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SPECIAL ARTICLE
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Patient-Centered Prescription Model to improve therapeutic adherence in patients with multimorbidity

Modelo de Prescripción Centrado en la Persona para mejorar la adherencia terapéutica en pacientes con multimorbilidad

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Abstract

To date, interventions to improve medication adherence in patients with multimorbidity have shown modest and inconsistent efficacy among available studies. Thereby, we should define new approaches aimed at improving medication adherence tailored to effective prescribing, with a multidisciplinary approach and patient-centered.

In this regard, the Patient-Centered Prescription Model has shown its usefulness on improving appropriateness of drug treatments in patients with clinical complexity. For that, this strategy addresses the following four steps: 1) Patient-Centered assessment; 2) Diagnosis-Centered assessment; 3) Medication-Centered assessment; and 4) Therapeutic Plan.

We propose through a clinical case an adaptation of the Patient-Centered Prescription Model to enhance both appropriateness and medication adherence in patients with multimorbidity. To this end, we have included on its first step the Spanish version of a cross-culturally adapted scale for the multidimensional assessment of medication adherence. Furthermore, we suggest a set of interventions to be applied in the three remaining steps of the model. These interventions were firstly identified by an overview of systematic reviews and then selected by a panel of experts based on Delphi methodology.

All of these elements have been considered appropriate in patients with multimorbidity according to three criteria: strength of their supporting evidence, usefulness in the target population and feasibility of implementation in clinical practice.

The proposed approach intends to lay the foundations for an innovative way in tackling medication adherence in patients with multimorbidity.

Resumen

Según los estudios disponibles, la eficacia de las intervenciones para mejorar la adherencia terapéutica en pacientes con multimorbilidad es limitada e inconsistente; por ello, debemos definir nuevos modelos de intervención que incorporen como elementos clave la atención centrada en la persona, el abordaje interdisciplinar y la orientación a la mejora de la adecuación terapéutica.

En este sentido, el Modelo de Prescripción Centrado en la Persona ha demostrado su capacidad para adecuar la prescripción a las necesidades de pacientes con complejidad clínica. Para ello, incorpora cuatro etapas consecutivas: 1) valoración centrada en el paciente; 2) valoración centrada en el diagnóstico; 3) valoración centrada en el fármaco, y 4) propuesta de plan terapéutico.

Proponemos, a través de un caso práctico, una adaptación del Modelo de Prescripción Centrado en la Persona como estrategia para mejorar la adherencia terapéutica. Para ello, en la primera etapa del modelo hemos incorporado una herramienta para la valoración multidimensional de la adherencia adaptada transculturalmente al español. Posteriormente, proponemos un conjunto de intervenciones a aplicar en las tres etapas restantes del modelo. Dichas intervenciones han sido identificadas en un resumen de revisiones sistemáticas y posteriormente seleccionadas mediante la metodología Delphi.

Todos estos elementos han sido considerados adecuados en pacientes con multimorbilidad por la solidez de su evidencia, su utilidad potencial en la población diana y la factibilidad de su aplicación en la práctica clínica.

La aproximación propuesta pretende sentar las bases de un modelo de cambio respecto al abordaje de la adherencia en el paciente con multimorbilidad.

KEYWORDS
Medication adherence; Inappropriate prescribing; Multimorbidity; Polypharmacy; Patient-centered care.

PALABRAS CLAVE
Adherencia terapéutica; Prescripción inadecuada; Multimorbilidad; Polifarmacia; Atención centrada en el paciente.

This article has been partially presented in Communication format at the 17th International Conference on Integrated Care, held in Dublin, Ireland, on May, 8th-10th, 2017.

Manuela is an 85-year-old woman, a widow with moderate level of disability for activities of daily living (Barthel Index: 55/100; Katz Index: F). At the same time, she presents severe disability for instrumental activities of daily living (Lawton-Brody Index: 2), retaining higher capabilities in terms of housework and telephone use. At the latest visit with her general practitioner, no cognitive decline was observed (*Short Portable Mental Status Questionnaire*: 2 errors). At social level, she has support by her daughter as informal caregiver; she lives next door to her mother so she helps her everyday with those activities that Manuela cannot conduct by herself.

Manuela is currently hospitalized due to a new heart failure decompensation. This clinical situation became worse after an acute exacerbation in her chronic renal disease, as well as by a hospital-acquired pneumonia. These health problems represent only one part of the syndromes and risk factors that Manuela has been collecting throughout her life, which overall determine major frailty[1] and use of healthcare resources.

As a consequence of the set of chronic conditions suffered by our patient, Manuela requires a highly complex drug therapy, as a result of multiple medications prescriptions, each of them with their own dosing regimen and administration instructions. When assessing her medication adherence, different causes for non-adherence were identified, associated both with medication administration and refilling.

Adherence in patients with multimorbidity. Where do we come from and where should we go to?

Manuela represents the typical profile of patient with multimorbidity, frequently seen in our daily clinical practice. Managing her highly complex drug therapy represents a challenge not only for healthcare professionals, but also for the patient, due to its potential to lead to non-adherence situations.

Approximately 50% of chronic patients present lack of adherence to prescribed treatments. This figure was originally described by Sackett *et al.*[2] almost four decades ago, and has remained the same until now[3]. This fact reflects the difficulty faced by health systems, professionals and patients to find an approach that will address the adherence problem effectively. Lack of adherence has been associated with a worse disease control, a reduction in life quality and survival, as well as with an increase in healthcare expense[4]. Therefore, it seems reasonable to classify lack of adherence as a real health problem. Its approach must be a priority for all agents involved.

Given the limited efficacy of efforts conducted so far in order to improve medication adherence in chronic patients, it is necessary to adopt a new approach. Its implementation should be prioritized to patients with multimorbidity, due to their clinical frailty, healthcare expenditure and higher disability and death[5]. This approach must look for an improvement in adherence not as a goal in itself, but as the means to obtain the best health outcomes in each patient.

The first stage to be considered in this process must be the selection of a valid tool for the evaluation of medication adherence in patients with multimorbidity. This tool must allow us to identify the barriers in each patient, and the extent to which they contribute to their overall adherence profile.

We have multiple methods available to assess medication adherence in elderly patients. According to the positioning document published by the *European Innovation Partnership on Active and Healthy Ageing*, there is no a gold standard to determine medication adherence in this type of patients[6]. Self-reported questionnaires stand out for their higher applicability and efficiency compared with other methods such as pill count or electronic monitoring devices. Moreover, questionnaires are the method for measuring medication adherence most frequently described in studies conducted in polymedicated patients[7], and they represent a useful tool for screening patients with a potential risk of non-adherence, as well as for identifying the reasons for non-adherence.

In this sense, and after a systematic review targeted to identify tools for assessing medication adherence in patients with multiple chronic conditions, a panel of experts selected the "Adherence to Refills and Medication Scale (ARMS)" questionnaire as the most appropriate method for assessing adherence[8]. The ARMS questionnaire was selected based on the strength of its supporting evidence, potential usefulness in the target population, and its feasibility of implementation in clinical practice. Originally validated in low literacy patients with chronic disease, it has been subsequently translated and adapted into Spanish for its use in patients with multiple chronic conditions[9]. The ARMS questionnaire includes 12 items, eight of them targeted to evaluate the process of medication administration, and the other four targeted to evaluate filling or refilling of prescriptions. Each item is structured for response on a Likert scale with responses of "none", "some", "most" or "all" of the time, which are given values from 1 to 4. Lower overall scores indicate higher adherence. This structure ensures a multidimensional approach to medication adherence, allowing subsequent individualized interventions on the basis of the barriers detected in each patient[10].

However, no method is considered sufficiently reliable and accurate to be used in isolation, and it is recommended to combine different methods[6]. Therefore, we must consider using an additional tool, such as pharmacy records. In any case, and for this specific population, their use will depend closely on their availability within health information systems.

The evidence available shows that the efficacy of the interventions to improve medication adherence is inconsistent among different studies; an improvement in adherence or health outcomes is observed in less than half of them[11,12]. Among the reasons that could explain their lack of success, we could highlight the lack of individualization and adaptation to the specific barriers in this group of patients. At the same time, unidisciplinary interventions focus on a single step of the medication use process, is an excessively partial view of the lack of adherence issue[10]. Likewise, the studies available present a high risk of bias, and are primarily focused on patients with single chronic conditions, thus leaving out frailty patients[11,12].

For all this, once an appropriated tool or tool combination has been selected for the assessment of medication adherence in patients with multimorbidity, we must define new intervention models. They should be characterized by an interdisciplinary approach and supported by a solid patient-centered theoretical framework which considers the personalization of the care plan to the characteristics, values and preferences of each patient[13-15].

To select the best interventions to improve adherence in older individuals, Marengoni *et al.*[13] led a panel of experts through modified RAND appropriateness methodology. Seven key interventions were identified: i) Comprehensive Geriatric Assessment (in combination with tools specifically designed to measure medication adherence), with the aim to assess the iatrogenic risk of the patient and reach an effective prescribing; ii) patient (and caregiver) education to improve patient empowerment; iii) optimization of treatment (reducing inappropriate prescribing and, when achievable, reducing polipharmacy); iv) use of adherence aids; v) physician and other healthcare professionals´ education on drug therapy and communication skills; vi) comprehensive adherence assessment, and vii) facilitating access to medicine by better integration of healthcare services, including community pharmacists and primary care physicians.

At the same time, the objective of the EdeMAPP Project (Strategy for Improvement of Medication adherence in Patients with Multimorbidity) was also to select appropriate interventions aimed at improving adherence in this population[16]. Based on an overview of systematic reviews and a modified Delphi methodology, it was identified the need to integrate within one single model of intervention, and according to the characteristics of each patient, the following actions: i) strategies to reduce medication regimen complexity through a simplify dosing schedule and/or deprescribing; ii) delivery personalized dosage systems; iii) strategies to promote communication between the healthcare professional and the patient; and iv) educational interventions for patients and/or primary caregivers regarding their primary condition, relevance of treatment, and medication adherence.

At this point, it is necessary to have a model for addressing patients with multimorbidity, which combines previous interventions with an interdisciplinary and patient-centered approach, therefore sensitive to patient preferences. In this sense, the Patient-centered Prescription (PCP) Model could be an ideal setting. It is characterized by a medication review that allows to adapt the drug therapy of patients with clinical complexity along three consecutive stages (patient-centered, diagnosis-centered, and drug-centered assessment) which lead to a final stage consisting in the proposal of a comprehensive treatment plan, previously agreed upon by consensus

with the patient and/or caregiver (figure 1)[17]. This approach would be consistent with the theory by McMullen *et al.*[18], which indicates effective prescribing must be one of the cornerstones of any intervention for adherence improvement. At the same time, this claim becomes particularly important in patients with multimorbidity, given the well-known relationship between comorbidity, polypharmacy and medication inappropriateness[19].

The interdisciplinary approach of the PCP Model, as a result of the collaboration of hospital pharmacists and geriatricians, among other healthcare professionals, has demonstrated a high performance in the improvement of medication appropriateness in frailty patients, both those admitted in an acute geriatric unit or in a residential and intermediate care center[20].Therefore, it is a model feasible to apply and sufficiently versatile to be targeted as a multidimensional strategy for improving medication adherence in patients with multimorbidity.

Figure 2 outlines the approach proposed to enhance medication adherence according to the PCP Model. This approach integrates within the four PCP Model stages those interventions that have been previously identified as adequate to improve medication adherence in patients with multimorbidity. Based on a multidimensional evaluation of medication adherence oriented to patient-centered assessment, it intends to improve patient adherence through an adaptation of drug therapy to their preferences and life expectancy. At the same time, during the educational and motivational interview, this approach attaches importance to the shared decision-process between patients, caregivers (if any) and healthcare professionals.

Application of the PCP Model to enhance medication adherence: a case report

Figure 3 describes the application of the PCP Model to improve the medication adherence of our patient Manuela, which is explained as follows.

According to the proposed strategy, the first stage in the application of the PCP Model is an initial evaluation of the medication adherence (figure 4). In said interview, Manuela described occasional forgetfulness associated both with medication refilling and administration. In the latter case, problems were mainly related with medication regimen complexity. Likewise, the patient confirms the non implementation and discontinuation of some of her drugs due to lack of tolerance. She also reveals an irregular persistence because of wrong administration of some drugs depending on symptomatic burden. All this underlines, lack of medication adherence during treatment initiation and implementation[21].

Based on previous assessment, as shown in Figure 4, it is possible to associate lack of medication adherence with different barriers or drivers. They must be taken into account when selecting the interventions for improving medication adherence. There are multiple factors determining medication adherence, both modifiable and non-modifiable[10]. However, in order to give a more intuitive approach, we could differentiate three main categories of factors that could be potentially prevented or modified through the application of the PCP Model: high complexity treatment, drugs-related adverse events, or inadequate knowledge and/or beliefs about drug therapy.

Medication complexity not only considers the concurrent use of multiple medications, but also dosage form, dosing frequency and additional administration instructions. All these factors can provide a significant increase in medication complexity, which is particularly relevant in geriatric patients, due to their higher frailty and frequent exposure to a high level of polypharmacy[22]. Medication complexity, measured through the Medication Regimen Complexity Index (MRCI)[23,24], has been associated with low medication adherence[25], a higher number of hospital admissions[24] and even with higher mortality[26].

There is no consensus regarding the threshold value for considering medication regimen complexity as clinically relevant. In a cohort of hospitalized patients admitted to an acute geriatric unit[27], lower medication adherence was associated with MRCI values > 33 after hospital discharge. In the specific case of Manuela, her MRCI value would be > 50. This circumstance, associated with forgetfulness when taking her medication, requires an approach to drug therapy appropriateness emphasizing strategies for reducing medication regimen complexity.

The application of the PCP Model in our patient would entail a significant reduction in medication complexity, mainly due to deprescribing strategies (diagnosis-centered assessment), and to a lower extent to dosing regimen simplification (drug-centered assessment). In this way, a reduction > 10 points according to the MRCI would be achieved. This reduction is clinically relevant according to the study by Wimmer *et al.*[26], where 10-unit increases in medication regimen complexity were associated with higher mortality [HR 1.12 (CI 95% 1.01 to 1.25)].

On the other hand, the experience of drug-related adverse effects shown in the multidimensional assessment of medication adherence is clearly a factor determining inadequate medication persistence. The application of the PCP Model through drug-centered assessment allows the identification and switching of high-risk medication for patients with multimorbidity. In this sense, it is very helpful to have different tools based on explicit criteria for the identification of inappropriate prescribing[28]. Likewise, we highlight the potential usefulness of a trigger tool to identify adverse drug events in elderly patients with multimorbidity[29]. Among their strengths, we highlight its applicability in our setting, as well as its design through modified Delphi methodology. At the same time, it is important to assess, and if needed, to reduce the anticholinergic burden of pharmacotherapy. Although no clear relationship has been established to date between high anticholinergic burden and lack of medication adherence[30], its association with functional and cognitive decline would justify the reduction

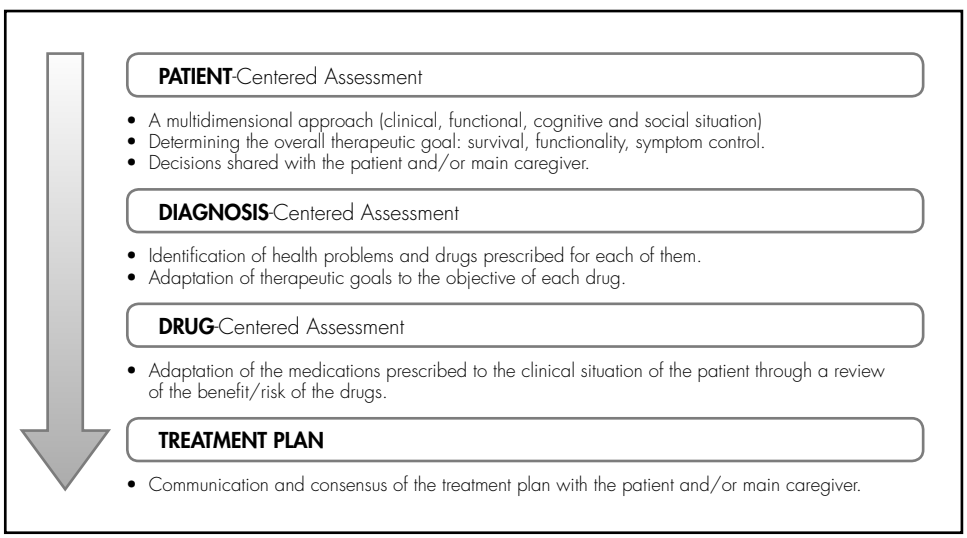

Figure 1. *Patient-centered Prescription Model.*

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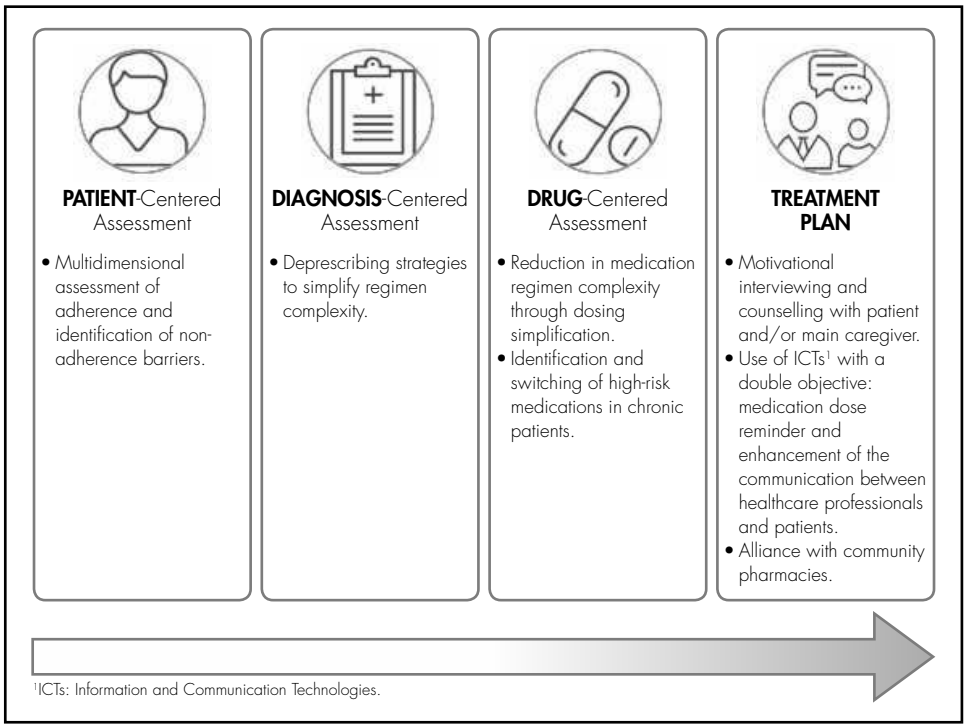

Figure 2. *Adaptation of the Patient-centered Prescription Model for enhance medication adherence.*

of anticholinergic burden as an intervention to improve both appropriate prescribing and medication adherence.

Finally, a third barrier for inappropriate adherence that can be identified in our patient through the use of the ARMS-e scale is an inadequate knowledge and/or patient beliefs about their pharmacotherapy. The application of the PCP Model includes in its last stage (treatment plan) a motivational interviewing and counselling with the patient and/or main caregiver/s, if any. Said meeting must have a triple objective: i) motivational, reinforcing the importance of medication adherence in order to achieve the desired therapeutic objective; ii) counselling, informing the patient about those aspects necessary for an adequate use of pharmacotherapy; and iii) based on shared decision making, taking into account patient and caregivers preferences[15].

This final stage of the PCP Model provides the opportunity to continue tailoring the intervention to the patient, through prescribing appropriate tools to help managing pharmacotherapy, based on their clinical and social context. The fact that our patient presents moderate level of disability and high regimen complexity requires considering different interventions including personalized dosage systems (PDS)[12].

A strategic alliance between hospital and community pharmacies has become an increasingly relevant aspect in this last stage of the PCP Model. Going deeper into the importance of the later agent as a health service provider, we must define referral circuits from the hospital setting for those patients that could benefit from medication refilling through PDS and/or motivational interviewing and counselling. These interventions would be delivered according to the medication adherence assessment performed on the first stage of the PCP Model.

Likewise, the use of certain information and communication technologies (ICTs) could be useful to us, with a double objective: i) medication reminder; and ii) promoting communication between the healthcare professional and the patient. However, there is no clear consensus about the feasibility of their use in patients with multimorbidity. Nevertheless, we must not rule out targeting ICTs to patient caregivers, given their frequent prominence in drug therapy management of frailty patients.

In any case, it is important to highlight that after a multidimensional assessment of medication adherence, the interventions to be conducted must not only target those problems identified (reactive interventions), but it is also necessary to prevent potential medication adherence problems, through the implementation of preventive interventions addressing modifiable barriers to adherence.

Looking into the future: From theory to practice

Interventions to improve medication adherence in patients with multimorbidity have shown limited and inconsistent efficacy among those studies available. Therefore, we should define new intervention models with patient-centered care, interdisciplinary approach and effective prescribing as key elements.

The previously described case represents a theoretical approach for a complex reality that shown every day in our clinical activity. When faced with these situations, we will usually act in an intuitive way. However, in order to optimize our interventions, we must apply action patterns foreseen to be effective and efficient. In this sense, the PCP Model represents an innovative strategy, conceptually accurate and, most of all, with a feasible application. In any case, the proposed PCP Model must be adequately validated as a tool for improving medication adherence in patients with multimorbidity. While we have this information, its presentation through a case report allows us to assess its applicability. Regarding its necessary validation, some questions arise, such as the adequate method to monitor change patterns in medication adherence or if, on the contrary, we should leave behind the measurement of a subrogate variable for the benefit of a patient reported outcome.

Likewise, patients with multimorbidity are characterized by a dynamic and variable evolution, requiring continuous monitoring. Therefore, an approach based on specific interventions won't be enough, and it will be require integrating and establishing alliances with other healthcare agents in every territory. In this context, the involvement of the community pharmacy as a provider of health services will be required; offering personalized dosage systems and follow-up and monitoring of medication adherence. On the other hand, we must not forget the increasing demand of health services at different levels of care of patients with multimorbidity. All this justifies driving the PCP Model through regional health system strategies, where different healthcare providers and agents will act in a coordinate and consistent manner in terms of addressing medication adherence.

For decision making process, the PCP Model attach particular importance to patient and caregiver (if any) counselling, motivation and involvement. It also considers that appropriate prescribing is an essential intervention for me-

dication adherence improvement. For this reason, it is necessary to ensure that those healthcare professionals involved will have adequate knowledge and skills regarding motivational interviewing and counselling, as well as sufficient ability in the setting of patient-centered prescribing.

The heterogeneity of healthcare teams and structures in different territories must not be a barrier for escalating the PCP Model to different settings, as long as the key elements of the model are incorporated. We consider that these elements are: the multidimensional assessment of medication adherence, its interdisciplinary approach, effective prescribing and, finally, a patient-centered care, therefore sensitive to patient preferences. On the other hand, and in order to ensure the sustainability of the PCP Model, it is necessary to introduce patient prioritization criteria; the use of new technologies could be valuable to this aim.

It is time, therefore, to innovate and take one step forward regarding medication adherence improvement in frailty patients, such as patients with multimorbidity. We are based on uncertain evidence, but we have a wide range of reasonable guidelines that must be useful as orientation at the time of reaching our objective successfully. This study intends to become the basis for a model of change for addressing medication adherence in patients with multimorbidity.

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Conflict of interests

No conflict of interest.

		Application of the PCP model for enhancing medication adherence. A case report		
Conditions at baseline	**Drug therapy at baseline**	**PATIENT-centered Assessment** Treatment objective: Maintaining functionality	**DIAGNOSIS & DRUG-centered Assessment** a. Deprescribing strategies b. Switching of high-risk medications c. Dosing simplification	**TREATMENT PLAN**
Hypertension	Amlodipine 5mg/12 hs. Doxazosin 4mg/12hs Hydrochlorothiazide 25mg/24hs.	Non-adherence barriers identified through the ARMS questionnaire (see details in Figure 4): High medication regimen complexity. Medication-related Adverse events. Inadequate knowledge and/or beliefs about drug therapy.	Lower limb oedema: HTN 130/80 mmHg Manidipine 10mg/24 hs.[a,b,c] Doxazosin 8mg/24 hs.[c] GFR 22ml/min: Urate 8.0 mg/dl Discontinue Hydrochlorothiazide 25mg/24 hs.[a,b]	Hospital setting: Motivational interviewing and counselling with patient and main caregiver + drug treatment plan provided at discharge. Prescription of a Personalized Dosage System. Community pharmacy: Educational reinforcement with patient and main caregiver Medication dispensing through Personalized Dosage System.
Coronary Heart Disease	ASA 100mg/24hs. Bisoprolol 5mg/24 hs. Isosorbide mononitrate 50mg/12 hs. Ranolazine 375mg/12 hs. Atorvastatin 40mg/24 hs.		Controversial efficacy: Barthel 55/100 Discontinue Ranolazine 375mg/12 hs.[a] CL 138 mg/dl; HDL 40mg/dl; LDL 50mg/dl Simvastatin 40mg/24 hs.[a]	
Congestive Heart Failure	Atenolol 50mg/12 hs. Furosemide 40mg/8 hs.		No changes.	
Diabetes Mellitus II	Repaglinide 0.5mg/12 hs.		HbA1c 6.5%; Glycemia: 86-140-130 Discontinue Repaglinide 0.5mg/12 hs.[a,b]	
Hyperuricemia (asymptomatic)	Allopurinol 100mg/24 hs.		Urate 8.0 mg/dl Discontinue hydrochlorothiazide Discontinue Allopurinol 100mg/24 hs.[a]	
Chronic Renal Impairment	No specific treatment.		No changes.	
Peptic Ulcer	Omeprazole 20mg/24 hs.		No changes.	
COPD	Ipratropium 40mcg/8 hs.		Tiotropium 5mcg/24 hs.[c]	
Gonarthrosis	Paracetamol 1g/8 hs. Calcium / Vitamin D 600mg/400IU/24 hs.		Primary prevention for osteoporotic fracture Discontinue Calcium / Vitamin D 600mg/400IU/24 hs.	
Insomnia	Lorazepam 1mg/24 hs. + 1 mg/prn.		Lorazepam 1 mg/prn[a,b,c]	
	MRCI: 52.5		**MRCI: 31.5**	

ASA: acetylsalicylic acid; CL: total choleresterol; COPD: chronic obstructive pulmonary disease; GFR: glomerular filtration rate; HbA1c: glycosylated hemoglobin; HDL: high density lipoprotein; HTA: hypertension; IU: international units; LDL: low density lipoprotein; MRCI: medication regimen complexity index; prn: *pro re nata*.

Figure 3. *Patient-centered Prescription Model for enhance medication adherence: a case report.*

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Adherence to Refills and Medications Scale (ARMS). Case Report.
Answer the following questions with: none, some, most, all.

		Potential drivers for non-adherence			
Questions	**Manuela's answers**	**High medication regimen complexity**	**Medication-related adverse events**	**Inadequate knowledge and/or beliefs about drug therapy**	**Socioeconomic aspects**
1. How often do you forget to take your medicine?[a]	Some	■			
2. How often do you decide not to take your medicine?[a]	Some		■	■	
3. How often do you forget to get prescriptions filled?[b]	Some	■			
4. How often do you run out of medicine?[b]	None	■			■
5. How often do you skip a dose of your medicine before you go to the doctor?[a]	None			■	
6. How often do you miss taking your medicine when you feel better?[a]	None			■	
7. How often do you miss taking your medicine when you feel sick?[a]	All		■	■	
8. How often do you miss taking your medicine when you are careless?[a]	Some	■			
9. How often do you change the dose of your medicines to suit your needs (like when you take more or less pills than you are supposed to)?[a]	None			■	
10. How often do you forget to take your medicine when you are supposed to take it more than once a day?[a]	Some	■			
11. How often do you put off refilling your medicines because they cost too much money?[b]	None				■
12. How often do you plan ahead and refill your medicines before they run out?[b]	Most	■			

[a]Items associated with medication administration; b. Items associated with medication refill.

Figure 4. *ARMS scale and drivers for non-adherence: a case report.*

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