notwithstanding, some studies reported different ranges of adherence for adult patients (40–60%) and children (25–75%), showing that only 50% of people take their medicines adequately [5]. A critical point is reached in certain disease states, such as asymptomatic conditions like hypertension, in which the incidence may approach 80% [4].

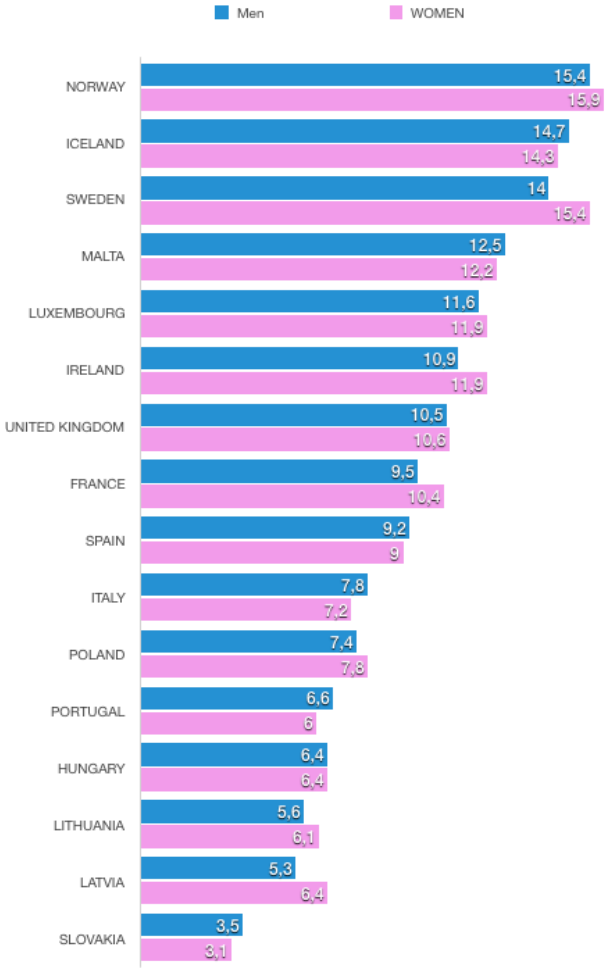


Figure 2 – Years of healthy life after the 65 years in Europe [3].

In the UK, it is estimated that the National Health System (NHS) spends every year almost £9 billion on medicines, issuing 927 million prescriptions. It is predicted a return greater than £100 million in unused drugs, which are then destroyed. The hospital admission costs attributed to patients not taking their prescribed medicine properly was determined to be between £36 million and £197 million per year [5].

In the United States of America (USA), medication non-adherence is predicted to incur in $100 to $300 billion of avoidable healthcare costs annually, representing 3–10% of total USA healthcare costs. It has been estimated that health-related productivity loss costs are 2.3 times higher than the direct healthcare costs. Annually, medication adherence in patients with one or more chronic vascular condition resulted in a reduction of the average medical spending by $8,881 in congestive heart failure, $4,337 in hypertension and $4,413 in diabetes. Improved adherence to diabetes medication could avert 699,000 emergency department visits and 341,000 hospitalizations annually, accounting a saving of $4.7 billion [4].

At this point, it is important to understand why is adherence a problem and what can health professionals do to raise awareness and control what really happens outside the clinic walls.

Patient adherence to prescribed medication regimens is a complex and multidimensional behaviour, and to figure out what is really happening, it is important to dissect the problem and intervene on the modifiable factors. To reach this objective we must pursue the reasons for non-adherence, paying attention to the intentional and non-intentional non-adherence. Therefore, there are those that classified this subject into patient factors (Table 1), medication factors (Table 2), health care provider factors (Table 3), health care system factors (Table 4), and socioeconomic factors (Table 5) as per recommendation from Miller et al and WHO [6].

Table 1 – Patient factors affecting medication adherence [6].

Factors	
Mental state	Behaviour/Attitudes/Habits
Depression	Non-adherence to follow ups
Lower Cognitive Function	Personality: Neuroticism
Memory	Use of complementary and alternative medicines
Executive Function	Concurrent use of OTC
Anxiety	Problem Drinking
Sleep Disturbances	Lower Self-Care
	Resisting Care
Physical Health	Lack of Interpersonal Relationships
Poor Dexterity	
BMI ≥ 25kg/m^2	Knowledge/Beliefs
Physical Function	Beliefs about medication
Impaired Hearing	Lack of perceived benefit of medications
Lower Self-Rated Health	Lack of medication knowledge
	Lack of knowledge about condition
Demographics	Health literacy
Old Age	Misunderstanding of verbal instructions
Male Gender	Lack if threatening view of illness
Low Education Level	Higher perceived illness burden
Married	
Language	Others
Culture	Living in own home
Ethnicity	Hospitalization in the past 6 months
	Chronic obstructive pulmonary disorder
Past Medical History	
History of Dizziness	

Table 2 – Medication factors affection medication adherence [6].

Factors
Drug
Formulation
Packaging
Drug storage issues
Drug handling
Lack of use of medication boxes
Necessity to cut tablets
Difficulty open containers
Drug regimen
Polypharmacy
Medication regimen changes
Complex dosing regimen
Others
Cost and lack of insurance coverage
Adverse drug reactions
Drug-drug interactions
Poor labelling instructions
Short-term medications
Lack of immediate consequences of missed doses

Table 3 – Health care providers' factors affecting medication adherence [6].

Factors
Poor communication
Lack of patient involvement
Lack of confidence in health care providers
Prescription by non-specialists
Lack of trust
Lack of review of medications
Dissatisfaction with doctor visits

Table 4 – Health care system factors affecting medication adherence [6].

Factors
Lack of patient education
Lack of follow-up
Lack of medication schedule
Shorter duration of prescription
Lack of community nursing services to pack the medications

Table 5 – Socioeconomic factors affecting medication adherence [6].

Factors
Lack of caregiver
Large caregiver burden

With the technological boom over the recent years, we were flooded with gadgets and devices that allow us that allow us to do practically everything in our everyday life, and the technological evolution is at a pace faster than ever. The rise of tele-monitoring devices is going to be a reality, not only to monitor bio-signals but to help us with medication compliance. In this matter some of them proved that the difference could be made resorting to this kind of technological approaches. WHO (2015) refers that the use of smartphones and SMS services are really a thing to consider not only because of its usability but because it really has proven to increase adherence in their cases-study.

At this point, it is important to know "the state of the art" of devices that were made only to help patients take their medicine, with special importance to the portable ones that do not imply the problem of these systems mobility. This is a topic with some published articles, but a field with a lot to be done since the systematic reviews of those studies always reveal the lack of participants and the small samples make the conclusions not as valid as the scientific world requires. Another aspect to account is the lack of usage of these technologies in the current clinical practice, since nowadays the main market for these devices are the medication clinical trials.

Thus, this dissertation reveals what has been done so far, the technological advances and what technology can offer, trying to understand and resume the strengths and weaknesses of the medication monitoring devices, to reach a proposal of the ultimate device and its importance in the future of clinical practice.

2. Methodology

We conducted an electronic literature search through PubMed (which includes information from MEDLINE, scientific journals on health and online books) and the The Cochrane Database of Systematic Reviews in order to find articles that relate the themes: Compliance/non-adherence; Medication Monitoring Devices; Tele-monitoring; Health Economics' and IoT enabled devices.

The key terms used were compliance, health economics, medication monitoring devices and filters were introduced that restricted the results to publications written in English, Portuguese and Spanish and those made in humans.

We supplemented the consultation performed in PubMed and Cochrane Database through a manual and internet based search, in the list of references of previously selected articles.

We developed the bibliographic review between 1992 and 2017, because the heterogeneity and value of the information.

PubMed results identified 8800 publications between all of the key terms used. Of the 8800 articles, we selected 70 that appeared relevant after consulting the summaries.

Of the 70 articles, we excluded 42 because of lack of relevant data.

Cochrane results identified 7004 publications among all of the key terms used. Of the 7004 articles, only 15 were selected, since most were already filtered in PubMed, and from those 15, 8 were excluded because of the relevance and heterogeneity of the methods.

Based on these selection criteria we selected 37 studies/important references.

Due to the heterogeneity of the articles, namely the different characteristics of the populations under study, as well as the objectives and methodology used, we did not carry out a formal meta-analysis.

3. Objective & Contextualization

The objective of this study, besides researching the information about medication intake monitoring devices and their potential usability in clinical practice, is to gather information in order to establish what are the main components for the best device, and its potential to be a game-changer to the non-adherence problem.

3.1. Why is therapeutic non-adherence a problem?

Potential health losses must be accounted in the current society, and the therapeutic non-adherence becomes a problem when the only way to prevent certain disease states is by tracking the prescribed medicine. Sometimes, the awareness and motivation of the patients for certain health problems, such as hypertension and high LDL cholesterol (dyslipidaemia), result in a sloppy and inadequate medicine intake, or in the worst scenario in complete neglect of the prescribed pill ingestion, without realizing the danger it may represent in a near future.

In the case of arterial hypertension, there are several studies and meta-analysis supporting the benefits of controlling the arterial pressure (AP) with a wide range of therapeutic "weapons". The main conclusion is that antihypertensive therapy is the most effective primary prevention strategy used against stroke [(7)]. A population-based study concluded that non-adherence to antihypertensive medication was associated with a 5.7-fold increased odd of fatal stroke during the year of death and a two-fold increased risk of non-fatal stroke (Table 6) [(8)]. In this matter, we cannot disregard the fact that stroke, only one of hypertension related complications, causes 11% of all deaths worldwide and is the second commonest cause of death after ischemic heart disease [(9)]. Additionally, in 2010, stroke-related disability was the third commonest cause of reduced disability-adjusted life-years [(10)].

As far as dyslipidaemia is concerned, many patients discontinue their medications because they perceive that non-specific complaints are drug related and then decide to terminate treatment on their own initiative without the input of healthcare professionals, as usual in this silent disease states. A review in statin non-adherence concluded that, non-adherence to evidence-based secondary preventive LDL cholesterol-lowering statin therapies increases the risk for recurrent cardiovascular and non-cardiovascular events, and all-cause mortality [(11)].

Another insidious and silent disease is osteoporosis, characterized by low bone mass and progressive microarchitectural deterioration of bone tissue. Bisphosphonates are considered the first line treatment for osteoporosis, mainly for post-menopausal women (most affected group) but also for men, patients receiving glucocorticoids, and in children with osteogenesis imperfecta. According to a meta-analysis of six studies, the risk for osteoporotic fractures was significantly lower in adherent patients, reaching 28% lower risk

for hip fractures. In an additional review of 17 cohort studies, it was found that osteoporotic patients with good adherence to bisphosphonates (Medication Possession Ratio > 90%) had odds ratio of 0.7 (95% Confidence Interval: 0.5-0.9) for fracture compared to non-adherent patients. The negative association between adherence and bisphosphonates has been corroborated by several analyses of large databases [12]. Despite being a well-known condition, adherence with bisphosphonates remains a serious clinical challenge in terms of public health. According to a Markov model simulation using published risk estimates, improving persistence with bisphosphonate treatment just by 20% could have the same impact as a 20.2% increase in clinical efficacy [13].

Table 6 – Annual relative risk ratios for non-fatal and fatal stoke according to the three-level definition of adherence prior to the first presentation of stroke of the end of follow-up [8].

Years [a]	Adherence [b]	Non-fatal stroke Relative risk ratio (95% CI)	Fatal stroke Relative risk ratio (95% CI)
-9	High	1.00	1.00
	Intermediate	1.98 (1.64 - 2.39)	2.78 (2.04 - 3.79)
	Poor	3.32 (2.59 - 4.25)	3.97 (2.60 - 6.05)
-8	High	1.00	1.00
	Intermediate	1.96 (1.64 - 2.34)	2.02 (1.47 - 2.79)
	Poor	3.07 (2.46 - 3.83)	2.94 (1.94 - 4.48)
-7	High	1.00	1.00
	Intermediate	1.96 (1.66 – 2.31)	2.68 (2.05 – 3.51)
	Poor	3.90 (3.19 – 4.76)	2.45 (1.55 – 3.87)
-6	High	1.00	1.00
	Intermediate	2.23 (1.92 – 2.55)	2.11 (1.58 – 2.82)
	Poor	4.14 (3.40 – 5.04)	4.13 (2.92 – 5.84)
-5	High	1.00	1.00
	Intermediate	2.21 (1.92 – 2.55)	3.75 (2.98 – 4.71)
	Poor	3.03 (2.49 – 3.69)	5.87 (4.34 – 7.96)
-4	High	1.00	1.00
	Intermediate	2.15 (1.88 – 2.47)	3.10 (2.46 – 4.91)
	Poor	3.57 (2.97 – 4.30)	6.21 (4.64 – 8.30)
-3	High	1.00	1.00
	Intermediate	2.21 (1.95 – 2.51)	2.75 (2.19 – 3.46)
	Poor	3.93 (3.29 – 4.68)	4.60 (3.32 – 6.37)
-2	High	1.00	1.00
	Intermediate	2.03 (1.80 – 2.30)	3.25 (2.63 – 4.02)
	Poor	3.89 (3.31 – 4.56)	7.53 (5.82 - 9.74)
-1	High	1.00	1.00
	Intermediate	2.55 (2.27 – 2.85)	3.39 (2.78 – 4.14)
	Poor	3.30 (2.81 – 3.88)	5.82 (4.56 – 7.45)
0	High	1.00	1.00
	Intermediate	1.72 (1.52 – 1.95)	3.60 (2.95 – 4.39)
	Poor	2.64 (2.21 – 3.15)	7.99 (6.28 – 10.18)

a – Years prior to the first presentation of stroke or the end of the follow-up
b – High adherence >80%; Intermediate adherence 30-80%; Poor adherence <30%

Changing the topic to psychiatric diseases, the pattern remains the same. In Bipolar Disorder (BD), the results of the European Mania in Bipolar Longitudinal Evaluation of Medication (EMBLEM) study, concluded that one in four bipolar patients were non-adherent to BD medication during the 21-month maintenance treatment after an acute manic/mixed episode. The results also confirmed that in these patients' non-adherent with BD medication was associated with poorer long-term clinical outcomes as well as increased costs of treatment. Non-adherent patients were less likely to achieve remission and recovery, while they were more likely to experience relapse, recurrence and hospitalization as well as attempt suicide during the 21-month follow-up. These findings were consistent with previous studies showing that non-adherence is a major contributor to relapse and hospitalization as well as suicide attempts or actual suicide [(14)].

In Schizophrenia, depending on the clinical setting, definition and assessment of adherence, duration of study, and characteristics of the study population, the prevalence of non-adherence is high and has been reported to range from 20% to 56% [(15)]. A study that used data from the Schizophrenia Health Outcomes (SOHO) concluded that non-adherence with antipsychotic medication in schizophrenia is common in the outpatient practice setting and influences long-term outcomes, while being associated with an increased risk of relapse, hospitalization and suicide [(16)].

By now, only pathologies that result in a chronic condition have been exposed, but if a look to more acute conditions is taken, many problems related to the pill ingestion can be identified.

In the case of bacterial infection, as we live in the antibiotic era, it is easy to assume that these drugs are permanently available in the arsenal of medicines. Unfortunately, the use or rather the misuse of antibiotics has been accompanied by the rapid emergence of antibiotic resistance [(17)]. Long or improper treatment regimens may also in some cases exert unnecessary evolutionary pressure on bacteria [(18)]. The problem begins with the lack of public knowledge about antibiotics, which led to their overuse. In a European survey performed in 2009, of those who had taken antibiotics within the last year, 20% claimed to have taken them for influenza, a viral malady, and only 36% of those surveyed answered correctly that antibiotics do not kill viruses [(19)]. In this example, the problematic of non-adherence is not approached, but rather the need for monitoring and control this kind of medicine. Motivated by this problem Laupland, *et al.* (2016) questioned: "*Will all bacteria be multidrug resistant in 2035?*", and reached the conclusion that may be the reality. However, they assume that there will be means to fight back these infections, and that is our choice to wait until resistance will reach an ultimate point where the economic, medical, and social environment will have to change to continue to manage these important infections [(20)] (Fig. 3). Each disease has its special challenges, and to answer the question to this problematic we must understand that people under certain disease states, such as the ones mentioned before, are not aware of the danger they are facing when they unconsciously neglect the treatment and stop taking the prescribed medication. And this is just the tip of the iceberg, many other

conditions may be aggravated and even fatal without the correct intervention, and we must assume that non-adherence cuts across all medical specialties.

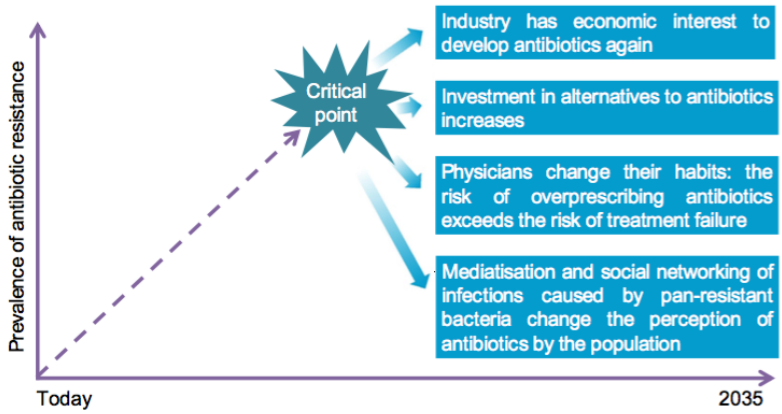


Figure 3 – Rise of antibiotic resistance up to a critical point where its perception by pharmaceutical industry, investigators, physicians, and population change [20].

3.2. Is it really important to take your medicines on the right time?

As widely known, therapeutic treatment plans are designed to ensure optimum therapeutic outcomes for targeted beneficiaries, reducing the risk of adverse events. Thus, if the patient optimally takes his medicine, the pharmacodynamic and pharmacokinetic properties of the medicines will be respected and the drug concentration-time courses in body fluids and in tissues will reach the greatest capacity without injury.

In the normal day scenario, is usual for the patient to take their medicines with some delay, in some cases within hours, without being aware of the consequences.

The concept of Chronotherapy refers to the use of circadian or other rhythmic cycles in the application of therapy and involves a huge broad of study fields, like pharmacology, biology and most medical specialties. This intuitive concept is founded but still isn't broadly applied in clinical practice [21].

With the genome project era, we are more aware than ever about the inter-individual variations and the impact that the individual metabolism has and how it interacts with the environment. Personalized medicine is rapidly becoming a reality. This innovative approach to disease prevention arises from the possibility of more precisely predicting a person's risk of disease onset based on each person's unique genetic makeup and clinical information [22].

Adding to this is the possibility of tailoring treatments based on the patient's unique genetic background, lifestyle factors, and environmental exposure—an area of study usually referred to as personalized therapy or, more recently, precision medicine [23].

There is a need to consider the many organizational levels, from molecular and cellular to tissue and organ, at which drugs can act when assessing their biochemical and physiological effects on the body. The notion of chronopharmacodynamics seems suited to weigh in on how circadian oscillation in a physiological system influences therapeutic outcome. Today, knowledge of the chronopharmacodynamic action of cardiovascular drugs, chemotherapeutic agents, analgesic and non-steroidal anti-inflammatory compounds, antidepressant drugs, anxiolytics, and antipsychotic compounds has conferred numerous benefits to patients with various clinical conditions (Fig. 4) [21].

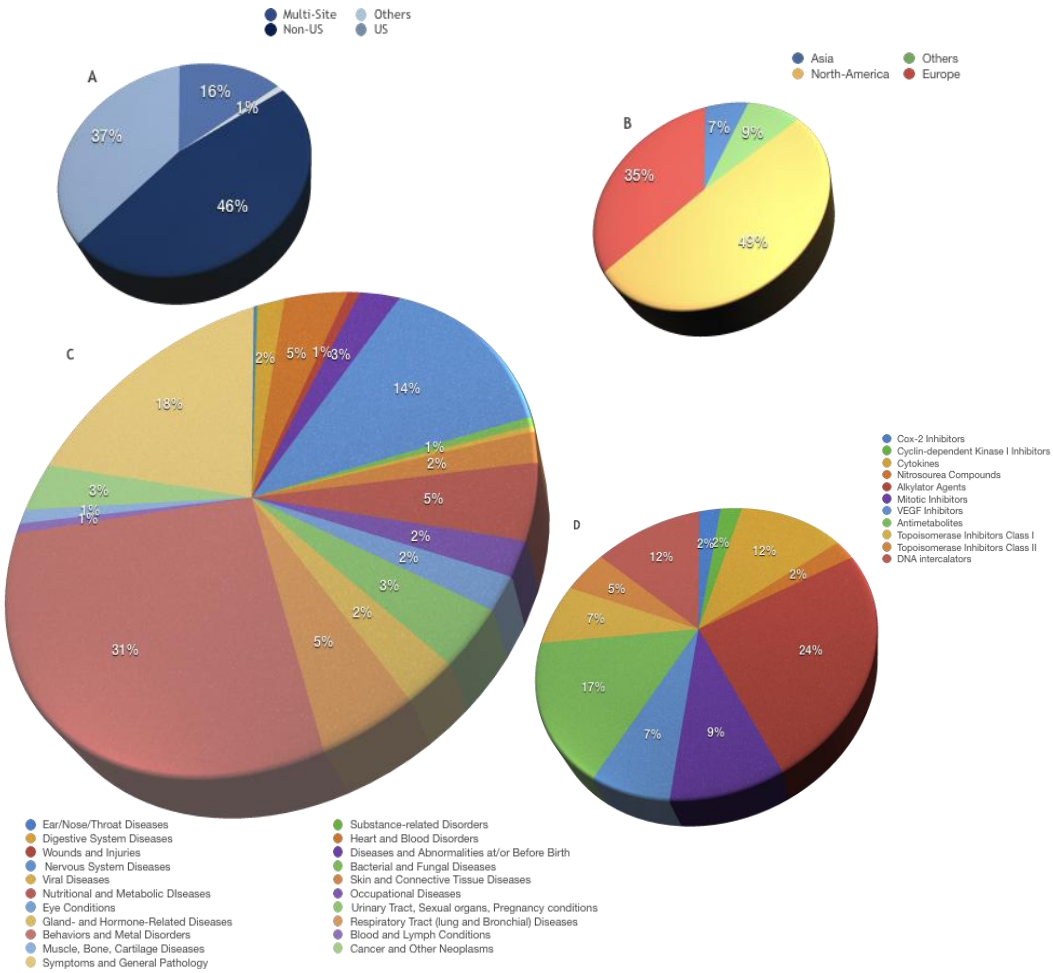


Figure 4 – The impact of chronotherapy in the clinical trial world [21].

A – Pie chart showing the distribution of currently listed clinical trials based on their geographic locations.
B – Pie chart illustrating clinical trials in which chronotherapy is considered part of the treatment by geographic locations.
C – Pie chart divided into sectors proportionate to the distribution of clinical trials involving a form of chronotherapy treatment categorized by disease condition
D – Pie chart showing the pharmacological categories of anticancer drugs whose pharmacokinetics, pharmacodynamics, tolerability and/or efficacy are influenced by circadian timing.
In all cases, categories are given as a percentage of the whole pie

This near future reality will present us the problem of managing information and the informatization of the health services will soon demand portable devices that interconnect the patients and the hospitals. The therapeutic treatment plans will become more patient friendly resorting to technology, and the possibility of exchanging information between the patient and the hospital may approach the patient to the health care providers making them feel more secure and comfortable with their health state.

3.3. How much non-adherence costs?

How much non-adherence costs? This is a question almost impossible to answer with a high degree of certainty.

First, we need to establish the extent of the problem, so the factors leading to loss must be understood. In this case, it is important to know the amount of potential health that is lost when the patient doesn't follow the therapeutic plan. Furthermore, with the increase of the life expectancy there was a need to create the concepts of DALY's (Disability-Adjusted Life Years) and QALY's (Quality-Adjusted Life Years). DALYs sum years of life lost due to premature mortality and years lived in disability/disease and a QALY is the arithmetic product of life expectancy combined with a measure of the quality of life-years remaining [(24)].

These concepts reflect the potential losses that occur when a disease (and its lack of treatment) or an accident causes a state of disability.

Thus, we need to think what this represents in terms of total health expenditure and understand the role of non-adherence in the determinants of health indicators to improve health status indicators contributing to a sustainable health service.

The actual spending on total health worldwide is on average 9.945%, of the gross domestic product (GDP), ranging from an average 5.7% in the low-income countries, to 12.3% in high-income countries [(25)].

In health economics, the most concerning situations about Portugal are the increase of long-term and chronic diseases. Those diseases require a long time of treatment and raise the overall costs of the system. Heart diseases, in a non-adherent patient, are more likely to require invasive treatment, rehabilitation and lifelong medication. Diabetes may result in multiple complications and in the elderly, which normally have more than one pathological condition; this disease may multiply their needs [(3)]. Furthermore, diabetes has a special impact in Portugal, with the highest prevalence in Europe (14%), and a total cost of 0.8% of the GDP, with some estimates pointing to 1% [(26)].

Taking a further step, the latest data brief of the National Institute for Health Care Management (NIHCM) foundation about the concentration of USA's healthcare spending concluded that the top 1% spenders account for more than 20% of the spending and the top 5% almost 50% of all health allocated resources (Fig. 5). Investigating the common conditions of these patients is, with no surprise, that in top 5 are uncontrolled hypertension, dyslipidaemia

and diabetes mellitus – as mentioned before some of the diseases with the lowest adherence rates (Fig. 6 and Fig. 7) [27].

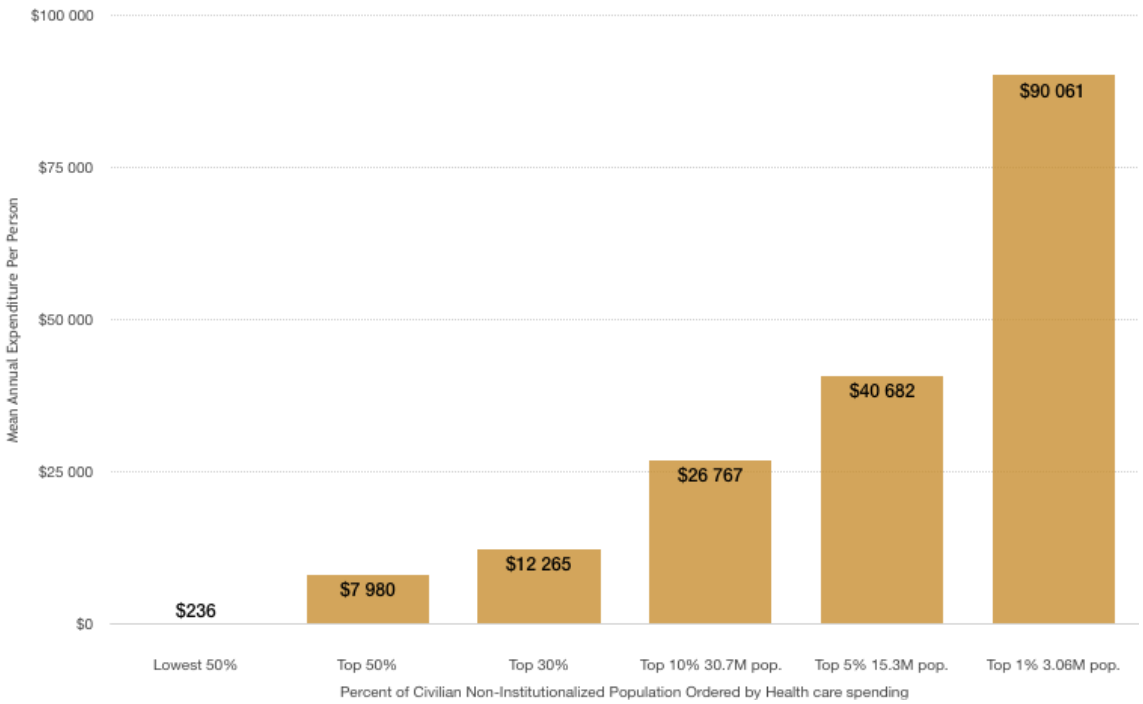


Figure 5 – Mean per-capita spending by spending group, 2009 [27].

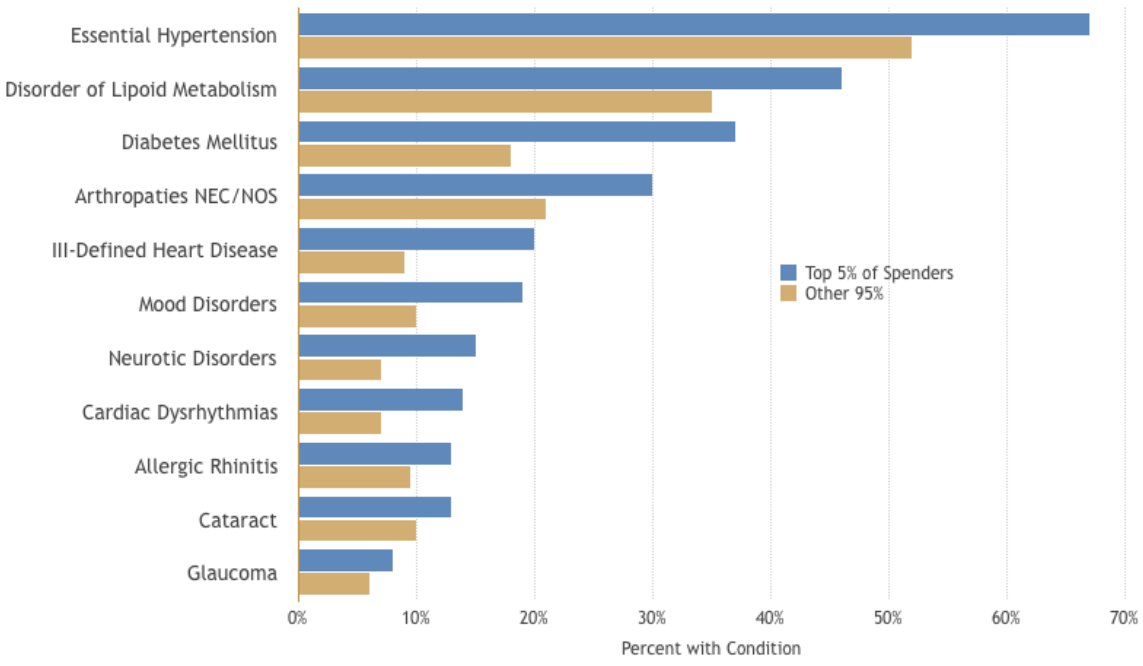


Figure 6 – Common conditions among elderly high spenders, 2006 [27].

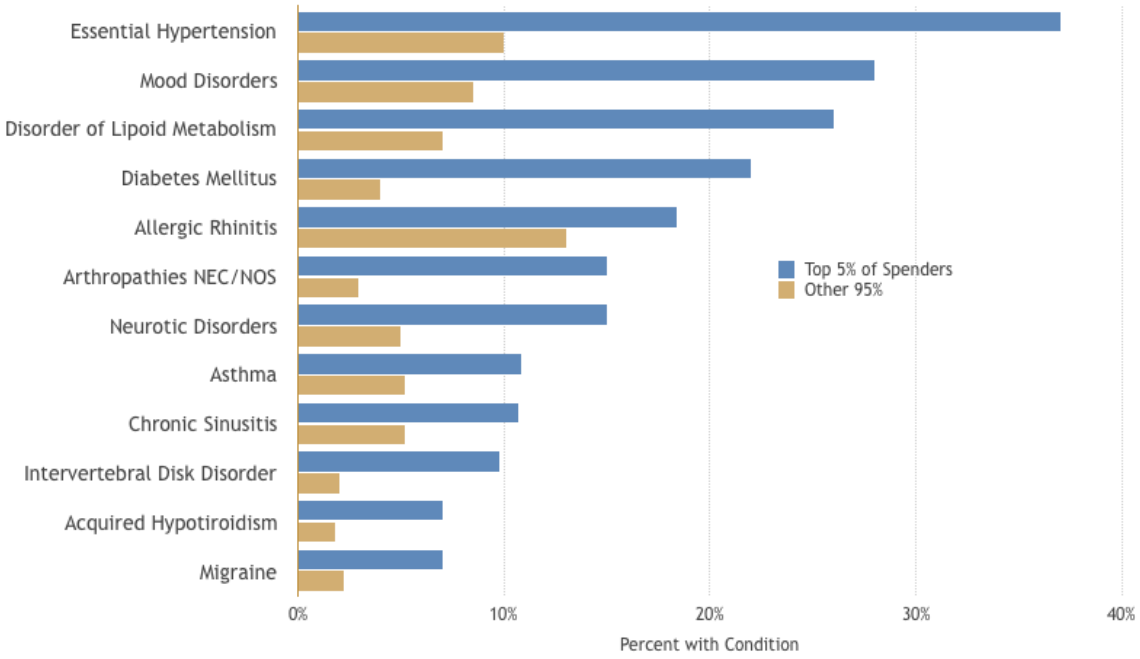


Figure 7 – Common conditions among non-elderly high spenders, 2006 [27].

Table 7 provides the UK statistics of the extent of the medication market, with net ingredient cost of £8,834 million and 43 million patients on prescribed medications. The cost to the UK government in untaken medicines has been estimated at around £100 million per year, and as stated before, is being regarded as a conservative estimation. So, as a solution the NHS created the automated pill dispenser project. This project collected data that clearly demonstrates that significant savings have been achieved. In total, the 251 participants have generated savings of £430k, an average saving of £1700 per person over a six-month period.

Table 7 – United Kingdom medication market [5].

UK Medication Market
✓ **927 million** prescription items dispensed per annum ✓ English average **17.8** prescription items **per head of population** ✓ Older people receive an average in **excess of 42.4 items** ✓ Net ingredient cost of **8,834 million**

The two largest areas of savings are home visits to prompt people to take their medication and an absence of hospital admissions for anyone using the pill dispenser. Home visits amounted to £107k and 52% of total social care savings and hospital admissions amounted to £151k and 68% of total health savings [5].

In addition, we should never underestimate the productivity losses associated with disease states. Mitchell & Bates (2011) show the results from a comprehensive evaluation of OptumHealth HRA data to determine the relationship between health status and productivity

loss among employed participants. They reached the conclusion that health conditions and lifestyle risk factors are associated with workplace productivity loss and reiterate the value of maintaining a healthy population. Moreover, it was determined practical estimates of the costs of productivity loss related to health (Fig. 8 and Fig. 9) [28].

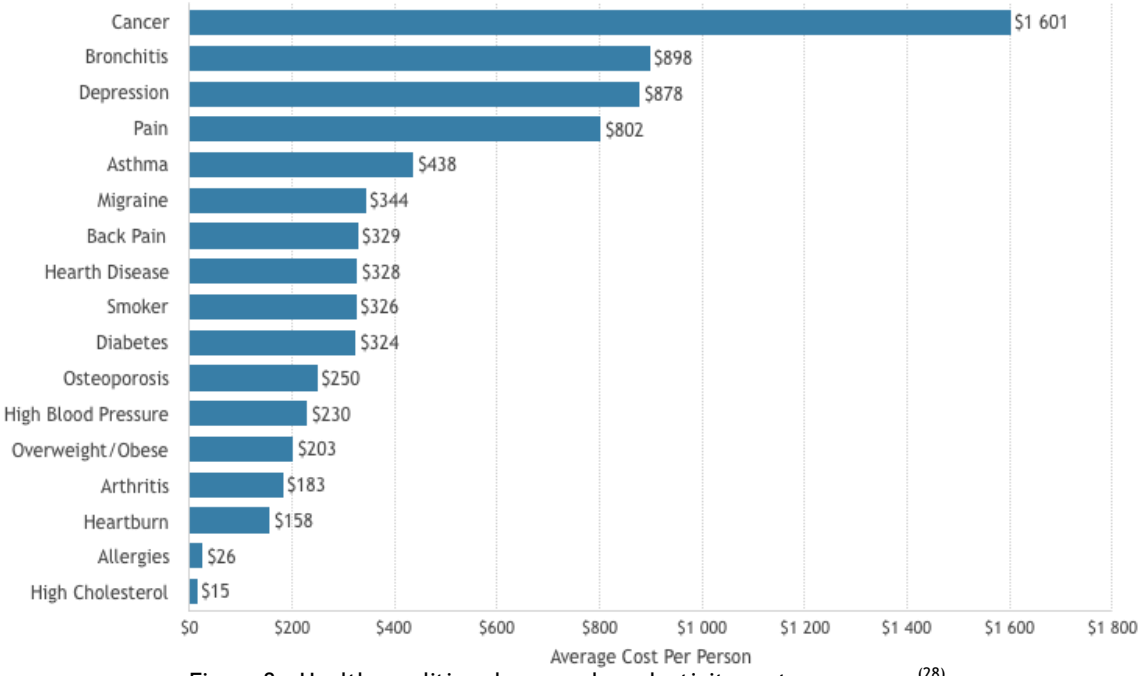


Figure 8 – Health conditions by annual productivity cost per person [28].

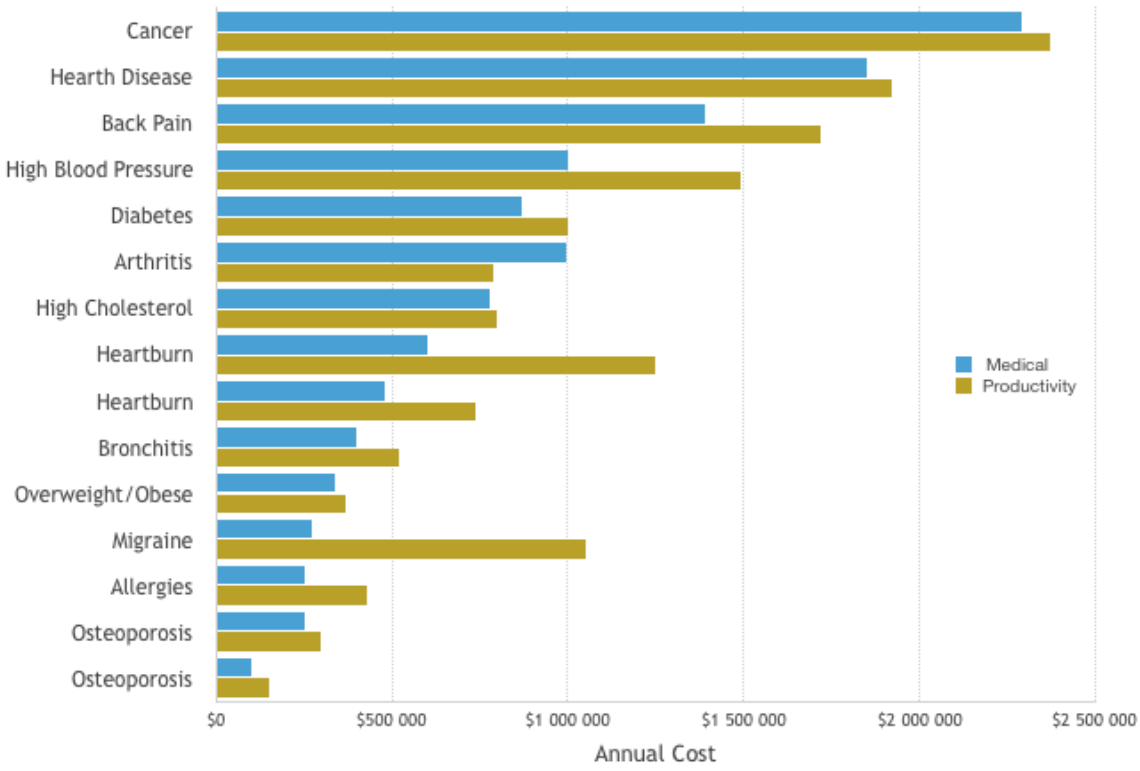


Figure 9 – Annual productivity and medical costs for average-size employer (10 000 employers) [28].

Although there is much information about isolated conditions and its economic burden, there are neither meta-analysis nor systematic reviews that expose the economic losses associated with non-adherence. Because of this fact, some examples using some of the diseases stated before will be presented.

In the case of osteoporosis, low adherence (MPR<50%) with bisphosphonates was associated with 18% higher medical costs compared with high adherence (MPR>80%) [(12)]. Comparable results were calculated using claims data of a subset of 37,096 elderly patients initiating osteoporosis therapy over a period of eight years. Noncompliant patients had higher total all-cause ($11,749 vs. $10,719), medical ($8768 vs. $6919), and osteoporosis-related medical costs ($630 vs. $560) than adherent patients (MPR > 80%) [(29)].

Moreover, Huybrechts *et al.* (2006) found that non-adherence to osteoporosis therapy was associated with a 37.2% higher rate of all-cause hospitalizations (adjusted per patient-month) as well as higher mean total health care charges [(30)].

Going back to the results of the European Mania in Bipolar Longitudinal Evaluation of Medication (EMBLEM) study, the total costs incurred by non-adherent patients during the trial period were significantly higher than those by adherent patients (£10231 vs £7379, $p < 0.05$). This disparity mainly resulted from differences in inpatient costs between the two groups. Inpatient costs of non-adherent patients were more than double those of adherent patients during the maintenance treatment (£4796 vs £2150, $p < 0.05$) [(14)].

Using USA claims data; they found that hospitalization costs were almost six times higher in irregular medication users ($9701) than in regular users ($1657) over a 12-month period [(31)].

Changing the topic to a condition that wasn't mentioned before in this dissertation, in chronic obstructive pulmonary disease (COPD), the Simoni-Wastila *et al.* (2012) study showed that adherent patients had higher costs for prescription medication compared with non-adherent patients. However, these costs were offset by lower inpatient and outpatient costs resulting in lower total spending for adherent compared to non-adherent patients, with a reduction of $3764 on Medicare spending [(32)].

Another study was the administrative database analysis of Toy *et al.* (2011). In addition to the influence of a 5% increase of adherence on healthcare utilization they also calculated related costs. To obtain a cost estimate reflecting the national population, patient data were weighted. Increasing proportion of days covered (PDC, is the method the authors chose to measure adherence) in 5% resulted in lower expenditures for inpatient and emergency room (ER) visits. In contrast, costs for outpatient visits would slightly increase. However, they concluded this would result in an overall net cost reduction of 2.2% in annual healthcare resource use and costs [(33)]. This is a very good example of a chronic disease trapped within the burden of non-adherence.

These examples reinforce the ideas stated before, showing that non-adherence is a serious public health problem. At the bottom line, it leaves the idea that there are more subjects and diseases to be analysed regarding the economics of non-adherence. The papers

describing the (non)-adherence advantages, disadvantages and costs were chosen because they provided a good source of information and the diseases they analyse are from completely different areas of Medicine, reinforcing the belief that non-adherence cuts across all medical specialties.

3.4. Electronic medication monitoring devices – What has been done so far?

The medication monitoring devices started to be developed decades ago, in the 80's [(34)], with the purpose of attributing value to clinical trials, in which the pill intake is the key to the outcomes. The pill intake is also a fundamental step to be proved in order to establish a relationship between the drug therapeutic and the symptomatic improvement, of patients under certain conditions.

They still are a key in the validation of these studies, but have almost zero application in the clinical day-to-day. There are various devices available either to help people to take their medication by simplifying administration, or by supporting them to remember to do so. These include: pill reminder charts, drug diaries, calendar clocks, telephone prompting service, multi-compartment compliance aids (MCAs), talking labels, voice reminders, watch reminders, daily pill boxes and automated pill dispensers.

Whilst these aids do work and many people have used them successfully for years, they do require the person using them to be able to manage the timing and frequency of consumption without prompting. These aids are often not adequate for people with more severe cognitive problems and some physical disabilities such as sight loss or dexterity problems [(5)].

Adherence rates among capable people still have a lot to improve, and the methods abovementioned may have some value but the real problem exists when people neglect their health condition because the lack awareness or some misbeliefs. This results in poorer health control and multiple losses as stated before.

So, resorting to two systematic reviews that were chosen because of the value of the data and the lack of other resources, details about these type of devices, their features and its adherence effectiveness are provided.

Paterson *et al*. (2016) made a comprehensive literature search of 10 databases, identified 805 abstracts and retrieved 99 full text papers, but only six of them met the inclusion criteria. The studies were small scale and only one was a well-conducted randomised controlled trial, overall methodological quality of the studies was poor.

The studies that filled the inclusion criteria were conducted between 2008 and 2013. All those studies included in the review had methodological problems. They were limited by small numbers, inadequate control groups and often included complex interventions of which

adherence technology was only a part. All off them aimed for different groups of treatments, covering different types of patients and diseases.

Notwithstanding its limitations, there is a lot of information that can be extracted from that reference. Furthermore, this systematic review covered six different devices, relying all of them on a pillbox. Two of the studies were designed to work connected to a smartphone application with alarms, medication history and recording of medicine taking. The others were designed to work only with pillboxes. Each one was different from the others, alongside visual and auditory alarms with the ability to record and upload data of the medication intake.

The technical specifications of each device are not described in the systematic review but the greater problems were connected with the usability, mobility of the device and the flexibility of timing of reminders.

The authors considered that, although positive effects on adherence were reported further, rigorously conducted, studies are needed to inform the use of electronic multi-compartment medical devices [35].

The second systematic review conducted by Checchi *et al*. (2014), identified 11,511 publications, of which 11,366 were deemed irrelevant after reviewing the titles and abstracts. Among the remaining 145 articles, 102 were excluded. The 43 remaining articles described, 37 unique studies including 4326 patients, of which 10 were patient interface–only and 29 were more complex interventions integrated into broader systemic interventions.

The studies that met the inclusion criteria were conducted between 1992 and 2014. Showing that this kind of solution was introduced before the Internet and Gadget boom of recent years.

This study divided the works in: patient interface–only devices vs. integrated interventions, and the studies that compared both approaches. In the patient interface-only devices, the electronic monitoring packaging (EMP) interfaced directly with the patient alone. In the other hand, the integrated interventions were defined by the integration of physicians, pharmacists, or other health professionals that would engage the patient in a targeted intervention to increase adherence with or without using electronic monitoring packaging-derived data.

Within the limited scope of these studies, simple devices that monitor and store adherence records and devices that combine digital displays with audible reminder alarms appeared to be the characteristics of EMP devices most useful for improving adherence.

In the group of patient-interface only, the effect of EMP on the proportion of patients who were adherent, the range of the increase was 1.0% to 49.5%. For the effect of EMP on mean levels of adherence, the range was from a decrease of 2.9% to an increase of 14.6%.

As far as the integrated interventions are concerned, the effect of EMP on the proportion of patients who were adherent, the range was −8.0% to 33.5%. For the effect of EMP on mean levels of adherence, the range was from 1.0% to 34.0%, of increased adherence.

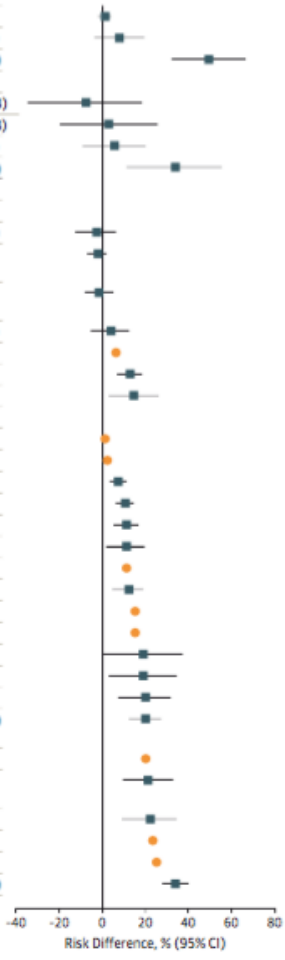
Difference in level of adherence at individual study level is presented in the Table 8. In addition, the authors highlighted a study conducted by McKenney *et al.* (1992) that measured adherence among patients with hypertension receiving medication containers was 94% with a digital display, higher for those receiving a digital display along with cards to record home and office blood pressure values (99%), and highest for those receiving the digital display, card, and a blood pressure cuff (100%, $p < 0.01$ for all 3 treatments compared with standard).

Nevertheless, numerous studies had methodological problems such as non-randomized designs. Authors of this review were not blinded to the study results when evaluating study quality and consider the need for higher-quality evidence to determine the effect, if any, of these low-cost interventions on the critical problem of medication non-adherence [(36)].

Additionally, with the work developed so far, is almost impossible to establish, with a high degree of certainty, the importance of monitoring devices in clinical practice, and its impact on the problem of non-adherence. Nevertheless, we can extract the strengths of other works and compile the information to achieve our objective.

Table 8 – Difference in level of adherence at individual study level, grouped by type of intervention [(36)]

	No. of Patients		Adherence (% Adherent or Mean)		Type of Device	Risk Difference, % (95% CI)
	Intervention	Control	Intervention	Control		
Proportion of patients adherent						
Patient interface only						
Barrios et al,[15] 2007	485	1038	92.0	91.0	1	1.0 (-2.0 to 4.0)
Kooy et al,[18] 2013	117	128	73.0	65.0	2	7.8 (-3.8 to 19.4)
Charles et al,[19] 2007	44	46	88.6	39.1	2	49.5 (32.4 to 66.6)
Integrated intervention						
Matsuyama et al,[42] 1993	15	17	80.0	88.0	1	-8.0 (-34.3 to 18.3)
Elixhauser et al,[35] 1990	31	37	68.0	65.0	1	3.0 (-19.8 to 25.8)
Kooy et al,[18] 2013	54	128	70.4	64.8	2	5.5 (-9.3 to 20.4)
Wu et al,[34] 2012	54	28	69.5	36.0	1	33.5 (11.6 to 55.4)
Mean level of adherence						
Patient interface only						
Vervloet et al,[24, 25, 26] 2010, 2011, 2014	48	57	65.5	68.4	5	-2.9 (-12.3 to 6.5)
Wagner and Ghosh-Dastidar,[16] 2002 (electronic monitoring)	60	57	91.4	93.8	1	-2.4 (-6.9 to 2.1)
Wagner and Ghosh-Dastidar,[16] 2002 (patient diaries)	56	57	92.4	93.8	1	-1.4 (-8.2 to 5.4)
Holló and Kothy,[20] 2008	34	34	85.3	81.6	2	3.7 (-5.3 to 12.7)
Christensen et al,[17] 2010	219	179	91.0	85.0	2	6.0
Laster et al,[23] 1996	13	13	95.8	83.1	4	12.7 (6.9 to 18.5)
McKenney et al,[21] 1992 (timepiece cap)	17	16	93.6	79.0	4	14.6 (2.8 to 26.4)
Integrated intervention						
Mengden et al,[53] 2006	44	18	99.0	98.0	3	1.0
Forni Ogna et al,[39] 2012	32	16	99.0	97.0	1	2.0
de Bruin et al,[32, 33] 2010[a]	66	67	NA	NA	1	7.4 (3.5 to 11.3)
Kruse et al,[44] 1994	15	9	92.0	81.5	1	10.5 (6.1 to 14.9)
Murray et al,[28, 29] 2004 and 2007	122	192	78.8	67.9	1	10.9 (5.0 to 16.7)
Russell et al,[47, 48] 2010 and 2011	5	8	88.0	77.0	1	11.0 (2.1 to 19.9)
de Bruin et al,[55] 2005	19	19	93.0	82.0	3	11.0
Sabin et al,[36] 2010	31	33	96.5	84.5	1	12.0 (4.6 to 19.4)
Rigsby et al,[38] 2000	37	18	75.0	60.0	1	15.0
Rosen et al,[58] 2004	16	17	80.0	65.0	4	15.0
Waeber et al,[49] 1999	6	6	83.0	64.0	1	19.0 (0.4 to 37.6)
Cramer and Rosenheck,[41] 1999	25	20	76.0	57.0	1	19.0 (3.3 to 34.7)
McKenney,[21] 1992 (timepiece cap + card)	17	16	98.7	79.0	4	19.7 (7.4 to 32.0)
Tashkin et al,[30] 1991 Nides et al,[31] 1993	116	89	60.2	40.4	1	19.8 (12.3 to 27.3)
Kozuki and Schepp,[43] 2006	15	14	88.0	68.0	1	20.0
McKenney et al,[21] 1992 (timepiece cap + card + cuff)	17	16	100.2	79.0	4	21.2 (9.6 to 32.8)
Okeke et al,[51] 2009	35	31	73.0	51.0	2	22.0 (9.2 to 34.8)
Mooney et al,[37] 2007	27	28	77.0	54.0	1	23.0
Schmitz et al,[40] 2005	22	24	73.0	48.0	1	25.0
Onyirimba et al,[46] 2003	10	9	81.0	47.0	1	34.0 (27.7 to 40.3)



3.5. Internet of Things and the information value loop – Is this the future?

The importance of data in delivering efficient, effective health care has long been obvious—and has never been greater. Today's medicine relies on analytic data for almost everything. And as far as adherence is concerned the only input, besides analytic control by blood sampling, is the patient-reported data on pill intake. Considering the relationship between doctors and patients isn't always good, and some inconsistencies in some patient treatments on day-to-day practice, the importance of monitoring this behaviour is bigger than ever. And we should consider the possibility that, even with a good patient-doctor relationship, non-adherence could still be a problem.

The increased focus on value-based care is shifting financial incentives to a model in which providers are compensated based on how their patients' fare, rather than by the number of tests, visits, or procedures performed.

Advances in sensor technology are making the creation of new data much easier. To be useful, all those data need to be communicated, aggregated, and analysed in ways that enable new and more e effective action.

Realizing the Internet of Thing's (IoT) full potential motivates a framework that captures the series and sequence of activities by which organizations create value from information: The Information Value Loop (Fig. 10).

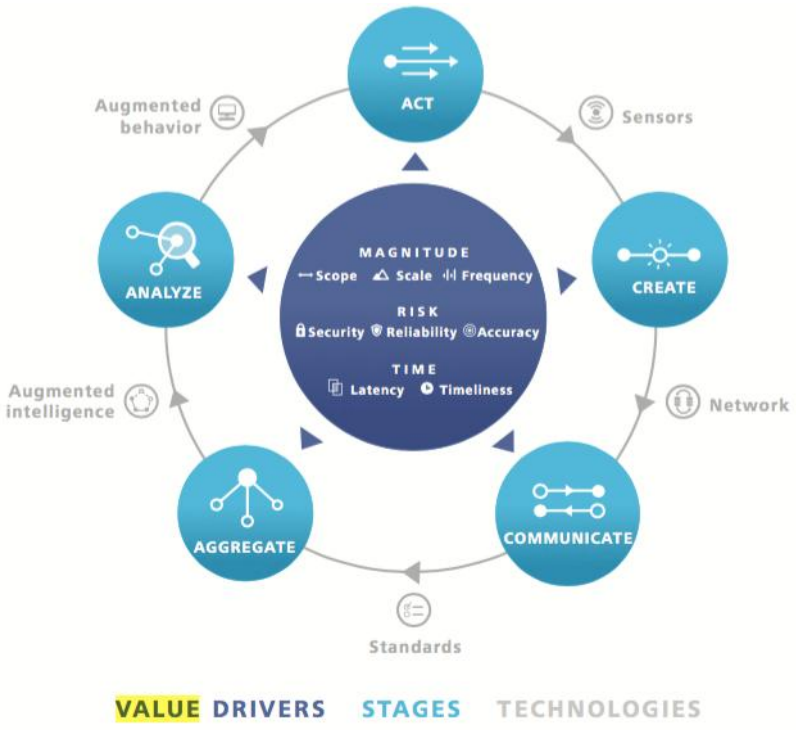


Figure 10 – The information value loop [37].

A few IoT-enabled devices are available to patients and providers to monitor diabetes, heart conditions, and other ailments. Despite these facts, the devices rarely are set up to export their data to a system that aggregates and shares information with all involved parties.

So, the real goal is to interconnect all ambulatory devices in order to send information to an IoT-based system that allows real-time monitoring by health professionals of patient's biosignals and adherence behaviour.

This tool would provide feedback to patients helping them engage and make better health and wellness decisions in real-time, decreasing the need for costly doctor visits, tests, and hospitalizations and reducing the rate of progression of the disease [37].

The creation of an interoperable device that could measure patient's adherence and at the same time be connected to all other medical devices and send their data could lead to greater home care and increased patient involvement, driving to better outcomes for patients and reduced cost for all.

4. Discussion

Understanding the fundamental problems of therapeutic adherence raises a lot of questions. In terms of social dynamics, two patients with the same health conditions, whichever they are, may present a lot of differences in terms of motivation to follow therapeutic plans and pursue healthy lifestyles. Furthermore, as doctors, we may share a paternalistic point of view of a person's health state, while trying to apply the best therapeutic options based on scientific evidence. The relationship between doctor and patient is a subject with a lot of underlying investigation and the keyword that we can find between all the articles, papers and books about it, is "trust".

Within all the information presented before in this dissertation we understand the need for this kind of devices. Taking a step further, and realizing the amazing impact that technology has empowering people through social media, gaming, and the high capacity of data transmission, is now imperative that health professionals engage and take a special role in the development of a sustainable healthcare system.

The impact of empowering patients to be more engaged in health control and improve their health habits, with a portable device attached to their medicines that can create a bridge rapidly evolving patient's health and professional healthcare domains, can't be measured with the tools and works developed until this date.

Imagine a healthcare system that can collect patient data and stream it to a telehealth centre where it is then analysed and compared with the profile of the patient. If any abnormal event occurs, a healthcare professional can then prioritize and dynamically allocate key healthcare resources to where they are needed most. In this case, abnormal event must be characterized, this meaning that with the monitoring of biosignals and medicine intake we can establish patterns that show the likelihood of an abnormal event, based on the collected data acquired by the different monitoring devices, that can be gathered and sent online by the portable monitoring device of therapeutic adherence.

And as shown before, the information value loop will generate more and more information that will allow us to understand the natural course of the diseases and maybe establish new diagnoses and lines of treatment based on the analytic data collected, benefiting from proximity, between the patient and the healthcare system, these kinds of technology offer.

Looking at the major evolution of social's awareness towards health, it's obvious that the personal and professional healthcare worlds are converging, with traditional models of care being challenged at every turn, and connected digital technology may be the key to empower patients to take care of their health and that of their loved ones. On the other hand, the doctors would have supplementary information about the patient's condition, and the certainty that the therapeutic plan is followed as previously accorded, potentiating the trust relation between doctor and patient.

The economic burden of non-adherence is, without a doubt, a preventable source of public and private spending. Looking at the information mentioned before; the top 5% spenders in health, account for almost 50% of all health allocated resources, furthermore, they share conditions such as uncontrolled hypertension, dyslipidaemia and diabetes mellitus, the same kind of diseases that share high rates of non-adherence. Only by this information we can't establish that those patients are non-adherent. But if we settle non-adherence rates as the ones verified by the articles mentioned before and account the potential health lost by those who don't follow the therapeutic plan and fit in the top 5% spenders group, we realize the potential economic savings that can be raised resorting to technology that can monitor adherence and other biosignals. This approach would ultimately lead to resolution and close control of minor events that, if uncontrolled would precipitate serious disease states.

Unfortunately, information about the clinical application of these devices in an integrated approach isn't available because of the lack of articles in this field. Most of them was just used to prove a concept and were then discontinued, as seen before. So, with today's published information is impossible to determine with a high degree of confidence the impact of these devices, once the clinical evidence supporting the use of today's technology on monitoring therapeutic compliance rates isn't strong enough.

Another important aspect to discuss is the Technology Industry that have a big role in developing and guarantee the reliability of medical devices. In this topic, we must discuss an important limitation attached to this industry, the industry lobby in the manufacture and in specific technologies may act as a barrier to interoperability between medical devices from different manufacturers. This reality and the need to prevent electronic waste motivated the European Union Council to approve a law that aims for a single universal charger, making us believe that are being made efforts to motivate a culture of cooperation and development between different market competitors of the technological industry, allowing the future medicine to take most of the possibilities that are yet to arrive.

Last but not least, this kind of integrated approach may be an important asset in the future of isolated populations with few or none healthcare providers. This vision of health would allow doctors to track fundamental biosignals that could reveal or exclude signs of disease. Admitting this kind of approach as a lot of limitations, the biggest one being the loss of contact that is fundamental between the patient and the doctor, it rises as a possibility to keep track and maintain these kinds of population with medical accompaniment.

Tele-monitoring as we know has a lot of potential growth, and with the new generation of doctors, used to deal with technology the potential health gains could surpass nowadays estimations.

5. Conclusion

Closing this dissertation, a lot of conclusions can be taken. In the beginning, the non-adherence factors were exposed in the tables 1 to 5. Taking a closer look, we can see that almost all those problems have a solution in common – the integrated approach with portable tele-monitoring devices. Table 1 expose patient factors leading to non-adherence, and none of them present limitations to the use of this technology, on the contrary, it's efficiency with mental despaired patients is proven and included in the article, and only the personality traits can't be modified.

The other pointed reasons to non-adherence can improve greatly with the integrated approach. Medication factors would be excluded once the medication handling, regimen and drug-drug interactions would have a closer control by doctors and pharmaceutics. Healthcare provider factors are due to the deterioration of the relationship doctor-patient. The major improvement of the portable tele-monitoring devices in this topic is the involvement required to make this system work, this meaning that once the patient and the doctor engage the integrated approach the patient involvement, the communication, and his confidence rises while the medication is obligatorily reviewed and the patient has a bridge to the Healthcare System.

Healthcare system factors could be the ones to have the biggest improvement, the empowerment of the patients would improve the patient's education towards his condition, provide a daily follow-up with reduced costs and the medication schedule would have to be discussed and planed, on the other hand a pharmacy based system would have to be integrated and would provide the patients a community service to pack the medication in a friendly way.

The last-mentioned point are the socioeconomic factors, and the problems presented are the large caregiver burden and the lack of caregiver. This problematic could be solved, in part, by the tele-monitoring of patients in remote areas and in populations with a low high ratio of patients per doctor. While patients nowadays still don't have a solution, the integrated approach would result in a close follow-up without the need of physical dislocation by the patient. The chronic problems with a close monitoring would result less acute events and therefore a more sustainable use of the Healthcare System.

Although all the studies in this area are involved in limitations, as shown before, the "perfect" portable tele-monitoring device can be projected. The elemental features of our proposal would be: small size and portability, customizable auditory or visual alarms linked to the medicine's schedule, real-time monitoring and interoperability with other medical devices. Another important feature is the option to connect the device to a smartphone and develop applications that would make the pill intake patient friendly.

In the recent days, big changes have occurred in life of all people, the evolution of technology has reached a point where almost everything is available at the touch of a button.

Technological devices fit within the lifestyle of the average person and present themselves with the potential to be the game-changer in therapeutic non-adherence. Despite these facts, the integrated response with the hospital, pharmacy and a cloud data integration software are the angular stone in which this kind of approaches should be built. The system upon this kind of devices are built in are as important as the devices itself. The management and treatment of the information is the key for the development in these approaches.

Lastly, it's important to highlight the fact that this is an unexplored area and the scientific articles published don't have good quality standards upon which we can establish, with a high degree of certainty, the importance of monitoring devices in clinical practice. But with the information stated before we believe in the potential of portable tele-monitoring devices to be a game-changer in patient therapeutic adherence.

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