World Journal of Pharmaceutical and Life Sciences
WJPLS
www.wjpls.org
SJIF Impact Factor: 6.129

DESIGN OF A NUTRITIONAL EDUCATION PROGRAM: INTERACTIONS BETWEEN DRUGS AND FOODS

Julia San Miguel Rodríguez*[1], Julita Rodríguez Barbero[1], Angel San Miguel Hernández[2], Angel San Miguel Rodríguez[3] and María San Miguel Rodríguez[3]

[1]Hospital Pharmacy Service. Río Hortega University Hospital.
[2]Clinical Analysis Service. Río Hortega University Hospital Valladolid. International University of La Rioja. Spain.
[3]Research Service. Río Hortega University Hospital. Valladolid Spain.

Corresponding Author: Julia San Miguel Rodríguez
Hospital Pharmacy Service. Río Hortega University Hospital.

Article Received on 29/05/2021 **Article Revised on 19/06/2021** **Article Accepted on 09/07/2021**

ABSTRACT

Introduction and justification: Drug interactions on food (IMA) are the modifications that the drug produces in the use of food or its components, which affect nutritional status. Currently, the high proportion of the elderly population, polymedicated and with nutritional deficiencies, contribute to the high frequency of AMI. These factors, together with the limited information about the patient, justify carrying out the project. **Objectives**: To design an education program aimed at adult patients who are under treatment with drugs that interact with food, to avoid negative repercussions on their nutritional status. **Design:** The project is carried out during 1 year, in 120 users of a pharmacy office in pharmacological treatment. The selected drugs belong to the groups with the highest consumption and with the most nutritionally relevant interactions: gastrointestinal protectants, lipid-lowering, antidepressants and antihypertensives. **Initial phase:** The degree of knowledge of patients about the influence that drug treatment can have on their nutritional status is evaluated. An individualized dietetic-nutritional education is carried out to avoid interaction, reinforcing education in eating habits and healthy living. **Follow-up phase:** Consultations are carried out 3 and 6 months after the start, to detect incidents and reinforce motivation and adherence to the proposed educational plan. **Evaluation phase**: The degree of compliance and patient satisfaction is assessed, a methodological tool to propose corrective measures if necessary. **Discussion:** The degree of ignorance expected of the patients is higher than 80%. This project provides a new vision in the approach to interactions from a multidisciplinary strategy. It would allow a comprehensive education from the nutritional perspectives by the dietician-nutritionist and pharmacologist. **Conclusions:** The implementation of this program could help to prevent pharmacological treatment from negatively affecting nutritional status.

KEYWORDS: Nutritional education program, interactions, drugs, foods.

INTRODUCTION

Interaction between food and drugs: Types

The first references to interactions between food and drugs date back to 1927 with Burrows and Farr.[1] when referring that the administration of mineral oils decreased the absorption of fat-soluble vitamins. However, it is from 1963 with Shee,[2] when the first studies regarding the interaction between monoamine oxidase inhibitor drugs (MAOI) and foods rich in biogenic amines begin.

Basically, interactions between food and drugs can be defined as the modifications produced by the drug in food intake and nutrient utilization and those produced by food in the pharmacological effects of the drug.[3] These are interactions that present a high frequency, inherent in the fact that everyone who is being treated with a drug ingests a variety of foods in their diet that can potentially interact.[4]

Another aspect for which it is important to know these interactions is because of the impact they can have on the nutritional status and health of the individual. This does not mean that they will always be harmful to the body; sometimes not only are they not, but they are considered beneficial as they improve the nutritional status or the therapeutic efficacy of the drug. Based on scientific evidence and clinical practice, it can be confirmed that those with negative repercussions predominate.[5]

It is important to bear in mind that the interactions between food and drugs have a double direction, depending on which of the two substrates is modified by

the action of the other. Taking into account which substrate is affected, they can be classified into:

1. Food-Drug Interactions (AMI) or food-drug interactions.
2. Drug-Food Interactions (MAI) or drug-food interactions.

1. Food-Drug Interactions (AMI)

They refer to the modifications that the food or some of its components produce in the medicine. These alterations in the behavior of the drug can occur when the food and the drug are in the gastrointestinal tract, and may be nonspecific due to the food or specific due to any of its components.[6] The nutritional status of the person and the nutritional composition of the diet are factors that decisively influence this type of interaction.[3]

The importance of these interactions is fundamentally from the pharmacological point of view, since they can condition the therapeutic efficacy of the drug. They can occur after the administration of a drug in acute or chronic treatment, not requiring a prolonged use of it. Based on their mechanism of action, pharmacokinetic and pharmacodynamic types can be differentiated.[3]

Pharmacokinetic type interactions

The presence of food or any of its components can interfere with the drug release, absorption, distribution, metabolism or excretion processes (LADME). By affecting the kinetic processes of the drug, it may happen that the desired levels of it are not obtained in the body, which will condition the efficacy and safety of the drug.[3,7]

The most frequent and relevant are those that affect the absorption process of orally administered drugs. In this sense, they can affect absorption at a quantitative level, so that higher or lower levels than expected can be obtained in the blood, which can lead to toxic effects or therapeutic ineffectiveness, respectively. Food can also condition the speed of absorption of the drug, which will affect situations in which a rapid onset of drug action is required.[3]

A group of drugs very representative of this type of pharmacokinetic interactions are oral anticoagulants (OAC), warfarin and acenocoumarol. Being drugs with a narrow therapeutic margin, a small change in drug levels in the blood can lead to important changes in the therapeutic effect. For this reason, special care must be taken in the intake of foods that can interact with them. High-fat foods such as avocados, decrease the absorption and increase the metabolism of ACOs. Foods such as beets, broccoli, cauliflower rich in indoles are metabolic inducers of cytochrome CYP1A2, thus reducing blood levels and the therapeutic effect of these drugs.[3]

Pharmacodynamic type interactions

This type of interaction occurs when the drug and the nutrient interact at the level of the mechanism of action, mainly by competition at the level of receptors or transport systems. In this way, they can enhance or antagonize the action of the drug, affecting the efficacy and safety of the drug.[3] They are less frequent than pharmacokinetics, since foods and drugs have essentially different mechanisms of action and their destinations in the body are also different.[6]

Among the pharmacodynamic interactions is the classic MAOI (moclobemide ...) that interfere with the metabolism of biogenic amines in our body, increasing levels of neurotransmitters (norepinephrine, adrenaline, dopamine, serotonin). Simultaneously, MAOIs also inhibit the metabolism of amines (tyramine, histamine), which are found in beverages and foods such as wines, beers, aged cheeses, sausages, fish pickles... When eating this type of food together with MAOIs, produces an increase in the effect of the drug, which may have clinical relevance since the increase in amines can produce hypertensive crisis.[3,7]

Both pharmacokinetic and pharmacodynamic interactions justify the importance of properly eating foods from the diet when taking some medications. In clinical practice, food can interfere with some medications and produce:

- An increase in the levels of the drug in the body or enhancement of its action that can sometimes lead to adverse reactions or toxic effects.
- A decrease in the levels of the drug in the body or a decrease in its action that can make the drug not achieve the desired effect or therapeutic ineffectiveness.

Table 1 lists AMI and their types.

Table 1. Food-Drug Interactions (AMI). Types. AMI, Food-Drug Interaction; LADME, Release, Absorption, Distribution, Metabolism, Excretion.

PHARMACOKINETIC AMI Food modifies LADME of drug	↑ drug levels → Toxicity ↓ drug levels → Ineffectiveness
PHARMACODYNAMIC AMI Food modifies drug action mechanism	Potentiation of drug action → Toxicity Toxicity Inhibition of drug action → Ineffectiveness

List of abbreviations and acronyms

ACO: Oral anticoagulants

AEMPS: Spanish Agency for Medicines and Health Products

ATC: WHO Chemical Therapeutic Anatomical Classification.

CHMP: European Committee for Medicinal Products for Human Use

CoQ10: Coenzyme Q10
DHD: Inhabitant Dose Day
EMA: European Medicines Agency
FDA: Food and Drug administration. Agency responsible for regulating food and drugs in the United States.
HMG CoA reductase: 3-hydroxy-3-methyl-glutaryl-CoA reductase enzyme
AMI: Food-Drug Interactions
PPIs: Proton Pump Inhibitors
SSRI: Selective serotonin reuptake inhibitors
ACEI: Angiotensin-I converting enzyme inhibitors AMI: Drug-Food Interactions
MAOI: Monoamine oxidase inhibitors
LADME: Drug release, absorption, distribution, metabolism, or excretion
LOPD-GDD: Organic Law 3/2018, of December 5, on the protection of personal data and guarantee of digital rights
NCL National Consumers League
OFC: Community Pharmacy Office
RGPD: Regulation 2016/679 of the European Parliament and of the Council of April 27, 2016 regarding the protection of natural persons with regard to the processing of personal data and the free circulation of these data

2. Drug-Food Interactions (AMI)

They refer to the modifications that the drug will produce in the food or in its components and that therefore will have repercussions at the nutritional level. Sometimes there is an alteration in the use of a food component, either a specific nutrient or an additive, which could be, for example, a vitamin, mineral... On other occasions, it affects the body's ability to maintain a nutritional state healthy.[6]

Those that are due to the drug's own therapeutic effect on the nutrient or those due to adverse or secondary effects of the drug can be strictly differentiated. The former are not considered IMA as such. As an example, we refer to the case of orlistat, an active principle that reduces the absorption of fats from the diet by a mechanism of inhibition of pancreatic and gastric lipases. By inhibiting lipases, ingested triglycerides are not hydrolyzed and their excretion in feces increases, increasing the elimination of fat-soluble vitamins A, D, E and K. However, it is not properly considered an interaction since it is the therapeutic indication of the drug itself.[8]

Unlike the interactions that affect the drug, they are generally related to the use of drugs in chronic treatments, that is, for long periods of time. If the treatment is acute or of short duration and the patient has a good nutritional status, it is difficult for these interactions to have a nutritional impact, since the body corrects the deficits with its own reserves.

Especially susceptible populations are the elderly, as they are usually polymedicated patients (more than five drugs) with chronic pathologies and more frequently present nutrient deficiencies. Other affected populations, although to a lesser degree, are children and adolescents due to the nutrient needs in these stages, greater than those of adults. Pregnant women are also a more susceptible population group.[9]

The influence of medication on general nutritional status can be due to many factors. Table 2 shows the most relevant ones.

Table 2: Drug-Food Interactions (IMA).

INFLUENCE OF THE MEDICINAL PRODUCT ON THE NUTRITIONAL STATUS
Modification of food digestion
Modification of nutrient absorption, metabolism and elimination → nutrient depletion
Modification of appetite
Weight loss/gain
Alterations of smell and / or taste
Gastrointestinal disorders: mucosal lesions, nausea, vomiting, diarrhea, constipation

The drug can affect the use of nutrients by interfering with the digestion process of food and the absorption, metabolism and elimination of nutrients. Some examples are collected:

1. Drugs that induce emesis by different mechanisms, such as certain chemotherapy drugs that cause nausea or vomiting by affecting the growing tissues of the gastrointestinal lining.
2. Antibiotics that, by inhibiting commensal bacteria, can lead to the growth of *Candida albicans.* This colonization by *Candida spp* can occur in the oral area leading to a reduction in oral intake or in other areas of the gastrointestinal tract producing malabsorption and diarrhea. Depending on the intensity of the colonization, both situations could have repercussions at the nutritional level.[9]
3. Some laxatives, of the mineral oil type and cathartic agents, which decrease gastrointestinal transit time and can cause loss of fat-soluble vitamins, such as vitamin A and E and sometimes calcium and potassium.[9] The alteration of these processes in some cases can cause depletion of minerals or vitamins and have nutritional and clinical relevance.[10]

Other drugs, regardless of their therapeutic action, can modify appetite either by mechanism of action at the central or peripheral level. Some serotonergic or adrenergic drugs can cause a feeling of satiety, loss of

appetite and increased energy expenditure, which can lead to weight loss.[9] On the contrary, other drugs, such as some antidepressants, are associated with weight gain.[11]

Other drugs can alter taste and smell, factors that influence food intake and can affect the nutritional status of individuals. Some medicines belonging to the group of quinolones and angiotensin-I converting enzyme (ACEI) inhibitors can cause alterations in both senses. Taste alterations can be quantitative such as hypogeusia or decreased appreciation of flavors and ageusia or absolute loss of taste. They can also produce qualitative alterations or dysgeusia with an unpleasant metallic, salty, acid, bitter taste.[12]

The mechanisms by which a drug can alter taste are variable. In some antidepressants it is produced by xerostomia or decreased saliva to move food to the taste buds. In captopril, it is related to the decrease in blood levels of zinc due to a chelation mechanism taking place.[13]

Taste alterations due to medications are usually dose dependent and disappear when the medication is discontinued. However, in some cases it is maintained after suspension.[4,13]

Prediction and prevention of food-drug interactions: multidisciplinary strategy

Most of the studies found in the bibliography agree that the key point to preventing undesirable interactions is knowing them. The better known the mechanism of action of the interaction between the drug and the food and the composition of the latter, the better it can be prevented and avoided.

For the knowledge of AMI whose consequence is pharmacological, we have very useful tools provided by drug regulatory agencies such as the European Medicines Agency (EMA) and specifically in Spain the Spanish Agency for Medicines and Health Products (AEMPS). The technical data sheet and the prospectus are the official documents approved by the AEMPS for each marketed drug, aimed at the doctor and the patient respectively. They include the appropriate form of administration of the drug indicating whether it should be taken on an empty stomach or the time of separation from food or if caution must be exercised with any specific food.[14]

Suspected clinically relevant adverse reactions due to AMI must be reported by professionals and / or the patient himself to the Spanish Pharmacovigilance System through the yellow card notification system.[6]

Likewise, the European Working Group on the Efficacy of Medicines (Efficacy Working Party) of the European Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) has prepared the "Guideline on the investigation of drug interactions".[15] This guide specifies the need to carry out pharmacokinetic studies of the influence of food intake in all investigational drugs. However, as in the documents prepared by the AEMPS, interactions are studied at the pharmacological level, not incorporating studies at the nutritional level.

No official documents of the type of technical sheets or leaflets have been found, in which the IMA whose consequence is nutritional are registered. It would be very useful to have guides prepared by the regulatory agencies for medicines and foods, in which the interactions with nutritional and clinical relevance are collected, subject to a periodic and systematic update.

The second point to adequately manage interactions and which is also collected in the bibliography, is the coordinated work of professionals involved in health and nutrition: doctor, pharmacist and dietician-nutritionist.[6]

It is important that the doctor, when prescribing a drug to the patient, is aware of the potential interactions that may affect the nutritional status of the patient or compromise the therapeutic efficacy of the drug.

The dietitian-nutritionist is the professional who can provide knowledge of the necessary and appropriate diets in the event that the drug affects the nutritional status. Likewise, it is an important link in advising the patient on maintaining the diet without sudden changes that may reduce the effectiveness of a treatment. The pharmacist is another link in the chain, who provides knowledge on how to take the medicine in relation to food (on an empty stomach, excluding certain foods...), to guarantee therapeutic efficacy avoiding adverse effects. It is important that the three links in the chain are interrelated, since in this way it is possible to provide the patient with the coordinated and necessary information to guarantee their health and adequate nutritional status.[16]

Selection and justification of study drugs

To carry out the project, drugs that have interactions with food from a nutritional point of view have been selected. In this selection, the drugs with the highest consumption and with interactions of greater nutritional relevance have been taken into account.

Table 3 shows the therapeutic subgroups of drugs most consumed in Spain at the primary care level, according to the Anatomical Therapeutic Chemical (ATC) classification, according to the 2018 annual report of the Pharmaceutical Benefit of the National Health System.[16]

Chemical Subgroup ATC4	No. Containers (thousands)	% containers/total	% increase in containers 2017/2016	DHD
A02BC Antiulcer: Proton pump inhibitors	66.671,1	7,1	-3,6	117,8
C10AA Lipid-lowering agents: HMG CoA reductase inhibitors	58.712,4	6,2	0,0	101,4
N05BA Anxiolytics: benzodiazepine derivatives	52.634,8	5,6	0,1	55,7
N02BE Analgesics and antipyretics: Anilides	38.346,9	4,1	1,6	24,9
B01AC Inhibitors of platelet aggregation, excluding heparin	30.883,0	3,3	-1,9	54,1
M01AE Anti-inflammatories: propionic acid derivatives	27.130,7	2,9	-3,2	25,8
C09AA ACE inhibitors, mono-drugs	23.827,4	2,5	1,8	69,6
N02BB Analgesics and antipyretics: pyrazolones	23.777,3	2,5	4,8	5,3
C09CA Angiostetin II antagonists, mono-drugs	21.304,6	2,3	0,6	52,1
N06AB Antidepressants: Selective serotonin reuptake inhibitors	19.828,4	2,1	1,0	48,4
N02AJ Opioid analgesics combined with other analgesics	19.258,6	2,0	3,6	10,0
C07AB Selective beta-blocking agents	17.931,1	1,9	7,5	18,5
C09DA Angiostensin II antagonists and diuretics	17.829,5	1,9	0,7	29,4
N06AX Other antidepressants	17.085,8	1,8	5,3	26,0
A10BA Hypoglycemic agents: Biguanides	16.062,0	1,7	-2,9	20,2

Table 3: Therapeutic subgroups of drugs most consumed in Spain at the primary care level. Annual report of the National Health System 2018. Observations: ATC = Anatomical, Therapeutic and Chemical Classification, Level 4: chemical subgroup. DHD = Population Dose Day. Ministry of Health, Consumption and Social Welfare. Alcantara information system.

Based on the bibliography and taking into account the drugs that belong to the groups that are most consumed, those used in chronic diseases have been selected, whose interactions affect the food or its components and that are more relevant at a nutritional level.

Table 4: Summarizes the sequential system followed for the selection of active principles.

Table 4: Selection criteria for study drugs. AP: active principle.

SEQUENCE	DRUG SELECTION CRITERIA
First	AP belonging to the most widely used pharmacological groups in Spain
Second	AP that produce interactions that affect food and its components and are used in chronic or prolonged treatments
Tercero	AP that originate interactions of greater nutritional relevance

Next, bibliographically argue and support the selection of therapeutic groups and drugs.

1. Antiulcer drugs: Proton pump inhibitors (PPIs)

PPIs are one of the most widely used therapeutic subgroups. In the report on the Pharmaceutical Benefit of the National Health System, it appears ranked number one in recent years.[16]

The active principles of this subgroup marketed in Spain are omeprazole, pantoprazole, esomeprazole, lansoprazole and rabeprazole, of which omeprazole and pantoprazole are the second and third most widely consumed active principles.[16] They act by reducing the amount of acid produced by the stomach and their most common therapeutic use is in the prevention and treatment of gastroduodenal ulcers and gastroesophageal reflux, among other pathological processes.

The decrease in the acidity of the gastric juice is related to the alteration in the absorption of certain nutrients, among which is cyanocobalamin or vitamin B12, vitamin C, calcium, magnesium and iron.

If there is no gastric acid, the release of vitamin B12 from dietary proteins does not occur and intestinal absorption of it does not occur due to a decrease in the intrinsic factor necessary for it. The presence of this vitamin is essential for the synthesis of nucleic acids, myelin and erythrocytes. Its deficit therefore can produce

various alterations such as palpitations, tingling, confusion, weakness and fatigue among others.[17,18]

Scientific evidence based on observational studies and on a systematic review and meta-analysis, supports the association between the use of PPIs for prolonged periods and vitamin B12 deficiency, as well as a dose-dependent relationship. Age is another potential risk factor since the elderly are more susceptible to vitamin B12 deficiency.[19,21]

It should be noted that some studies have not found an association between the use of PPIs and vitamin B12 deficiency.[22,23] All of this and in accordance with the recommendation of the American Gastroenterological Society.[24] leads us to think that prospective studies are needed over long periods of time to have more solid evidence. A decrease in acidity also affects the absorption of vitamin C, since dehydroascorbic acid, an oxidized form of ascorbic acid, is irreversibly hydrolyzed and cannot be absorbed, thus reducing plasma levels of vitamin C. This vitamin is essential in the formation and maintenance of bones, skin and connective tissue of blood vessels, tendons... Its deficit can cause weakness and pain in joints, dental fragility, gingivitis, poor wound healing...[4]

Calcium absorption occurs at the intestinal level through two mechanisms, passive diffusion and active transport. The decrease in acidity caused by PPIs, decreases the majority absorption that takes place in the duodenum by active transport. Systematic reviews and meta-analyzes of observational studies indicate that there may be a moderate increase in the risk of fracture with the use of PPIs, but there is no strong evidence of the effect of duration or dose-response.[25,26]

In the case of hypomagnesemia associated with the use of PPIs, the mechanism of action is unknown. It is an essential micronutrient for the proper functioning of the nervous and muscular system and its deficiency can cause drowsiness, weakness, muscle cramps, seizures ... In most studies, a greater association is found in the case of prolonged treatments, high age and women.[27,28] A systematic review and meta-analysis of observational studies found that hypomagnesemia can vary between PPIs, being higher with pantoprazole and lower with esomeprazole.[29]

There is also evidence that PPIs negatively affect the absorption of iron from the diet. Since most of the iron in the body is found as part of the hemoglobin of erythrocytes, its deficiency is the main cause of anemia.[30]

Iron in the diet is available in two forms: heme iron (ferrous) and non-heme iron (ferric). Ferrous iron is found primarily in animal products, makes up about 30% of our total iron intake, and is easily absorbed. Ferric iron, which is found in foods of plant origin, to be absorbed must be previously transformed to its ferrous form, for which it needs an acid medium.[13]

PPIs cause a decrease in absorption mainly related to ferric iron, which is the main form of iron in the diet. Groups with limited consumption of meat or foods of animal origin have a greater risk factor for iron depletion when they are on long-term treatment with PPIs. People with low iron levels prior to the start of PPI therapy are considered a risk population, since in healthy individuals the absorption of ferrous iron is sufficient to cover daily needs but in patients with iron deficiency it is not.[13,30]

Based on the evidence, it can be considered that where the use of PPIs may have greater nutritional relevance is in the elderly population with pathologies in which high doses are necessary and for long periods. Table 5 shows the interactions of PPIs on nutrients.

Table 5: Interactions of PPIs on nutrients and risk factors. PPIs, Proton Pump Inhibitors; Faith, iron; (1): Population considered at risk only for the decrease in iron absorption.

Pharmacological group	Drug	Nutrient affected	Effect on nutrient	Risk factors/population
PPIs	Omeprazole Pantoprazole Esomeprazole Lansoprazole Rabeprazole	Vitamin B_{12} Vitamin C Calcium Magnesium Iron (1)	↓absorption ↓absorption ↓absorption ↓absorption ↓absorption	Older age Time with PPIs Gastric pathology Vegetarians (1) Previous Fe deficiency (1)

2. Lipid-lowering drugs. HMG CoA reductase inhibitors: Statins

The pharmacological group of inhibitors of the enzyme 3-hydroxy-3-methyl-glutaryl-CoA reductase (HMG CoA reductase), better known by the name of statins, occupies the second place of the therapeutic subgroups most consumed in Spain.[16] Of the statins marketed, atorvastatin is the most widely consumed active ingredient in Spain and simvastatin is among the 20 most consumed active ingredients, according to the latest data published and available from the Ministry of Health, Consumption and Social Welfare.[16]

Its mechanism of action consists basically in the inhibition of HMG CoA reductase, which is responsible for the conversion of 3-hydroxy-3-methyl-glutaryl-coenzyme A into mevalonic, which is a precursor of cholesterol. By reducing cholesterol and lipid levels in the blood, they are used in the prevention of cardiovascular and coronary diseases, a highly prevalent pathology and a high risk of morbidity and mortality.

Despite being effective drugs in these pathologies, myopathies constitute a potentially serious adverse effect that can range from simple myalgia to severe rhabdomyolysis. These symptoms have been associated with statin-induced depletion of coenzyme Q10 (CoQ10) and concomitant vitamin D deficiency.[13]

The administration of statins can reduce the serum levels of CoQ10, a fat-soluble compound similar to vitamins, present in the cells of the human body, which is obtained from the diet and endogenous synthesis. It is part of the electron transport chain in mitochondria and therefore plays an important role in energy metabolism.[4]

The decrease in serum levels of CoQ10 when administering statins is due to the fact that it is an intermediate product in the mevalonic pathway, a pathway that is inhibited by HMG CoA reductase inhibitors. This effect has also been shown to be dose dependent.[4]

It is unknown whether serum CoQ10 levels necessarily reflect significant changes at the muscle level; However, it has been seen that in elderly patients the risk of decreased muscle CoQ10 is greater. Some studies have found that the decrease in CoQ10 is related to exercise intolerance and myalgia and that its supplementation reduces myopathy associated with statin treatment.[31]

There is controversy between the relationship between the use of statins and the impact on vitamin D levels, and the mechanism of the interaction and the effect on the levels is currently unknown. It has not been possible to compare the levels of 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D obtained in different studies due to the existence of confounding factors related to diet, supplementation, sun exposure.[32]

Results obtained from various studies are consistent in that patients with statin-induced myopathy have lower levels of vitamin D than asymptomatic patients. However, the results are not yet conclusive and more extensive prospective studies are needed.[13]

Table 6 shows the interactions of statins at the nutritional level.

Table 6: Interactions of HMG CoA reductase inhibitors: Statins, on nutrients. HMG CoA, 3-hydroxy-3-methyl-glutaryl-coenzyme A; CoQ10, coenzyme Q10; (1): Advanced age and High dose are risk factors related to a decrease in CoQ10; (2): Patients with statin-associated myopathy have lower levels of vitamin D.

Pharmacological group	Drug	Nutrient affected	Effect on nutrient	Risk factors/population
HMG CoA reductase inhibitors: Statins	Atorvastatin Simvastatin Fluvastatin Lovastatin Pitavastatin Pravastatin Roxuvastatin	CoQ10(1) Vitamin D(2)	↓ serum levels ↓ endogenous production ↑/ ↓ serum levels	Old age (1) High dose (1) Statin-associated myopathy (2)

3. Antidepressants

The group of antidepressants is subdivided into several subgroups with different mechanisms of action. This group has been selected because in addition to being depression the most prevalent mental health pathology, it includes the subgroup of selective serotonin reuptake inhibitors (SSRIs), which is among the 10 most used.[16] and monoamine oxidase inhibitors (MAOIs) as they are one of the first known interactions with clinical repercussions.[3]

MAOIs are drugs that will affect the absorption and use of biogenic amines (tyramine, histamine) found in fermented foods such as cheese, wine ... By inhibiting oxidative deamination, these amines accumulate and are responsible for the increase in drug effect. This potentiation of the effect may have clinical relevance since the increase in amines can produce hypertensive crisis.[3,7]

It should be noted that the use of MAOIs at present is not relevant, most of them are no longer marketed and have been displaced by safer antidepressants such as tricyclics or SSRIs.

Some of the antidepressants are associated with loss of appetite, such as moclobemide (MAOI).[33] and fluoxetine (SSRI).[11,34] The latter is also associated with short-term weight loss, generally regain weight after 6 months of treatment.[11,34]

However most SSRI antidepressants are associated with weight gain. Despite the fact that they are selective serotonin reuptake inhibitors, anorectic action would be expected, it seems that this inhibition is not entirely selective, so that by acting on other neurotransmitters it cancels this anorectic action. On the other hand, weight gain is associated with a multifactorial origin related to the improvement of the depressive process, such as increased sleep patterns and regaining lost weight.

Uguz et al.[11] found that 40.6% of the patients had a weight gain of 7% or more with citalopram, escitalopram, sertraline and paroxetine, in contrast to fluoxetine. Short-term and long-term studies suggest

strong associations between the use of these antidepressants and weight gain. Some studies have found that weight gain is greater during the second and third year of treatment.[35]

In the systematic review and meta-analysis by Khanassov et al.[36] numerous studies show a significant association between the use of SSRIs and the risk of osteoporosis, finding that the risk of fracture is dose and duration dependent. Complementary studies are needed to assess the efficacy of calcium and vitamin D supplementation together with SSRIs, on bone mineral density (BMD) and the risk of fracture.

Table 7 shows the interactions of some antidepressants at the nutritional level.

Table 7: Alterations related to nutritional status produced by antidepressants. MAOI, Monoamine Oxidase Inhibitors; SSRIs, Selective Serotonin Reuptake Inhibitors; (1): Fluoxetine is associated with loss of appetite and weight; (2): Fluvoxamine, Paroxetine, Citalopram, Escitalopram, Sertraline, are associated with weight gain.

Pharmacological group	Drug	Alterations related to nutritional status Impact	Repercussion
MAOI	Moclobemide	↑ serum amine levels (with foods rich in biogenic amines: aged cheeses, wine ...) ↓ Appetite	Hypertensive crisis Anorectic state
SSRI	Fluoxetine (1) Fluvoxamine (2) Paroxetine (2) Citalopram (2) Escitalopram (2) Sertraline (2)	↓ Appetite (1) ↓ Weight (1) ↑ Weight (2) ↓ Calcium / vitamin D	Anorectic status Obesity risk Osteoporosis Risk

4. Antihypertensives: Angiotensin-I converting enzyme (ACE) inhibitors

ACEIs are among the ten most widely used pharmacological groups.[16] They are indicated in arterial hypertension, heart failure, myocardial infarction and diabetic nephropathy. The drugs marketed in Spain belonging to this group are: captopril, cilazapril, enalapril, fosinopril, lisinopril or trandolapril Long-term treatment can cause alterations in the sense of smell or taste, this effect being more pronounced with captopril than with enalapril or other ACE inhibitors. Despite these differences, a class effect is suggested that is related to angiotensin II inhibition, decreased serum zinc, and increased urine zinc.[13] In the specific case of captopril, hypogeusia or decreased flavor appreciation seems to be related to a radical with a thiol group present in the molecule that can chelate zinc in serum and increase its excretion. In some people, ageusia or absolute loss of taste even occurs temporarily. Likewise, cases of dysgeusia with a constant unpleasant metallic, bitter or salty taste have been described.[4,13] Taste alterations due to medications are usually dose dependent and disappear when treatment with the medication is discontinued. However, in the case of captopril, it is sometimes maintained after discontinuation, although the most common is that they occur in the first months of treatment and disappear without the need to withdraw the drug.[4,13] ACE inhibitors can cause retention of potassium in the kidney through their inhibitory effect on aldosterone secretion. Factors that may contribute to an increased risk of hyperkalemia have been identified, including older age, diabetes, heart failure, kidney disease, use of potassium-sparing diuretics, potassium supplements, or potassium-rich diets.[37]

Table 8 shows the interactions of ACEI drugs at the nutritional level.

Table 8: Alterations related to nutritional status produced by the group of antihypertensive inhibitors of the angiotensin-I converting enzyme. ACEI, Angiotensin-I converting enzyme inhibitors; (1): The decrease in serum zinc is related to taste disturbances.

Pharmacological group	Drug	Nutrient affected	Alterations	Risk factors/population
ACEI	Captopril Cilazapril Enalapril Fosinopril Lisinopril Trandolapril	↓ Serum zinc(1) ↑Zinc in urine ↑ Serum potassium	Smell and taste disturbances (1): Hypogeusia Dysgeusia Ageusia	Old age Diabetes Heart failure Kidney disease K-sparing diuretics Potassium supplements Potassium-rich diets

Justification

Interest arises from the high frequency of AMI potentials.[4,6] coupled with the few measures in practice to detect and avoid them.

Currently, a large number of drugs are available, with the therapeutic arsenal growing. The population has a longer life expectancy, with a high proportion of the multipathological and polymedicated elderly population receiving chronic treatments. All this contributes to the potentially very high number of interactions.[4,9]

The bibliography reveals that drug interactions that affect food are little studied and known by dietitians-nutritionists and by other health-related professionals.[4,6,9] The lack of consensual guidelines and protocols for application in nutritional and clinical practice makes it difficult to correctly manage these types of interactions. All of this may have an impact on the lack of transmission to the patient of some recommendations that may be important to properly take certain medications in relation to food.[6] Not all interactions are negative, but it must be taken into account that in some cases they can be negative and they can be nutritionally relevant.[4,5,9,13] It has been considered that the Community Pharmacy Office (OFC) can be an ideal place to find out about the medications that the population is taking, and to detect interactions.

The main orientation of this project is that the dietitian-nutritionist gives the patient the necessary information to properly maintain their nutritional status and that it is not altered by the intake of medications that, used chronically, can alter it.

OBJECTIVES

Design an education program aimed at users of a pharmacy who are under chronic treatment with drugs that interact with food, to avoid negative repercussions that affect their diet and nutritional status.

- Evaluate the degree of knowledge of patients about the influence that the pharmacological treatment they receive can have on their diet and nutritional status.
- Carry out an individualized dietetic-nutritional education, to prevent drugs from negatively affecting their nutritional status, reinforcing education in eating habits and a healthy life based on the pathology and drug.
- Carry out an individualized monitoring plan for each patient to detect any type of incidence and reinforce motivation and adherence to the proposed educational plan.

METHODOLOGY

1. Ethical and legal requirements. The treatment of sensitive personal data that affect health-related areas is subject to the duty of confidentiality and professional secrecy. In this sense, the realization of this project will comply with the fulfillment of Regulation (EU) 2016/679 of the European Parliament and of the Council of April 27, 2016 regarding the protection of natural persons with regard to data processing personal data and the free circulation of these data (RGPD) (38) and Organic Law 3/2018, of December 5, on the protection of personal data and guarantee of digital rights (LOPD-GDD) (39).

The user will be guaranteed confidentiality and will be informed of the personal data that will be collected to carry out the project.

2. Selection of patients, inclusion and exclusion criteria. The population targeted by the project will be made up of users of the urban OFC, which serves a population of around 2,500 inhabitants. The selection of patients is made according to the following inclusion and exclusion criteria.

Inclusion criteria

OFC user patient, of legal age, being treated with one of the drugs selected in the project (Table 9).

- User of the OFC, of legal age, responsible for the medication of a patient who is being treated with a drug from those selected in the project (Table 9), justifying the link between her and the patient.
- Acceptance to participate voluntarily and freely in the project.
- Signature of the informed consent.

Exclusion criteria

- Does not meet the inclusion criteria.
- Cessation of the use of drugs or changes in the prescription before completion.

Table 9: Active ingredients included. PPIs, Proton Pump Inhibitors; MAOI, Monoamine Oxidase Inhibitors; SSRIs, Selective Serotonin Reuptake Inhibitors; ACEI, Angiotensin-I converting enzyme inhibitors.

Pharmacological group	Active Ingredients
Antiulcer PPIs	Omeprazole Pantoprazole Esomeprazole Lansoprazole Rabeprazole
Lipid-lowering drugs: Statins	Atorvastatin Simvastatin Fluvastatin Lovastatin Pitavastatin Pravastatin Roxuvastatin
Antidepressants: MAOIs	Moclobemide
SSRI	Fluoxetine Fluvoxamine Paroxetine Citalopram Escitalopram Sertraline
ACE inhibitors	Captopril Cilazapril Enalapril Fosinipril Lisinopril Trandolapril

3. Personal, material and financial resources

Personal equipment. The central professional of the project is the dietician-nutritionist. He will be in charge of detecting and correcting AMI that affect aspects related to food and nutrition. They will be responsible for carrying out individualized nutritional education in these patients, to prevent the drug from negatively affecting their nutritional status. Likewise, it will reinforce education in eating habits and lifestyle based on the pathology and drug.

However, it is a project in which three types of professionals are involved: medical, pharmacist and dietician-nutritionist. This fact of being multidisciplinary, gives it added value since it allows educating and informing the patient from a more comprehensive perspective. The pharmacist collaborates in the project directly, since he will inform the patient of the aspects related to the correct taking of the drug in relation to food from the pharmacological point of view.

Although the doctor does not collaborate directly in the project, as he is the prescriber of the drugs involved, he is indirectly related. The prescription of the patient includes the professional data of the doctor, which allows contact with him in the occasions that by affecting the health of the patient, it is considered necessary.

Material resources. At the OFC, there is a closed space, separate from the dispensing area, in which individualized education will take place. The existence of this space that guarantees privacy is essential to carry out this project since health-related aspects constitute sensitive information and it is necessary to safeguard confidentiality.

The office has the necessary computer and bibliographic resources to be able to carry out the activities related to the project.

Documentary material. The following documents are necessary to carry out the project:
Project information and informed consent
Patient file containing the following information:

- Personal information.
- Data related to the pathology and medication.
- Data of nutritional interest, eating habits and lifestyle.
- Degree of knowledge of the patient about the impact of the drug on a nutritional level.

Assessment questionnaire with which it is intended to know

- Degree of compliance.
- Degree of satisfaction.

Educational material: Information sheets for the patient Drug-Food. One of the key points of the project is the educational support material that will be delivered to the patient. This material consists of an information sheet for the patient on how to properly take the drug in relation to food, avoid negative nutritional repercussions and improve dietary and lifestyle habits.

The file is prepared based on the bibliographic arguments of each pharmacological group included in the justification section. It collects information adapted to any user independent of their nutritional or pharmacological training or knowledge. In this information sheet, general questions will be answered in a clear and simple way but whose answer is different depending on the drug. Some of them are shown below:

- Can the medicine affect my nutritional status?
- What foods can be recommended to improve my nutritional status?
- How do I reduce the problem of loss of appetite?
- Do I have to eliminate any food or drink from the diet?

Likewise, specific questions will be answered depending on the specific pharmacological group and the relevant nutritional aspects will be reported in each case.

Economic resources. The performance uses the infrastructure of the OFC in which it is to be performed, taking advantage of its material resources and the presence of a dietitian-nutritionist incorporated into the OFC staff. This fact makes the project economically viable for the OFC.

However, in tables 10 and 11, the estimate of the specific cost that will affect the realization of this project is detailed.
During the year the project lasts, it is estimated that the number of patients who will be seen by the dietitian-nutritionist is 120, an average of 2 per day.

The number of consultations per patient is 4 (1 initial, 2 follow-up and 1 evaluation). The average duration of the sessions is estimated to be 45 minutes for the initial consultation and 15 minutes for the follow-up and evaluation consultations. The daily estimate of the time devoted by the dietician-nutritionist to this project will therefore be higher during the first three months in which the initial consultations of the 120 patients will be carried out and will be reduced in the 9 months in which the consultations will be carried out. monitoring and evaluation.

In carrying out the initial 120 consultations, considering an average of 45 minutes per patient, an average of 90 hours will be used. In carrying out the 360 follow-up and evaluation consultations, considering an average of 15 minutes per consultation, an average of 90 hours will be used.

Based on this estimate, the average time spent by the dietitian-nutritionist in each patient is 1.5 hours, which means a total average time of 180 hours per year, which is equivalent to an average of 15 hours per month. The

monthly cost estimate is made assuming that the dietician-nutritionist uses an average of 15 hours per month of the contractual time in carrying out the project. Considering a salary of € 1.200/month, the impact of said salary on the time dedicated to the project would be € 100/month.

Table 10: Estimated cost in human resources. D-N, Dietitian-nutritionist; C, query; pcte, patient.

Personnel	No. Consultations	No. Consultations	Time	Cost
D-N	Mean: 2 patients/day Total: 120 patients	1 Initial C / pcte 2 C Follow-up / pcte 1 C Evaluation / pcte Total: 480 consultations	Average: 45 min (Initial C / pcte) 45 min (2C Follow-up + 1C Evaluation / pcte) Total: 180 h (15 h / month)	€ 100 / month Total: € 1,200 / year

Table 11: Estimated cost of material resources. OFC. Community pharmacy office.

Material resources	Cost
Office for interviews, education and consultations	Available at OFC
Computer, printer, computing resources and stationery resources	Available from OFC
Documentary material: Patient files, Questionnaires…	75 €
Educational material delivered to the patient: Information sheets …	100 €

The estimated cost of this project represents a total of € 1.200 for the OFC in human resources and € 175 in material resources, that is, a total of € 1,375, which would be equivalent to € 140 per month.

4. Procedure. The circuit begins when the user accesses the OFC with a prescription for one of the active principles included in Table 9. The procedure is carried out in a personal and individualized way for each patient.

-Initial phase. An initial informative interview is carried out in which the patient is invited to participate in the project. You are informed that the objective is educational and that its purpose is to prevent the drug from negatively affecting your nutritional status and to reinforce healthy eating and lifestyle habits.

If the patient agrees to participate in the project, they can join and make the first consultation, immediately or make an appointment as soon as possible. In this first consultation, the Informed.

Consent is provided for you to read and sign, and the Patient File is filled out. The degree of knowledge of him is evaluated to avoid potential interactions that negatively affect his diet and nutritional status. Likewise, the education is provided orally, answering the questions or doubts that they raise and the drug-food information sheet is given.

Follow-up phase. Three and six months after the initial consultation, the patient is summoned for two follow-up consultations. The objective of these is to check if the patient follows the indicated plan, detect any problem that may have arisen and reinforce her motivation and adherence.

Evaluation phase. Nine months later, a final consultation is completed in which the patient performs a Compliance and Satisfaction Assessment Questionnaire.

5. Temporalization and schedule. The patient inclusion period takes place during the first three months. In these three months, therefore, the 120 initial consultations will be carried out, at an average of 2 daily.

It will be carried out individually for each patient during a period of nine months from their inclusion in the same until the end.

Two follow-up consultations will be carried out in the third and sixth months of the initial consultation and an evaluation consultation in the ninth month to assess the degree of compliance and satisfaction. Given that patients are being incorporated throughout the first three months, the total duration of the project will be one year. Given that each patient attends four consultations, the total number of consultations made in the year is 480, which is equivalent to an average of 40 consultations per month or 2 consultations per day (assuming the exclusion of the days of the month corresponding to days rest and holidays).

6. Development of the project according to the pharmacological group. The educational work, the follow-up and the evaluation of each patient will be carried out in a personal and individualized way. However, there is basic and general information that should be given to every patient for each specific drug. Next, the general aspects to be taken into account when preparing the patient file and the drug-food information sheet will be presented, depending on the pharmacological group or type of drug. This does not exclude that if the patient demands more information or another level of it, it will be provided.

Antiulcer: Proton pump inhibitors (PPIs)

As already indicated in the justification for the selection of PPIs, this pharmacological group, in chronic use, can produce deficits in the absorption of vitamin B12, vitamin C, calcium, magnesium and iron.[17-30]

Patient file under treatment with PPIs: general aspects

In the file that is prepared for each patient, it is important to collect all the factors considered to be risky. The age of the patient, the time of use of the drug, the dose and the digestive pathology will be collected. The decrease in micronutrients is generally greater when the time of use is prolonged and the patient has a digestive pathology that requires high doses. Another aspect that is important to collect is if the patient presents any condition with iron deficiency, indicating if he is a vegetarian or if he eats little animal food. If the patient has analytical data, at least those related to plasma levels of vitamin B12, calcium, magnesium and iron will be included.

Information sheet for PPIs: general aspects.

The basic information that the patient who begins or is on chronic oral treatment with omeprazole, pantoprazole, esomeprazole, lansoprazole or rabeprazole, should answer the following questions:

- **How does the drug work?.** It works by reducing the amount of acid produced by the stomach and thus prevents and treats gastroduodenal ulcers, gastroesophageal reflux and other digestive diseases.
- **How should I take it, with food or without food?**. If you have to take it once a day it is advisable to take it first thing in the morning half an hour before breakfast. Swallow it whole with the help of a glass of water. In the specific case of Esomeprazole, it can be dispersed in water if you cannot swallow it or if you are using a nasogastric tube.
- **Can it affect my nutritional status?.** Taking the drug for long periods (more than 6 months) can decrease the absorption of some micronutrients from foods such as magnesium, calcium, iron, vitamin B12, and vitamin C.
- **What foods can be recommended to improve my nutritional status?.**

Foods rich in magnesium: chard, spinach, sunflower seeds, wheat bran, almonds, cashews, peanuts….
Foods rich in calcium: dairy, sardines, nuts, green vegetables ... especially if it presents risk factors for the development of osteoporosis.
Foods of animal origin rich in iron and vitamin B12: beef or lamb type meats and organ meats (kidneys, liver), fish and shellfish (sardines, herring, mackerel, salmon, clams...).
Foods rich in vitamin C: fruits (kiwi, orange, lemon, papaya, strawberry,,,), vegetables (broccoli, Brussels sprouts, red pepper ...)

• **Is it advisable to carry out an analytical test to assess my nutritional status?.** If you are in chronic treatment for more than 6 months, it may be advisable to perform periodic control tests to measure your levels of magnesium, calcium, iron, vitamin C and vitamin B12. Depending on the analysis, it will be recommended if adequate supplementation is necessary.

There are two aspects that should not be forgotten in the case of PPIs, as they may be nutritionally relevant: To alleviate or try to avoid iron deficiency, the recommended foods are those that have iron in the ferrous form, that is, foods of animal origin.[13,30]

The use of foods rich in vitamin B12 can contribute to reducing the deficit of vitamin B12. If it already exists, it cannot be resolved by eating more foods that contain it, since the lack of acidity prevents vitamin B12 from being released from food and absorbed. This does not happen with the foods that are enriched in this vitamin since in this case it does not have to be freed of the proteins of the foods; These foods enriched in vitamin B12, depending on the type of deficiency, can constitute an alternative to the administration of vitamin B12 intramuscularly.[17,18]

Hypolipemic agents. HMG CoA reductase inhibitors: Statins

The inclusion of patients undergoing statin treatment in the project places us especially in situations in which the presence of the dietitian-nutritionist is of great relevance. The contribution in aspects related to diet and healthy life are essential in the normalization of hypercholesterolemia and lipid disorders.

File of the patient in treatment with Statins: general aspects.

Aspects related to eating and living habits will be collected in the patient's file. Likewise, the age and dose of the drug will be collected, since advanced age and high dose are risk factors related to a decrease in coenzyme Q10.

If the patient has analytical data, at least those related to lipid profile, CoQ10 and vitamin D will be collected.

Likewise, it will be included if the patient presents myalgia or muscular discomfort associated with the use of statins. As seen in the selection of drugs, although the mechanism is unknown, patients with statin-induced myopathy have lower levels of vitamin D.

Information sheet for Statins: general aspects

In the case of statins, we find an interaction between the drug and the food in both directions. The drug can affect nutritional status.[4,13] and food can affect the drug.[14] Therefore the patient will be informed of both aspects. The nutritionist will give education in the nutritional field and the pharmacist in the pharmacological field. The basic questions to be answered are as follows:

• **How does the drug work?**. The drug belongs to the group known as Statins that act by lowering cholesterol and lipid levels in the blood.

• **How should I take it?.** With food or without food? You should take the medicine whole, without crushing it with a glass of water. You can take it with or without food, as it does not interfere with its absorption. Always take it at the same time of day, preferably at night or at

bedtime, which is when cholesterol is primarily synthesized.

• **Can it affect my nutritional status?.** Taking statins chronically can lower blood levels of coenzyme Q10, a vitamin-like compound, which is involved in the metabolism of most of our cells.

• **What foods can be recommended to improve my nutritional status?.** Including in your diet, three days a week fish and nuts or seeds (pistachios, walnuts, sesame seeds...) and daily five fruits or vegetables (strawberries, oranges, cauliflower, carrots, broccoli, spinach...), can increase the CoQ10 levels.

• **What dietary and lifestyle recommendations can improve the lipid profile?**. In case of overweight, reduce it with a hypocaloric diet. Use olive oil and avoid coconut and palm oils (present in precooked, fried and pastries). Use little oil in cooking, preferably grill and grill and avoid fried and stews. Use salt in moderation. Increase the consumption of white fish and especially blue fish (tuna, sardines, trout, mackerel, salmon ...). Reduce the consumption of red meat, eggs, whole milk and derivatives. Avoid drinking alcohol. Avoid smoking. Perform physical exercise on a regular basis.

• **Do I have to eliminate any food or drink from the diet?**. To answer this question, it should be noted that not all statins behave the same in relation to food. In general, the following differentiation is established:

1. **Simvastatin, Atorvastatin and Lovastatin**: While being treated with any of these three statins, you should avoid taking grapefruit juice at any time of the day. Grapefruit juice in large quantities increases the levels of these drugs in the blood, which may increase their adverse effects and toxicity.[14]
2. **Fluvastatin, Pitavastatin, Pravastatin and Roxuvastatin:** They do not interact with grapefruit juice. Therefore, they can be the alternative for people who cannot eliminate this drink from their diet.[14]

In this group of drugs, the dietitian-nutritionist will carry out nutritional education, reviewing and improving her diet and lifestyle with the patient. It will emphasize the interaction of the statin with food, especially in relation to the decrease in CoQ10, which may be related to myalgia and exercise intolerance.[31] Since these are patients with hyperlipidemia, foods rich in CoQ10 such as red meat should be avoided, recommending nuts, seeds or fish. It is expected to achieve normalization of CoQ10 with the diet in most patients, without having to use supplementation

Antidepressants

Moclobemide (MAOI) and SSRIs are drugs that will affect appetite and weight. Moclobemide and fluoxetine are associated with decreased appetite (33, 34). In the case of citalopram, escitalopram, fluvoxamine, paroxetine and sertraline, due to the fact that they are selective serotonin reuptake inhibitors, an anorectic action would be expected, but it seems that by acting on other neurotransmitters this action is nullified. Weight gain is variable, some studies estimate around 7% or more.[11] However, in clinical practice, patients have the feeling that they are gaining more weight.

In this type of drug, the educational support by the dietician-nutritionist will be very oriented to the aspects of appetite and weight. In the cases that require it, a dietary support will be carried out.

Patient file on antidepressant treatment; general features

The role of the dietitian-nutritionist in this type of patient is important, since it is estimated that in weight variation there are factors other than the use of the specific medicine, related to lifestyle and eating habits that may be conditioned by the depression itself. It is important to record it in the patient file. Information.

Sheet for Moclobemide

The basic questions to be answered in the drug moclobemide are the following:

- **How does the drug work?.** It is an MAOI-type antidepressant that increases the levels of neuronal transmitters, thus improving depression.
- **How should I take it, with food or without food?.** Take it after meals with a little liquid.
- **Can it affect my nutritional status?.** This medicine does not change the absorption or use of nutrients, but it may cause a decrease in appetite.
- **How do I reduce the problem of loss of appetite?.**

Some suggestions that can help you are:
Eat smaller but more frequent meals.
Establish a meal plan and stick to it.
Drink liquids before or after meals, not at meals.
Do not eat foods high in fiber or high satiating power.
Eat foods with high nutritional power.
Get regular physical exercise.

• **Do I have to eliminate any food from the diet?.** You should avoid eating foods rich in amines (in amounts greater than 100 grams in a meal) and especially if you have high blood pressure as it could cause a hypertensive crisis.

Foods rich in amines include aged cheeses, fish pickles, cold cuts, meat and yeast extracts, caviar, beans, chocolate, chicken and beef livers, figs, and large amounts of beverages such as wine, beer, tea, or coffee.

Avoid taking tyramine-rich foods simultaneously for the duration of treatment and three weeks after treatment.

Information sheet for Fluoxetine

The basic questions to be answered in the drug fluoxetine are the following:

• **How does the drug work?.** Fluoxetine is an antidepressant that inhibits serotonin reuptake by increasing levels of this neurotransmitter and thus

improving depression and obsessive-compulsive disorders.

• **How should I take it, with food or without food?**. You can take it with or without food.

• **Can it affect my nutritional status?.** This medicine does not change the absorption or use of nutrients, but it may cause a decrease in appetite and weight loss.

• **How do I reduce the problem of loss of appetite?.** Some suggestions that can help you are:

Eat smaller but more frequent meals.

Establish a meal plan and stick to it.

Drink liquids before or after meals, not at meals.

Do not eat foods high in fiber or high satiating power.

Eat foods with high nutritional power.

Get regular physical exercise.

Reduce the consumption of coffee and tobacco.

• **Do I have to eliminate any food or drink from the diet.** You should not take it with alcohol.

Information sheet for other SSRIs

The basic questions to be answered in other SSRI drugs: citalopram, escitalopram, fluvoxamine, paroxetine and sertraline are the following:

• **How does the drug work?.** It is an antidepressant that inhibits the reuptake of serotonin by increasing its levels and thus improving depression and obsessive-compulsive disorders.

• **Can it affect my nutritional status?.** This medicine does not change the absorption or utilization of nutrients, but slight weight gain may occur in some people.

• **How can I prevent the problem of weight gain?.** Some suggestions that can help you are:

Eat fruits and vegetables several times a day.

Reduce the consumption of foods high in simple sugars and saturated fats.

Consume low-fat milk and dairy.

Respect schedules and be methodical with meals.

Avoid sedentary life and do physical activity on a regular basis.

Check your weight weekly.

• **Do I have to eliminate or add any food to the diet?.** You should not take it with alcohol.

Anti-hypertensive: Angiotensin-I converting enzyme (ACEI) inhibitors

A class effect of ACE inhibitors is depletion of zinc levels and increased potassium levels. The decrease in serum zinc in the body has also been related to the alterations produced in the senses of taste and smell. These aspects can lead to nutritional problems not only due to the deficit itself, but also due to a poor diet due to the fact that the intake of some foods can be unpleasant. The dietitian-nutritionist will offer guidelines to help alleviate and solve these problems.

An added aspect is the fact that arterial hypertension is a pathology in which the dietitian-nutritionist can have a relevant role. As in the case of patients receiving statins, in patients with ACE inhibitors, aspects related to diet and lifestyle are essential in maintaining a normalized and stable blood pressure.

Patient file on ACEI treatment: general aspects

In the patient's file, aspects related to eating and living habits will be collected, noting if there are problems with alterations in the smell or taste of food. Likewise, the dose and time of use of the drug and if it presents cardiovascular pathologies will be collected. If the patient has analytical data, at least those related to zinc, potassium and blood pressure measurements will be collected.

Information sheet for ACEI

The basic information that the patient who initiates or is on chronic oral treatment with captopril, cilazapril, enalapril, fosinopril, lisinopril or trandolapril must answer the following questions.

• **How does the drug work?.** It is an antihypertensive that belongs to the group of angiotensin converting enzyme I (ACE) inhibitors. It works by relaxing blood vessels and thereby reducing blood pressure, improving some heart or kidney pathologies.

• **Can it affect my diet?.** Sometimes the drug can cause changes in the smell or taste of food. It may not appreciate the flavors or that it appreciates them in an unpleasant metallic type, intense sweet ... In a few months it usually disappears.

• **How can I reduce smell and taste alterations?.** Some suggestions that can help you are:

Take cold foods as they generate less odors.

If you don't appreciate the flavors, use more spices but not more salt or sugar.

If you appreciate a metallic taste, use plastic cutlery and avoid canned food.

Sucking on ice during a meal makes the taste buds numb.

Carry out good hygiene, rinsing and brushing the teeth, tongue and oral cavity.

• **Can it alter my nutritional status?. What foods should I eat or avoid?**. It can decrease the level of zinc in the blood, necessary for the immune system:

Some foods rich in zinc are: meat, seafood, chocolate, almonds, hazelnuts, brown rice, cereals ...

It can increase potassium levels in the blood. Some dietary tips to reduce potassium in the diet are:

Soak legumes, vegetables, potatoes ..., changing the water after two or three hours.

Discard the cooking water and do not use it in sauces or broths. Moderate foods rich in potassium: dietary salt, milk, coffee, whole foods, nuts, soups, bananas, oranges, strawberries ... Frozen foods have less potassium than fresh foods.

• **Some dietary and lifestyle recommendations to improve blood pressure**

In case of overweight, use a low calorie diet.

Avoid the consumption of alcohol and stimulating drinks (coffee, cola...).

Avoid smoking.

Perform physical exercise on a regular basis.

Live a relaxed life, stress can increase blood pressure.
Reduce foods with high salt content (precooked, fast food, prepared sauces, margarines,...)
Avoid seasoning with salt; To increase the flavor use techniques such as steaming, olive oil or other seasonings.

Methodology for project evaluation and data analysis

The measure of the degree of knowledge of the patient, the first objective of the project, will be obtained from the answers to the questions that will be formulated and collected in the first interview in the patient's file. As this questionnaire is carried out individually, it will allow us to adapt the education and information provided to the degree of knowledge.

Figure 2: Shows as an example some of the questions used to assess the degree of knowledge of the patient.

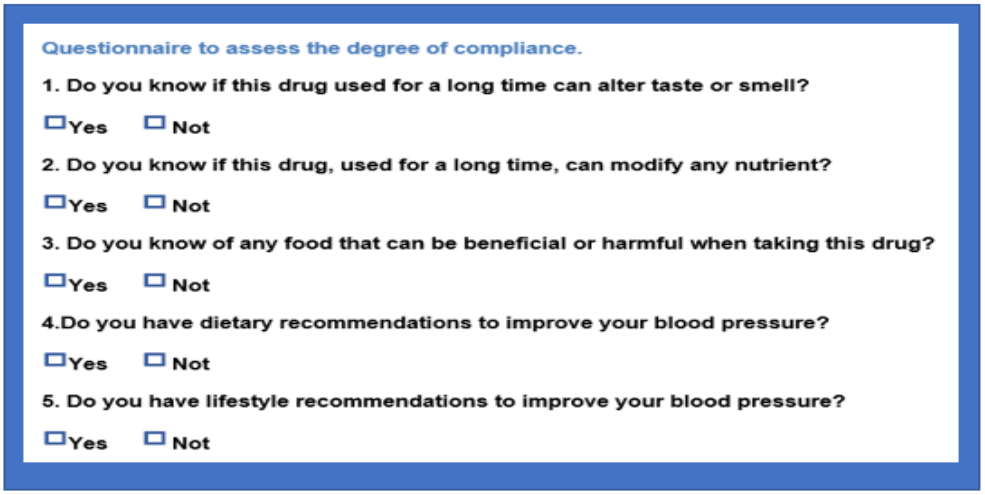

Figure 2: Questionnaire to assess the degree of knowledge.

The two interviews carried out in the follow-up phase will make it possible to check if the patient is following the indicated plan, detect any problems that may have arisen and reinforce their motivation and adherence.

The evaluation questionnaire that will be carried out in the final interview will allow to know the degree of compliance and the degree of satisfaction. This final questionnaire will be anonymous so that the patient does not feel coerced in the answers.

Figure 3 shows some of the questions used as shown in the questionnaires that will be passed on to the patients and which are listed in the corresponding annexes mentioned above.

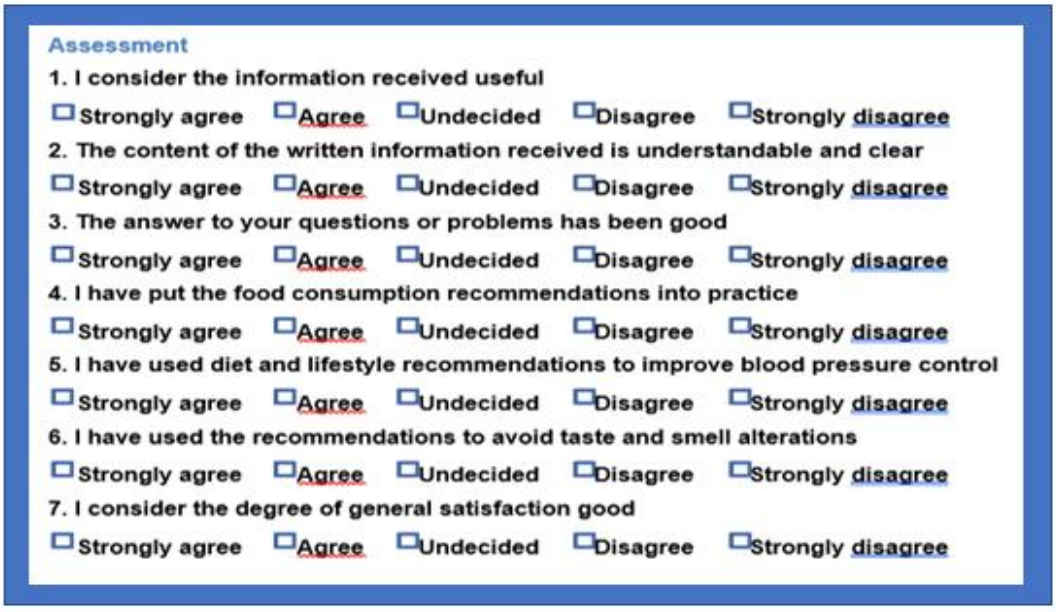

Figure 3: Questionnaire to assess the degree of compliance and satisfaction.

The user will answer the questions asked using a linear scale of five items. The Likert frequency scale has been selected, a validated scale widely used to measure the behavior and attitude of the respondents (40).

Data analysis will allow us to obtain the percentages of patients who consider oral and written information useful or not. Likewise, we can assess whether the information provided in the files is sufficiently clear and understandable and whether the doubts or problems raised by the patients have been satisfactorily answered. The degree of compliance with the recommendations regarding the consumption of certain foods during treatment with certain drugs will be measured. Likewise, the degree of compliance with the recommendations regarding dietary and lifestyle habits will be measured.

These evaluation questionnaires constitute the methodological tool that will allow us to propose corrective measures based on the results of compliance and satisfaction.

DISCUSSION

The importance of knowing the interactions between food and drugs is fundamentally due to their high frequency and the potential impact on a nutritional and pharmacological level.

Despite being more frequent than drug-drug interactions, there are fewer studies and they are more unknown. A recent PubMed review reveals that the number of published studies describing the potential effects of drug interactions is more than 100 times higher than those describing food-drug interactions.[4]

Depending on the substrate most affected and therefore its impact, two types of interaction between food and drugs can be differentiated. Sometimes it is the food, or the nutritional state that modifies the levels or action of the drug in the body, conditioning its efficacy and safety. These AMIs have repercussions at the pharmacological level. Likewise, drugs can modify nutrient utilization and alter nutritional status. These MAIs are therefore important from a nutritional point of view.

The project has focused on AMIs with nutritional repercussions, which are related to the use of drugs for long periods of time. At present, the high proportion of the aging population, polymedicated, with chronic treatments and with nutritional deficits, contributes to potentially very high such interactions.[4,9]

For the knowledge of AMI whose consequence is pharmacological, information tools are available at the professional and patient level provided by different organisms and regulatory agencies such as AEMPS.[14] and EMA.[15] However, the scarcity of guides and resources for the knowledge of AMI whose repercussion is nutritional, makes it difficult for professionals to correctly handle this type of interaction. This has repercussions in the lack of transmission to the patient of recommendations on the correct intake of drugs without negatively affecting the nutritional status.[6]

The Food and Drug administration (FDA) website has a section for consumers on drug interactions with each other and with food.[41] Likewise, the FDA, in coordination with the national consumer association of the United States, National Consumers League (NCL), has published a patient-oriented guide in online and paper versions, which includes drug interactions with food. The positive aspect of this guide is the quality of the information and the adaptation of the contents to the understanding of the patient. However, it presents important limitations since it does not include all the active principles and its orientation is more pharmacological than nutritional.[42]

In this same sense, other online applications have been found on food and drug interactions that have a dual orientation towards the professional and the user. However, it is information that the user rarely reaches and that focuses mainly on the pharmacological aspects of interactions between food and drugs.[43]

The information found, although it may be useful for the patient, can never be considered a substitute for personal and individualized information adjusted to their particularities and idiosyncrasies. The drugs selected for the project are used in highly prevalent pathologies and belong to the pharmacological groups with the highest consumption in Spain,[16] all of them presenting interactions with repercussions at the nutritional level: PPIs.[17-30] statins.[31,32] SSRI antidepressants.[33-36] and ACEI.[4,13,37]

Despite being drugs with high consumption and used in highly prevalent pathologies, no studies or educational projects of interactions with nutritional repercussions have been found. However, educational programs have been found at the pharmaceutical care level in patients with pathologies or drugs similar to those in our project.

In this sense, educational programs have been found that assess the degree of knowledge of users, which is consistent with the first objective of our project. The study carried out by Mateos at an OFC in Zaragoza Spain.[44] evaluated the knowledge that patients undergoing treatment with statins have of the interaction of these drugs with grapefruit juice. The results obtained showed very high levels of ignorance on the part of the patient, to which the severity of the interaction is added. Only 14.9% of the patients had been informed of this interaction by the pharmacist and only 1% also by the doctor. Of the rest of the uninformed patients, 17.5% had taken grapefruit juice. When these drugs are administered simultaneously with grapefruit juice, atorvastatin levels increase by around 80% and those of simvastatin and lovastatin by around 260%. These high figures of misinformation confirm the importance of the

dietitian-nutritionist in patient education. Likewise, programs have also been found that, based on the degree of knowledge of the patient, carry out an educational intervention adapted to her needs, which coincides with the second objective of our project. In the Community of Castilla La Mancha, a pharmaceutical care program was carried out in hypertensive patients, in which 80 OFCs were involved, monitoring 6 patients for OFC for 6 months. In this program, as in our project, an intervention adapted to the needs of the patient was carried out, evaluating the degree of knowledge of it, analyzing drug interactions and improving education on lifestyles and use of drugs. Likewise, information sheets were used as educational support material.[45]

Numerous initiatives similar to the previous one have been found with hypertensive patients in OFC whose objective is to know and improve eating and living habits. In the educational program carried out by Baquero and Sánchez.[46] in an OFC in Galicia, 73.3% of the patients in the study admit that they know and follow an adequate diet in the first interview. The value found despite the limitations due to the subjectivity in the response and the biases depending on the level of life and education of the patients, indicates that education can provide a significant margin for improvement.

In a pharmaceutical care program carried out by 40 OFCs in Belgium, patient education was conducted on antidepressant treatment. Although their advice was predominantly at the pharmacological level, aspects related to lifestyle and diet were also influenced, as in our project.[47]

In our specific case, the implementation of the educational program aimed at patients undergoing chronic treatment with drugs that interact with food, aims to avoid negative repercussions that affect the nutritional status and overall health of the patient.

To do this, based on a prior evaluation of the degree of knowledge of the patient, it is intended to carry out an individualized dietary and nutritional education, to prevent the drug from negatively affecting their nutritional status, reinforcing education in habits based on the pathology and drug food and healthy living.

At the end of this educational project, it is intended to evaluate the impact that said program has on the patient by assessing the degree of compliance with the recommendations and the degree of satisfaction.

Expected results

Degree of knowledge of the patient about the potential impact of the interaction

Despite being drugs with high consumption and that are used in highly prevalent pathologies (depression, hypertension, prevention of gastroduodenal ulcers, hyperlipidemia...), it is expected to obtain a high degree of ignorance on the part of the patient, as stated in pharmaceutical care programs in similar cases.[44-47]

In the four groups of drugs studied, it is expected to find percentages of ignorance in aspects related to the interaction higher than 80%. Taking into account the data in the bibliography for these drugs, it is expected to find that only between 15 and 20% of the patients have received information.[44,45,47]

Better results are expected in relation to aspects related to eating habits and lifestyle in patients with hypertension or hyperlipidemia. The degree of knowledge is expected to be greater than 70%.[44,46]

Degree of compliance and satisfaction

A high degree of patient compliance is expected. The patient is concerned about her health and is concerned about nutritional aspects. The existence of four consultations during the development of the program is a fundamental element to guarantee motivation and, as a consequence, patient compliance and satisfaction. Carrying out the first consultation will be fundamental in the educational sense and the motivation of the patient. The fact that prior to carrying out the education, their degree of knowledge is evaluated, allows oral education to be individualized to the needs of the patient. Likewise, it allows the dietician-nutritionist to know the degree of understanding of the patient and if it is necessary to orally reinforce the information collected in the written information sheet that is delivered. These facts will contribute to improve the adherence of the patient to the nutritional guidelines and recommendations that are proposed.

The incorporation of follow-up consultations is important to rescue the less motivated patient and reinforce correct habits in terms of taking drugs and nutritional and lifestyle recommendations.

The fact that they are short consultations and that they can be adapted to the times of dispensing the medication, can be an aspect that favors the continuity of the patient until the end of the project.

Degree of abandonment

Based on the comments in the previous point, a low degree of abandonment is expected. A percentage of less than 10% is contemplated, considering that it is mainly due to patients excluded from the program due to a change in medical treatment before the end of the project.

Strengths of the educational program

The OFC being the obligatory step of the primary care patient for the acquisition of medicines, it is an ideal place to know the medicines that the population takes, detect interactions with food and educate the patient.

A strength of the program is the contribution of a more comprehensive education to the patient, from the nutritional and pharmacological perspectives. This can be carried out by being carried out in an OFC and being approached by a multidisciplinary team with the joint presence of the pharmacist and dietician-nutritionist.

The great strength of the program is the joint presence of the pharmacist and the dietitian-nutritionist, which allows for patient education from the pharmacological and nutritional perspectives, that is, from a more comprehensive perspective.

The dietitian-nutritionist will take care of detecting and correcting the AMI that affect aspects related to food, appetite and nutritional status. The pharmacist will be responsible for avoiding AMI that affect the efficacy or toxicity of the drug. Both form the team involved in educating the patient on the correct intake of medications in relation to food. Their participation in patient education is clearly differentiated, but both are complementary.

Limitations of the practical development of the project and alternatives to resolve incidents

This is a study limited in the selected drugs and in duration.

Regarding drugs, designing a project of this type that included all drugs that could cause interactions with food would be overwhelming. It is important to have selected the interactions with nutritional repercussions of the most widely used drugs and the most prevalent pathologies.

The most relevant practical limitation is time, since AMIs with nutritional repercussions do not happen quickly as happens with AMIs with pharmacological repercussions. Due to this, this project has been designed as an educational project.

The alternative of prolonging the study time would allow not only to carry out patient education and follow-up consultations, but also to assess the real impact at the nutritional level.

Possible practical applications of the project result and improvements compared to what is current

1. It would be very interesting to develop this type of multidisciplinary strategies in which medicine and food are approached from a pharmaceutical point of view and from a dietary and nutritional point of view.
2. Today there are already a significant number of OFCs offering their professional services for pharmacists and dietitians-nutritionists. However, the role that the latter usually perform is mainly directed to the performance of diets and nutritional corrections not related to interactions.
3. An important improvement would be to dedicate part of the work time of the dietitian-nutritionist at the OFC to this type of multidisciplinary project for the detection of interactions with nutritional repercussions. The joint presence of both professionals allows us to cover these interactions from the pharmacological and nutritional points of view. It is a novel contribution with great benefit at the patient level.
4. One more step would be the inclusion of the dietitian-nutritionist in the National Health System in public and private health, since the importance of diet and nutritional status in health is obvious. In this way, by becoming one more link in the health chain, it could be involved in carrying out multidisciplinary projects in which the patient was cared for from the pharmaceutical and nutritional dietary perspectives.
5. This project opens a door to a quite unknown and little exploited world. The dedication of resources to finance projects of this type improves the pharmaceutical and nutritional care of the patient and ultimately has an impact on improving the health of the population. In addition, it is important to point out that carrying out this type of project is also beneficial for the professionals involved, since it allows them to provide higher quality services and increase their demand and requirements from the patient.

CONCLUSIONS

An education program has been created to avoid drug-food interactions with nutritional repercussions.

This program will be carried out in the users of a pharmacy office in treatment with medicines belonging to the pharmacological groups of greater consumption and with interactions with repercussions at the nutritional level.

It is expected that less than 20% of patients have received information related to the interaction and that more than 80% do not know how to prevent the drug from negatively affecting their diet and nutrition.

It is expected that individualized dietetic-nutritional education for each patient will help prevent the drug from negatively affecting their nutritional status and reinforce education on eating habits and a healthy life.

With individualized follow-up consultations, it is hoped to resolve incidents and strengthen motivation and adherence to the proposed educational plan.

The approach to the interactions between foods and drugs by a multidisciplinary team will allow the patient to provide a comprehensive education from the pharmacological perspective by the pharmacist and nutritional by the dietitian-nutritionist.

BIBLIOGRAPHY

1. Burrows MT, Farr WK. The action of mineral oil per os on the organism. Proc Soc Exper Biol Med, 1927; 24: 719-23.
2. Shee JC. Pargyline and the Cheese Reaction. BMJ., 1964; 1(5395): 1441.
3. Madurga M, Sánchez F. Interacciones adversas de alimentos y medicamentos: tipos, su identificación y actualización. Anales de la Real Academia de Farmacia, 2018; 84: 216-25.
4. Mohn ES, Kern HJ, Saltzman E, Mitmesser SH, McKay DL. Evidence of drug–nutrient interactions with chronic use of commonly prescribed medications: An Update. Pharmaceutics, 2018; 10(36): 1-45.
5. Amadi CN, Mgbahurike AA. Selected food/herb-drug interactions: mechanisms and clinical relevance. Am J Ther, 2018; 25(4): 423-33.
6. San Miguel MT, Sánchez JL. Interacciones alimento/medicamento. Inf Ter Sist Nac Salud, 2011; 35(1): 3-12.
7. Portal de salud Castilla y León: portal del medicamento. Interacción alimento-medicamento. [Internet]. Valladolid: Sanidad Castilla y León, 2019. Available in: https://www.saludcastillayleon.es/portalmedicamento/es/noticias-destacados/destacados/interaccion-alimento-medicamento.
8. Ficha técnica de Orlistat Stada®. [Internet]. Centro de información on line de la Agencia Española de Medicamentos y Productos Sanitarios. Available in: https://cima.aemps.es/cima/dochtml/ft/83430/FT_83430.html
9. Ötles S, Senturk A. Food and drug interactions: a general review. Technol Aliment, 2014; 13(1): 89-102.
10. Boullata JI. Drug-nutrition interactions and the brain: it's not all in your head. Curr Nutr Rep, 2019; 8(2): 92-98.
11. Uguz F, Sahingoz M, Gungor B, Aksoy F, Askin R. Weight gain and associated factors in patients using newer antidepressant drugs. Gen Hosp Psychiatry, 2015; 37(1): 46-48.
12. Schiffman SS. Influence of medications on taste and smell. World J Otorhinolaryngol Head Neck Surg, 2018; 4(1): 84-91.
13. Samaras D, Samaras N, Lang P, Genton L, Frangos E, Pichard C. Effects of widely used drugs on micronutrients: A story rarely told. Nutrition, 2013; 29: 605–10.
14. Centro de información on line de la AEMPS. [Internet]. Madrid: Agencia Española de Medicamentos y Productos Sanitarios. Ministerio de Sanidad, Servicios Sociales e Igualdad. Available in: https://cima.aemps.es/cima /publico/home.html.
15. European Medicines Agency (EMA). Guideline on the investigation of drug interactions. [Internet]. London: Committee for Medicinal Products for Human Use (CHMP), 2012. Available in: https://www.ema.europa.eu /en/documents/scientific-guideline/guideline-investigation-drug-interactions-revision-1_en.pdf
16. Ministerio de Sanidad, Consumo y Bienestar Social. Prestación farmacéutica en el sistema nacional de salud. Informe anual del sistema nacional de salud, 2018. [Internet]. Madrid: Ministerio de Sanidad, Consumo y Bienestar Social; 2019. Available in: https://www.mscbs.gob.es/estadEstudios /estadisticas/sisInfSan SNS/tablasEstadisticas/InfAnualSNS2018/Cap.7_Farmacia.pdf.
17. De la Coba C, Argüelles-Arias F, Martín de Argila C, Júdez J, Linares A, Ortega-Alonso A et al. Efectos adversos de los inhibidores de la bomba de protones: revisión de evidencias y posicionamiento de la Sociedad Española de Patología Digestiva. Rev Esp Enferm Dig, 2016; 108(4): 207-24.
18. Stabler SP. Vitamin B-12 Deficiency. N Engl J Med, 2013; 368: 149-60.
19. Lam JR, Schneider JL, Zhao W, Corley DA. Proton pump inhibitor and histamine 2 receptor antagonist use and vitamin B-12 deficiency. JAMA, 2013; 310(22): 2435-42.
20. Jung SB, Nagaraja V, Kapur A, Eslick GD. Association between vitamin B12 deficiency and long-term use of acid-lowering agents: a systematic review and meta-analysis. Intern Med J., 2015; 45(4): 409-16.
21. Linder L, Tamboue C, Clements JN. Drug-induced vitamin B12 deficiency: a focus on proton pump inhibitors and histamine-2 antagonists. J Pharm Pract. 2017; 30(6): 639-42.
22. Attwood SE, Ell C, Galmiche JP, Fiocca R, Hatlebakk JG, Hasselgren B, et al. Long-term safety of proton pump inhibitor therapy assessed under controlled, randomised clinical trial conditions: data from the SOPRAN and LOTUS studies. Aliment Pharmacol Ther. 2015; 41: 1162-74.
23. Haenisch B, Von Holt K, Wiese B, Prokein J, Lange C, Ernst A et al. Risk of dementia in elderly patients with the use of proton pump inhibitors. Eur Arch Psychiatry Clin Neurosci. 2015; 265: 419-28.
24. Freedberg DE, Kim LS, Yang, Y. The risks and benefits of long-term use of proton pump inhibitors: expert review and best practice advice from the American Gastroenterological Association. Gastroenterology, 2017; 152: 706–15.
25. Poly TN, Islam MM, Yang HC, Wu CC, Li YJ. Proton pump inhibitors and risk of hip fracture: a meta-analysis of observational studies. Osteoporos Int., 2019; 30(1): 103-14.
26. Zhou B, Huang Y, Li H, Sun W, Liu J. Proton-pump inhibitors and risk of fractures: an update meta-analysis. Osteoporos Int. 2016; 27(1): 339-47.
27. Liao S, Gan L, Mei Z. Does the use of proton pump inhibitors increase the risk of hypomagnesemia: An updated systematic review and meta-analysis. Medicine (Baltimore), 2019; 98(13): e15011.
28. Srinutta T, Chewcharat A, Takkavatakarn K, Praditpornsilpa K, Eiam-Ong S, Jaber BL et al.

Proton pump inhibitors and hypomagnesemia: A meta-analysis of observational studies. Medicine (Baltimore), 2019; 98(44): e17788.
29. Cheungpasitporn W, Thongprayoon C, Kittanamongkolchai W, Srivali N, Edmonds PJ, Ungprasert P et al. Proton pump inhibitors linked to hypomagnesemia: a systematic review and meta-analysis of observational studies. Ren Fail, 2015; 37: 1237-41.
30. Lam JR, Schneider JL, Quesenberry CP, Corley DA. proton pump inhibitor and histamine-2 receptor antagonist use and iron deficiency. Gastroenterology, 2017; 152: 821–29.
31. Skarlovnik A, Jani´c M, Lunder M, Turk M, Sabovic M. Coenzyme Q10 supplementation decreases statin-related mild-to-moderate muscle symptoms: a randomized clinical study. Med Sci Monit, 2014; 20: 2183–88.
32. Anagnostis P, Adamidou F, Slavakis A, Polyzos SA, Selalmatzidou D, Panagiotou A et al. Comparative effect of atorvastatin and rosuvastatin on 25-hydroxy-vitamin D levels in non-diabetic patients with dyslipidaemia: a prospective randomized open-label pilot study. Open Cardiovasc Med J., 2014; 8: 55–60.
33. Ficha técnica de Manerix® (moclobemida). [Internet]. Centro de información on line de la Agencia Española de Medicamentos y Productos Sanitarios. Available in: https://cima.aemps.es/cima/dochtml/ft/59169/FT_59169.html
34. Serralde-Zúñiga AE, Gonzalez AG, Rodríguez-Carmona Y, Melendez G. Fluoxetine for adults who are overweight or obese. Cochrane Database Syst Rev., 2019; 10: CD011688.
35. Gafoor R, Booth H, Gulliford M. Antidepressant utilisation and incidence of weight gain during 10 years' follow-up: population based cohort study. BMJ, 2018; 361: k1951. doi: 10.1136/bmj.k1951 https://www.bmj.com /content/361/bmj.K1951.
36. Khanassov V, Hu J, Reeves D, van Marwijk H. Selective serotonin reuptake inhibitor and selective serotonin and norepinephrine reuptake inhibitor use and risk of fractures in adults: A systematic review and meta-analysis. Int J Geriatr Psychiatry. 2018; 33(12): 1688-708.
37. Raebel MA. Hyperkalemia associated with use of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers. Cardiovasc Ther., 2012; 30(3): 156-66.
38. Reglamento (UE) 2016/679 Del Parlamento Europeo y del Consejo de 27 de abril de 2016, relativo a la protección de las personas físicas en lo que respecta al tratamiento de datos personales y a la libre circulación de estos datos y por el que se deroga la Directiva 95/46/CE (Reglamento general de protección de datos). Diario Oficial de la Unión Europea nº 119/1, (4 mayo), 2016.
39. Ley Orgánica 3/2018, de 5 de diciembre, de Protección de Datos Personales y garantía de los derechos digitales (LOPD-GDD). Boletín Oficial del Estado número 294, (6 diciembre), 2018.
40. Matas A. Diseño del formato de escalas tipo Likert: un estado de la cuestión. REDIE [internet], 2018; 20(1): 38-47. Available in: http://www.scielo.org.mx /scielo.php?script=sci_arttext&pid=S1607-40412018000100038&lng =es&nrm=iso. ISSN 1607-4041.
41. Food and Drug Administration. Avoiding Drug Interactions. [Internet]. Available in: https://www.fda.gov/consumers/consumer-updates/avoiding-drug-interactions.
42. Avoid Food-Drugs interactions. A Guide from the National Consumers League and U.S. Food and Drug Administration, 2014.
43. Merck Manual Consumer Version Nutrient-Drug Interactions. Lynch SS. University of California San Francisco School of Pharmacy. Disponible en: https://www.merckmanuals.com/home/drugs/factors-affecting-response-to-drugs/drug-interactions.
44. Mateos MT. Conocimiento de los pacientes en tratamiento con estatinas de su interacción con zumo de pomelo. VII Congreso Nacional de Farmacéuticos Comunitarios, Zaragoza 26-28 de mayo 2016. Farmacéuticos Comunitarios, 2016; 8(1).
45. Programa de atención farmacéutica en pacientes hipertensos en Castilla-La-Mancha. [Internet]. Consejo de Colegios Oficiales de Farmacéuticos de Castilla-La Mancha (COFCAM) Fundación Pharmaceutical Care España. Available in: https://tevafarmacia.es/ofservicios/iniciativas/programa-de-atencion-farmaceutica-en-pacientes-hipertensos-castilla-la, 2015.
46. Baquero A, Sánchez P. Efectividad de las modificaciones de estilo de vida sobre el control de la presión arterial en pacientes hipertensos. Farmacéuticos Comunitarios, 2016; 8(3): 12-17.
47. Liekens S, Vandael E, Roter D, Larson S, Smits T, Laekeman G et al. Impact of training on pharmacists' counseling of patients starting antidepressant therapy. Patient Education and Counseling, 2014; 94: 110–15.