INTERVENCIÓN DEL FARMACÉUTICO COMUNITARIO EN LA MEJORA DE LA ADHERENCIA TERAPÉUTICA Y EN LA DETECCIÓN DE DISCREPANCIAS EN EL USO DE MEDICAMENTOS

Tesis Doctoral · 2020 · Ainhoa Oñatibia Astibia

eman ta zabal zazu

Universidad del País Vasco

Euskal Herriko Unibertsitatea

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"I think goals should never be easy, they should force you to work, even if they are uncomfortable at the time"

Michael Phelps

Intervención del farmacéutico comunitario en la mejora de la adherencia terapéutica y en la detección de discrepancias en el uso de medicamentos

Ainhoa Oñatibia Astibia · Tesis doctoral
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i. GLOSARIO

ACTG	AIDS Clinical Trials Group
ADEOS	Adherence Evaluation of Osteoporosis Treatment
ANCOVA	Análisis de covarianza
ANOVA	Análisis de varianza
ARMS	Adherence to Refills and Medication Scale
ASRQ	Brief Adherence Self-Report Questionnaire
AUR	Appliance Use Review
AVAC	Años de vida ajustados por discapacidad
BARS	Brief Adherence Rating Scale
BMQ	Brief Medication Questionnaire
CGCOF	Consejo General de Colegios Oficiales de Farmacéuticos
CPCRA	Community Programs for Clinical Research on AIDS
CPCS	Community Pharmacist Consultation Service
CQR	Compliance-Questionnaire-Rheumatology
c-RCT	Cluster Randomized Controlled Trial
CT	Colesterol total
DRG	Diagnosis-related group
ECHO	Economic, Clinical and Humanistic Outcomes
EPOC	Enfermedad pulmonar obstructiva crónica
FC	Farmacéutico comunitario
FIP	International Pharmaceutical Federation
FNI	Frazier Noncompliance Inventory

Foro AF-FC	Foro de Atención Farmacéutica en Farmacia Comunitaria
HR	Hazard Ratio
IC	Intervalo de confianza
ICER	Relación coste-efectividad incremental
IMC	Índice de masa corporal
INT	Grupo intervención
ISPOR	Sociedad Internacional de Farmacoeconomía e Investigación de Resultados Sanitarios
ITAS	Immunosuppressive Therapy Adherence Scale
ITAS-M	Medication Immunosuppressive Therapy Adherence Scale
MAP	Médico de Atención Primaria
MAQ	Morisky Adherence Questionnaire
MDDS	Medication discrepancy detection service
ME	Medication error
MedMaIDE	Medication Management Instrument for Deficiencies in the Elderly
MOS	Medical Outcomes Study
MPR	Medication Possession Ratio
MS_TAQ	Multiple Sclerosis Treatment Adherence Questionnaire
MUR	Medicines Use Review
NHS	Sistema Nacional de Salud británico
NOINT	Grupo no intervención
OMS	Organización Mundial de la -Salud

OR	Odds ratio
OSI	Organización Sanitaria Integrada
OTC	Over the counter
PDPCCR	Programa de Detección Precoz de Cáncer de Colon y Recto
PESBUM	Programa de Educación Sanitaria sobre el Buen Uso de los Medicamentos
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRM	Problemas relacionados con la medicación
RCT	Randomized controlled trial
RNM	Resultados Negativos asociados a la Medicación
RUM	Revisión del Uso de Medicamentos
SAC	Stoma Appliance Customisation
SEFAC	Sociedad Española Farmaceuticos Comunitarios y De Familia
SEFH	Sociedad Española Farmacia Hospitalaria
SEPAP	Sociedad Española de Farmacéuticos de Atención Primaria
SERAD	Self-Reported Adherence Questionnaire
SMAQ	Simplified Medication Adherence Questionnaire
SNS	Sistema Nacional de Salud
SPD	Sistema personalizado de dosificación
SPFA	Servicios Profesionales Farmacéuticos Asistenciales
SRSI	Self-Rating Scale Item
TRQ	Tablets Routine Questionnaire

VAS	Visual Analog Scale
VIH	Virus de la Inmunodeficiencia Humana


INTRODUCCIÓN

1. SERVICIOS PROFESIONALES FARMACÉUTICOS ASISTENCIALES

1.1 ¿Qué son los Servicios Profesionales Farmacéuticos Asistenciales (SPFA)?

Los farmacéuticos, independientemente del área profesional en la que ejerzan, han ido desarrollando su profesión en un ámbito que cada vez se ha tornado más asistencial. Los años 60 marcaron un gran cambio en esta evolución, con la aparición de lo que se denominó *farmacia clínica*, pero no fue hasta 1990 cuando Hepler y Strand definieron el concepto de *atención farmacéutica* como "la provisión responsable de la farmacoterapia con el propósito de alcanzar unos resultados concretos que mejoren la calidad de vida de cada paciente" (1). Tras esta definición, la Organización Mundial de la Salud (OMS) concretó y unificó las responsabilidades del farmacéutico en el denominado "Informe Tokio", basándose en lo que representaba la atención farmacéutica (2). Además, algunas entidades como la Sociedad Americana de Farmacéuticos Hospitalarios publicaron recomendaciones para poder seguir los procedimientos en base a la misma filosofía (3).

A nivel nacional hubo múltiples barreras que dificultaron la implantación de la atención farmacéutica, entre las cuales destaca la falta de unidad en los mensajes ofrecidos por los expertos y las instituciones. Por este motivo, la Organización Farmacéutica Colegial puso en marcha el *Foro de Atención Farmacéutica* (Foro), un grupo de trabajo compuesto por el Ministerio de Sanidad, el Consejo General de Colegios Oficiales de Farmacéuticos (CGCOF), la sociedades científicas de Farmacia Comunitaria (SEFAC), Atención Primaria (SEFAP) y Farmacia Hospitalaria (SEFH), la Fundación Pharmaceutical Care España, el Grupo de Investigación en Atención Farmacéutica de la Universidad de Granada y la Real Academia Nacional de Farmacia, con el objetivo de generalizar la práctica de la atención farmacéutica a nivel nacional (4). En 2008, las instituciones del Foro vinculadas con la farmacia comunitaria consideraron necesario trabajar en la misma línea, pero por separado, por lo que nació un grupo denominado *Foro de Atención Farmacéutica en Farmacia Comunitaria* (Foro AF-FC). El objetivo principal de Foro AF-FC era contribuir a la implantación de los Servicios Profesionales Farmacéuticos Asistenciales (SPFA) en la farmacia comunitaria. Desde entonces, y hasta el día de hoy, el Foro AF-FC ha

trabajado para mantener una homogeneidad en los proyectos y servicios, utilizando para ello una terminología consensuada, apoyando la implantación de SPFA e incrementando la colaboración entre las distintas organizaciones del grupo. Actualmente, constituye un agente indispensable en el ámbito de la atención farmacéutica (5) y los manuales que han editado a lo largo de estos años han servido de referencia para toda la profesión a nivel nacional (6).

En este marco, el Foro AF-FC (7) define los SPFA como: "*Aquellas actividades sanitarias prestadas desde la farmacia comunitaria por un farmacéutico que emplea sus competencias profesionales para la prevención de la enfermedad y la mejora tanto de la salud de la población como la de los destinatarios de los medicamentos y productos sanitarios, desempeñando un papel activo en la optimización del proceso de uso y de los resultados de los tratamientos. Dichas actividades, alineadas con los objetivos generales del sistema sanitario, tienen entidad propia, con definición, fines, procedimientos y sistemas de documentación que permiten su evaluación y retribución, garantizando su universalidad, continuidad y sostenibilidad*".

Esta definición engloba la idea de que los SPFA: (i) son actividades sanitarias, (ii) son actividades que se prestan desde la farmacia y, por lo tanto, pueden englobar aquellas que se realizan fuera de la farmacia comunitaria, (iii) las realiza un farmacéutico titulado, (iv) están orientadas a prevenir la enfermedad y mejorar la salud de los pacientes, (v) están orientadas tanto a humanos como a animales, (vi) presentan características diferenciales, y (vii) deberían de estar remunerados para garantizar su sostenibilidad.

Potenciar actividades asistenciales orientadas, fundamentalmente, a la mejora del estado de la salud del paciente es uno de los principales objetivos del profesional sanitario. En este sentido, se ha demostrado que con la implantación de los SPFA se consiguen beneficios a nivel de la sociedad, del colectivo profesional farmacéutico y del propio farmacéutico comunitario, además de las mejoras a nivel del paciente (Figura 1).

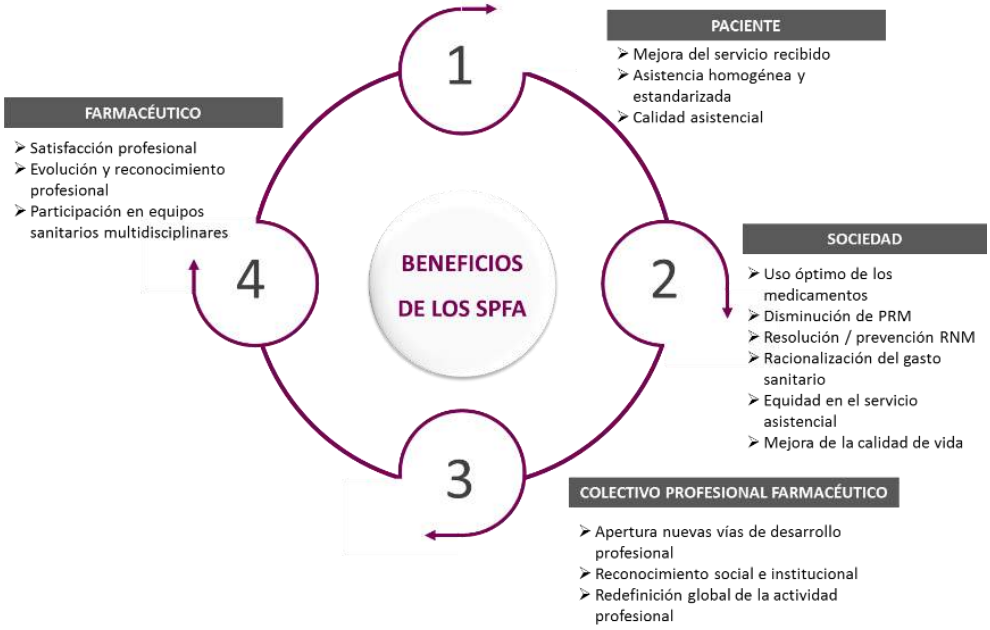

Figura 1. Beneficios de los Servicios Profesionales Farmacéuticos Asistenciales (6). PRM: Problemas relacionados con los medicamentos; RNM: Resultados negativos asociados a la medicación.

1.2. Clasificación de los SPFA

Con el objetivo de homogeneizar la definición de SPFA en la práctica diaria de la farmacia comunitaria, Foro AF-FC propone una clasificación de dos tipos de servicios: servicios de atención farmacéutica y aquellos relacionados con la salud comunitaria (Figura 2), en la que todos ellos cumplen una serie de requisitos como los recogidos a continuación:

(i) Se prestan desde la farmacia comunitaria.

(ii) Los realiza un farmacéutico o bajo su supervisión.

(iii) Son competencia del farmacéutico comunitario (FC).

(iv) Están alineados con los objetivos generales del sistema sanitario,

(v) Están protocolizados de tal forma que presentan una definición, objetivos, procedimiento y documentación que permiten su evaluación y retribución.

(vi) Son servicios universales, continuos y sostenibles.

(vii) Sirven para prevenir la enfermedad, son útiles para mejorar la salud de la población, sirven para mejorar la salud de los destinarios, de sus medicamentos o productos sanitarios y/o el farmacéutico desempeña un papel activo en la optimización del proceso de uso o tratamiento de los resultados.

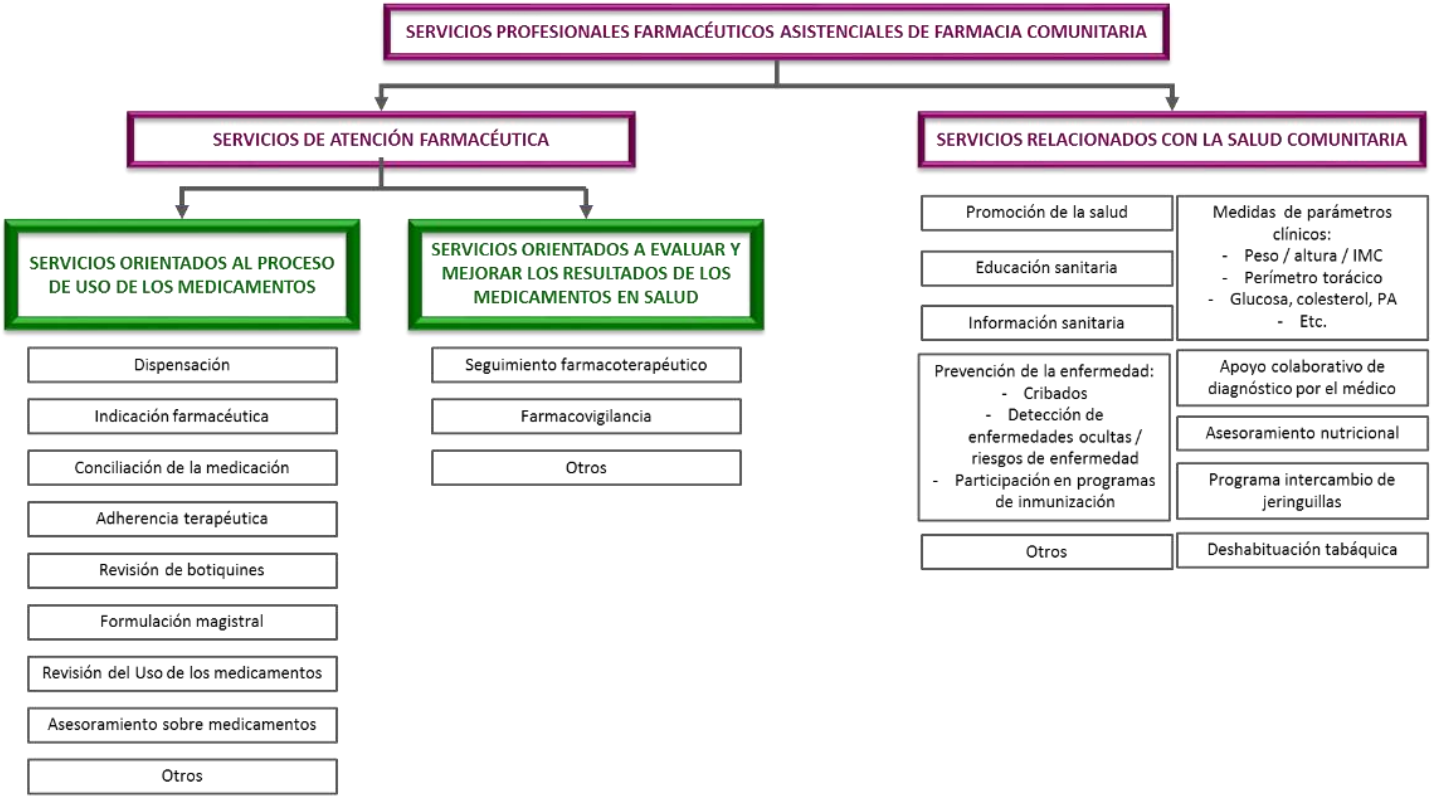

Figura 2. Clasificación de los servicios profesionales farmacéuticos asistenciales de farmacia comunitaria (7)

La implantación de los diferentes SPFA en la farmacia comunitaria ha permitido ofrecer una amplia cartera de servicios a la población, entendida ésta como "un conjunto de actividades sanitarias, independientes entre sí, con estructura, definición, objetivos, procedimientos consensuados y sistemas de documentación, que se desarrollan desde la farmacia comunitaria por parte del personal que realiza su trabajo en la misma" (8). Así, estas actividades se diferenciarán de aquellos servicios, que aun estando relacionados con la salud y/o el bienestar de la población, no cumplen los criterios para considerarse SPFA. Ejemplo de ello son, el consejo dermofarmacéutico o elaboración de dietas, entre otros.

Tanto la *International Pharmaceutical Federation* (FIP) como la OMS, coinciden en que no existe futuro profesional del FC en el mero hecho de la dispensación (9). De ahí que la generalización de una cartera de servicios farmacéuticos sea una oportunidad para la evolución de la práctica farmacéutica asistencial (8).

1.3 Remuneración de los SPFA

El reto actual para la plena implantación y generalización de los SPFA en la farmacia comunitaria es la remuneración, ya que si una actividad no genera una rentabilidad es muy probable que en un futuro cercano deje de proveerse (10). Para conseguir que un servicio sea remunerado, éste debe demostrar que genera rentabilidad, que produzca beneficios económicos a la administración, que es beneficioso para el prestador del servicio, y que mejora el estado de salud o calidad de vida del paciente.

La remuneración puede hacerse de diferente forma en función del servicio y persona o entidad financiadora: (i) El paciente paga el servicio de forma íntegra, (ii) el paciente paga parte del servicio y la administración el resto, o (iii) la administración paga el servicio de forma íntegra.

A nivel nacional, el servicio primordial que presta la farmacia comunitaria es la dispensación de medicamentos. Los medicamentos, a excepción de algunos que no están financiados, se financian con cargo del Sistema Nacional de Salud (SNS) y el copago del paciente, el cual varía en función de la edad y los ingresos del paciente.

Por otra parte, el sistema de retribución de la dispensación de la farmacia comunitaria se basa fundamentalmente en un margen sobre el precio del medicamento. Otros servicios llevados a cabo en la farmacia comunitaria que son remunerados por la administración a nivel nacional se recogen en la tabla 1.

El programa de mantenimiento de metadona fue el primer SPFA implantado en las farmacias comunitarias de España, concretamente en el año 1995 en la Comunidad Autónoma Vasca. A día de hoy, este servicio está remunerado en 22 provincias de 10 comunidades autónomas y la remuneración puede variar desde 54 € a 67 € paciente/mes.

El servicio de *Tratamiento observado directamente* de tuberculosis se realiza actualmente en las tres provincias de la Comunidad Valenciana. Otras comunidades como la del País Vasco, han tenido este servicio remunerado pero debido a la falta de usuarios demandantes actualmente no se ofrece.

El test rápido del virus de la inmunodeficiencia humana (VIH) se realiza de forma remunerada, en 18 provincias de 5 comunidades autónomas. La remuneración de este servicio se hace por parte de la administración y por parte del usuario. Dependiendo de la comunidad, el usuario puede pagar entre 5-10 € por test realizado y la administración remunera a la farmacia entre 10 y 20 € por test. En el Principado de Asturias, la administración solamente cubre los gastos de material y gestiona la retirada de residuos, pero no remunera de forma directa a la farmacia por lo que no se ha tenido en cuenta como un SPFA remunerado.

El servicio de ayuda domiciliaria lleva en activo en el País Vasco desde el 2009, y a día de ho,y en otras comunidades solamente se ofrece este servicio en la provincia de Soria como SPFA remunerado. La administración o la diputación provincial en caso de Soria, paga a la farmacia de forma similar por cada paciente.

En Cataluña, actualmente, existen otros tres SPFA que solamente son remunerados en esta comunidad. Es el caso del *Programa de Detección Precoz de Cáncer de Colon y Recto* (PDPCCR), el programa de *Red de Farmacias Centinela* y el Programa de *Educación Sanitaria sobre el Buen Uso de los Medicamentos* (PESBUM). En cada uno

de estos servicios, la administración paga a la farmacia por cada muestra recogida y enviada, de forma anual por la oferta del servicio o por cada sesión impartida por el farmacéutico comunitario (FC), respectivamente.

Por último, en la Comunidad Foral de Navarra, desde el año 2019 la administración remunera a la farmacia por cada acto de dispensación que realiza dentro del servicio de *Dispensación de Medicamentos Extranjeros.*

Tabla 1: Servicios profesionales farmacéuticos asistenciales remunerados por las administraciones.

SERVICIO	CCCAA	PROVINCIA	REMUNERADOR	REMUNERACIÓN	COMIENZO
Programa de mantenimiento con metadona	Aragón	Huesca	Administración autonómica	54,29 € /paciente /mes	1998
		Teruel			
		Zaragoza			
	Asturias, Principado de	Asturias	Administración autonómica	66,75 € /paciente /mes	2007
	Balears, Illes	Balears, Illes	Administración autonómica	2,25 € /paciente /día	1998
	Canarias	Santa Cruz de Tenerife	Administración autonómica	1,89 € /paciente /día	2002
	Castilla - La Mancha	Albacete	Administración autonómica	67 € /paciente /mes	1999
		Ciudad Real			
		Cuenca			
		Guadalajara			
		Toledo			
	Cataluña	Barcelona	Administración autonómica	Precio fijo por cada Orden Medica / paciente / mes	1998
		Girona			
		Lleida			
		Tarragona			
	Extremadura	Cáceres	Administración autonómica	50 € /paciente /mes	2015
		Badajoz			
	Murcia, Región de	Murcia	Administración autonómica	50 € /paciente/mes	2001
	Navarra, Comunidad Foral de	Navarra	Administración autonómica	65 € /paciente /mes	1996
	País Vasco	Araba/Álava	Administración autonómica	58,14 € /paciente /mes	1995
		Bizkaia			
		Gipuzkoa			

Tabla 1 (cont.): Servicios profesionales farmacéuticos asistenciales remunerados por las administraciones.

SERVICIO	CCCAA	PROVINCIA	REMUNERADOR	REMUNERACIÓN	COMIENZO
Tratamiento observado directamente Tuberculosis	Comunidad Valenciana	Alicante/Alacant Castellón/ Castelló Valencia/València	Administración autonómica	53,06€ / paciente / mes	2002
Test rápido de VIH	Balears, Illes	Balears, Illes	Administración autonómica + usuario	Usuario: 5€ / test Administración: 10€ / test	2013
	Cantabria	Cantabria	Administración autonómica + usuario	Usuario: 5€ / test Administración: 20€ / test	n.d.
	Castilla - León	Ávila Burgos León Palencia Salamanca Segovia Soria Valladolid Zamora	Administración autonómica + usuario	Usuario: 5€ / test Administración: 11€ / test	2010
	Cataluña	Barcelona Girona Lleida Tarragona	Administración autonómica + usuario	Usuario: 10€ / test Administración: 8€ / test	2012
	País Vasco	Araba/Álava Bizkaia Gipuzkoa	Administración autonómica + usuario	Usuario: 5€ / test Administración: 13,05€ / test	2009

Tabla 1 (cont.): Servicios profesionales farmacéuticos asistenciales remunerados por las administraciones.

SERVICIO	CCCAA	PROVINCIA	REMUNERADOR	REMUNERACIÓN	COMIENZO
Ayuda domiciliaria (SPD)	Castilla y León	Soria	Diputación provincial	6,5€ / paciente / semana	2018
	País Vasco	Araba/Álava	Administración autonómica	31,63€ / paciente / mes	2009
		Bizkaia			
		Gipuzkoa			
Programa de Detección Precoz de Cáncer de Colon y Recto (PDPCCR)	Cataluña	Barcelona	Administración autonómica	1 € / muestra recogida y enviada	2012
		Girona			
		Lleida			
Red de farmacias Centinela	Cataluña	Barcelona	Administración autonómica + Colegio Farmacéutico de Cataluña	1000 € / año	2016
		Girona			
		Lleida			
		Tarragona			
Programa de Educación Sanitaria sobre el Buen Uso de los Medicamentos (PESBUM)	Cataluña	Barcelona	Administración autonómica	Administración: pago al farmacéutico comunitario por sesión impartida	2019
		Girona			
		Lleida			
		Tarragona			
Distribución de medicamentos extranjeros	Navarra, Comunidad Foral de	Navarra	Administración autonómica	4€ / paciente / dispensación	2019

n.d.: No disponible.

En otros países como Inglaterra, Australia, Nueva Zelanda o Canadá la remuneración de los SPFA es cada vez mayor.

En el caso de Inglaterra, la financiación de la farmacia comunitaria se compone de una tasa de cobertura para los servicios esenciales más la retribución de los servicios avanzados, y otros márgenes (11). Los servicios esenciales son aquellos que todas las farmacias deben ofrecer, mientras que los avanzados son opcionales (12). La dispensación se reconoce como un servicio esencial y se abona una cantidad económica fija por cada acto (13). Dentro de los servicios avanzados, la remuneración depende del servicio, como son el *Medicines Use Review* (MUR), *Appliance Use Review* (AUR), *Stoma Appliance Customisation* (SAC), *Flu Vaccination Service* y el *NHS Community Pharmacist Consultation Service* (CPCS) (14). Todos los pagos son abonados por el Sistema Nacional de Salud inglés (NHS).

En caso de Australia, además de la dispensación de medicamentos, las farmacias que forman parte del programa llamado *Community Pharmacy Agreement* reciben remuneración por parte del Gobierno Federal en programas de adherencia de medicamentos, de uso de medicamentos, programas específicos para *los Aboriginal and Torres Strait Inslander People*, programas de apoyo rural y programas de salud. Existen otros servicios de revisión de la medicación y de inmunización que también son remunerados en algunos casos (12).

En Nueva Zelanda, el Departamento de Salud de cada distrito es el encargado de remunerar a la farmacia por cada acto de dispensación. Además de la propia dispensación, existen otros servicios financiados como es el caso del servicio a pacientes crónicos, el servicio de seguimiento a pacientes sometidos a tratamientos con anticoagulantes, la Revisión del Uso de Medicamentos (RUM), evaluación de medicamentos, servicio de dispensación de clozapina, servicios de atención en residencias y servicios de co-dispensación de opioides (11).

En Canadá, el sistema de retribución es diferente en función de la jurisdicción de cada provincia, por lo que la remuneración de los servicios también es diferente en cada región. Por ejemplo, en la mayoría de las regiones se remunera algún servicio

de inmunización pero solo en tres de ellas se financia el servicio de la revisión de la medicación (11).

1.4. Errores de medicación y SPFA

Los errores de medicación se definen como "*cualquier evento prevenible que pueda causar o conducir a un uso inadecuado de medicamentos o daños al paciente mientras el medicamento está bajo el control del profesional de la salud, el paciente o el consumidor*" (15). Los factores que predisponen la aparición de estos errores pueden estar asociados a los profesionales de la salud, los pacientes, el ambiente de trabajo, los medicamentos, los sistemas informáticos y/o a la comunicación de atención primaria y secundaria (16).

En el año 2000, el grupo de trabajo de Ruiz Jarabo y cols. (17) establecieron 13 procesos de la cadena terapéutica en los que hay una mayor posibilidad de error, como son: (i) la transición asistencial, (ii) selección y adquisición, (iii) prescripción, (iv) transcripción, (v) validación, (vi) preparación en farmacia, (vii) dispensación, (viii) almacenamiento, (ix) preparación en la unidad de enfermería o por el paciente cuidador, (x) administración en la unidad de enfermería o por el paciente cuidador, (xi) monitorización del paciente/tratamiento, (xii) educación al paciente, y (xiii) automedicación/utilización medicamentos *over the counter* conocidos como medicamentos OTC. En función de en dónde haya estado el problema se implementa un procedimiento distinto con el responsable sanitario correspondiente.

Esta clasificación, orientada al ámbito hospitalario, se puede adaptar al de la farmacia comunitaria especificando los puntos críticos de la cadena terapéutica donde el farmacéutico juega un papel importante tanto en la prevención e identificación como en la reducción de los errores de medicación. Entre estos puntos se destacan la revisión y la monitorización del tratamiento (Figura 3).

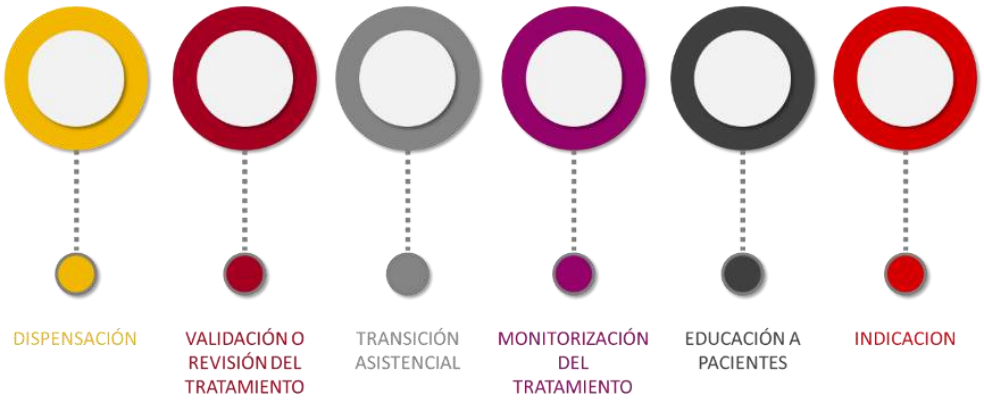

Figura 3. Puntos críticos de la cadena terapéutica donde el farmacéutico comunitario puede intervenir para prevenir, identificar o reducir los errores de la medicación.

La mayoría de los SPFA se relaciona con alguno de estos puntos de la cadena terapéutica, ya que contribuyen a la identificación, disminución o prevención de los errores de la medicación (Tabla 2).

Tabla 2: Servicios Profesionales Farmacéuticos Asistenciales que están implicados en los puntos críticos de la cadena terapéutica.

Punto crítico de la cadena terapéutica	SPFA implicados
Dispensación	Dispensación Formulación magistral
Validación o revisión del tratamiento	Detección discrepancias de medicamentos Revisión del uso de los medicamentos Revisión de botiquines Seguimiento farmacoterapéutico
Transición asistencial	Conciliación de la medicación
Monitorización del tratamiento	Adherencia terapéutica Seguimiento farmacoterapéutico Farmacovigilancia
Educación a pacientes	Asesoramiento sobre medicamentos
Indicación	Indicación

SPFA: Servicio profesional farmacéutico asistencial.

Ante el aumento del consumo de medicamentos que existe actualmente, los SPFA pueden mejorar la calidad de vida de los pacientes ya que están orientados a garantizar un uso más seguro, efectivo y eficiente de los medicamentos (7).

El presente trabajo se centra en dos puntos de la cadena terapéutica: (i) En la validación o revisión del tratamiento con el servicio de detección de discrepancias de los medicamentos, y (ii) en la monitorización del tratamiento, con el servicio de adherencia terapéutica. Ambos servicios están estrechamente relacionados con la polimedicación, ya que una cantidad elevada de medicamentos prescritos puede interferir en una correcta adherencia terapéutica, y puede dar lugar a más discrepancias entre lo que el paciente tiene prescrito en su hoja de tratamiento activo y lo que realmente toma. Además, los dos servicios están relacionados con una adecuada toma de la medicación. El servicio de adherencia terapéutica tiene como objetivo que la toma del medicamento se haga de acuerdo a la posología prescrita, mientras que el servicio de detección de discrepancias vela porque no haya diferencias entre los medicamentos que el paciente tiene prescritos y los que realmente toma.

2. ADHERENCIA TERAPÉUTICA

2.1. Definición y terminología

La *adherencia* se define como "*el grado en el que la conducta de un paciente, en relación con la toma de medicación, el seguimiento de una dieta o la modificación de hábitos de vida, se corresponde con las recomendaciones acordadas con el profesional sanitario*" (18). Esta definición de la OMS del año 2003 se basa en la anterior propuesta por Haynes y Sackett (19) y Rand (20) para el término *cumplimiento* y actualiza la definición acordada por los participantes en la reunión de adhesión de la OMS de junio de 2001, donde se acordó definir la adherencia como "*la medida en que el paciente sigue las instrucciones médicas*" (21).

A pesar de que la Sociedad Internacional de Farmacoeconomía e Investigación de Resultados Sanitarios (ISPOR) definiera como sinónimos los términos *adherencia* y *cumplimiento,* ambos tienen un matiz distinto. El término *cumplimiento* está relacionado con un enfoque de obediencia y sumisión por parte del paciente, mientras que el término *adherencia* tiene en cuenta el consentimiento del paciente y la colaboración activa entre este último y el profesional sanitario (22,23). Por ello, en el presente documento se utilizará únicamente el término *adherencia* y siempre referido a la adherencia a la medicación, entendida como el proceso por el cual los pacientes toman cada medicamento según lo prescrito (24).

Además de la *adherencia,* también se debe considerar la *persistencia*, es decir, cuánto tiempo un paciente toma de forma adecuada el medicamento, la cual se define como "e*l tiempo que transcurre desde el inicio al final del tratamiento de un paciente*" (25) (Figura 4).

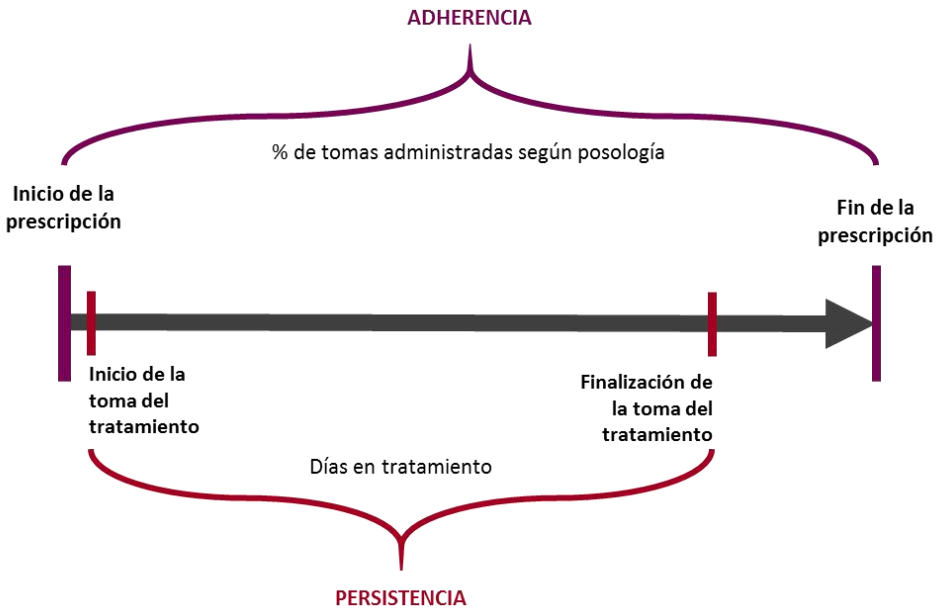

Figura 4. Representación gráfica de la adherencia y la persistencia (26).

2.2. La falta de adherencia, un problema de salud pública

El envejecimiento, el sedentarismo y los hábitos de vida no saludables de la población están dando lugar a un incremento de enfermedades crónicas a nivel mundial, sobre todo en los países desarrollados. Actualmente, más de la mitad de la población adulta y en torno al 10% de la población infantil presenta una enfermedad crónica diagnosticada (27). Las principales enfermedades crónicas, también llamadas enfermedades no transmisibles, incluyen las enfermedades cardiovasculares, las enfermedades respiratorias crónicas, el cáncer y la diabetes (28). El tratamiento farmacológico es la principal estrategia terapéutica en los pacientes crónicos. Sin embargo, se estima que el 50% de los pacientes con patologías crónicas, no siguen de forma adecuada el tratamiento farmacológico. En la actualidad, la falta de adherencia al tratamiento farmacológico, constituye un gran problema de salud pública y un gran reto a abordar por los sistemas sanitarios (18).

La falta de adherencia puede presentarse de distintas formas (24):

- Inicio tardío: Retraso en el comienzo del tratamiento con respecto a la prescripción médica.
- Sin inicio: Cuando el paciente ni siquiera comienza con el tratamiento.
- Implantación sub-óptima: Cuando el tratamiento no se toma de la misma forma que la prescrita.
- Discontinuación anticipada: Cuando el paciente interrumpe el tratamiento antes de la fecha de finalización.

Independientemente de la forma en la que se presente, la falta de adherencia a los tratamientos farmacológicos presenta unas consecuencias a nivel clínico, económico y humanístico (Figura 5).

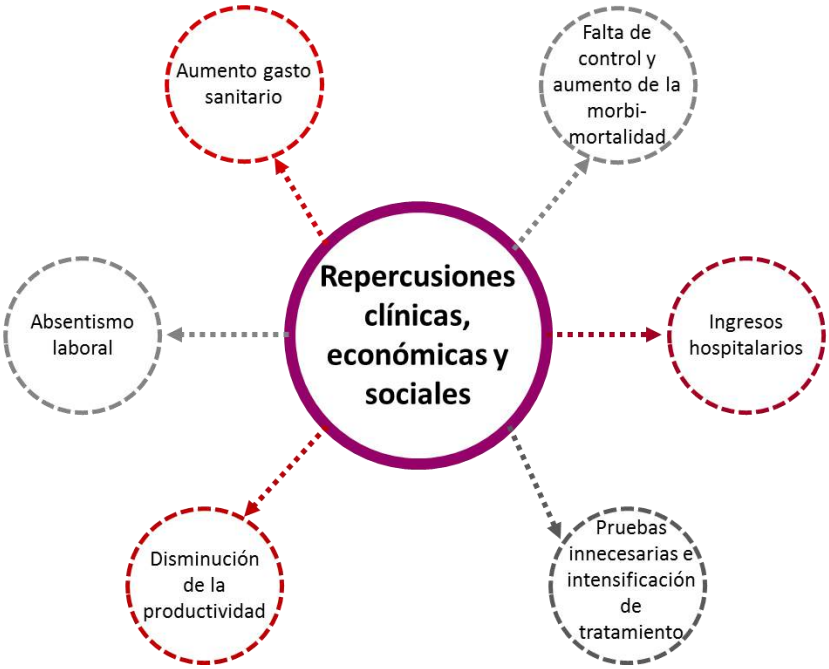

Figura 5: Repercusiones clínicas, económicas y sociales de la falta de adherencia.

A nivel **clínico,** la falta de adherencia está estrechamente relacionada con el fracaso terapéutico, ya que la efectividad del medicamento se ve comprometida cuando la

toma no se hace de acuerdo a la posología prescrita, con el consecuente impacto negativo en la salud del paciente (24). Estas consecuencias clínicas, no obstante, dependen del tipo de medicamento, del grado de falta de adherencia o de la eficacia, entre otros factores. Además, se ha demostrado que este fenómeno repercute en la calidad y esperanza de vida de las personas, disminuyendo el perfil de seguridad de los tratamientos y aumentando el riesgo de hospitalizaciones y de morbi-mortalidad. Se estima que el 4,3% de las hospitalizaciones y 125.000 muertes anuales a nivel mundial se deben a la falta de adherencia. Varios estudios muestran que un alto porcentaje de estos problemas relacionados con la falta de adherencia, se correspondían con tratamientos farmacológicos utilizados en enfermedades cardiovasculares, en su mayoría prevenibles con un buen control de la adherencia (29,30).

A todo lo mencionado anteriormente hay que añadir el gran impacto **económico** que supone la falta adherencia para los sistemas sanitarios. Las consecuencias económicas se derivan de problemas de salud o complicaciones asociadas a la falta de adherencia al tratamiento farmacológico, y que hubiesen sido evitadas con la toma adecuada del mismo. El consumo de estos recursos sanitarios, representa el 4,6% del gasto mundial anual en salud (31). Los últimos datos reflejan que el coste económico anual de la falta de adherencia, ajustado por enfermedad y por persona, oscila entre 949 y 44.190 dólares a nivel mundial (32). Así, en un estudio que utilizó el modelo Markov, concluye que, por ejemplo, en el caso de las enfermedades cardiovasculares el aumento en un 10% de la adherencia evitaría 8.700 muertes y 7.650 eventos cardiovasculares, además de suponer un ahorro del gasto sanitario de 75 millones de euros (33).

La falta de adherencia también presenta consecuencias **humanísticas o sociales**, como el aislamiento, que se acentúan más en enfermedades con elevada carga social como pueden ser las enfermedades mentales o el VIH, entre otras. Además, la falta de adherencia está relacionada con el absentismo laboral y como consecuencia con una disminución de la productividad (34).

De cara a un futuro no muy lejano, cabe destacar que los costes económicos, clínicos y humanísticos seguirán aumentando a medida que lo hagan las enfermedades crónicas y, con ello, la tasa de pacientes no adherentes (25).

2.3. *Causas y factores de la falta de adherencia*

La adherencia es un fenómeno multidimensional determinado por cinco grupos de factores: los sociales y económicos, los relacionados con el sistema sanitario, los relacionados con la enfermedad, los relacionados con el tratamiento y los relacionados con el paciente (Figura 6).

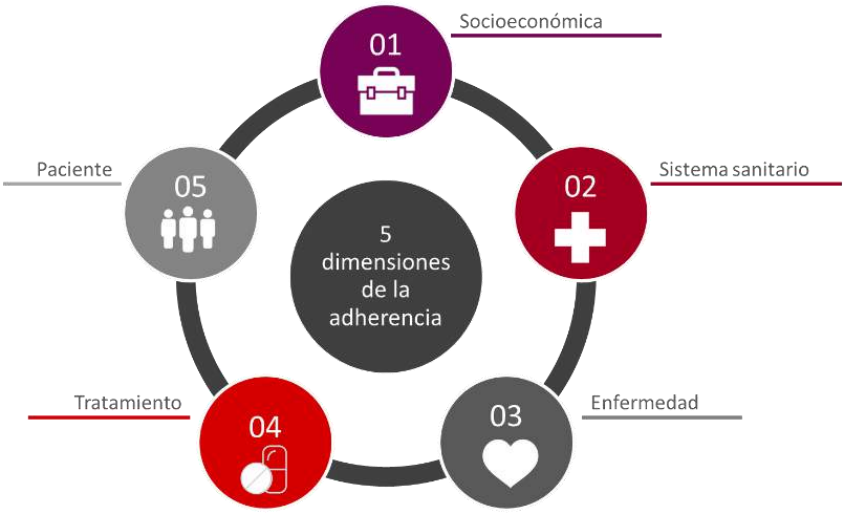

Figura 6. Factores que influyen en la adherencia al tratamiento (18).

Dentro de la **dimensión socioeconómica**, la pobreza, el bajo nivel educacional, el desempleo, la falta de apoyo social efectivo, las condiciones de vida inestables, las largas distancias al centro de salud o el elevado coste de la medicación tienen un impacto negativo en la adherencia del paciente al tratamiento (18). Estudios recientes afirman que pertenecer a una minoría étnica puede estar asociado a una menor

adherencia, mientras que un mayor estatus financiero y una mejor posición socioeconómica parecen tener un impacto positivo (35). Además, la raza, se asocia a menudo con creencias culturales, y la edad, es otro factor que influye en la adherencia (18). Por ello, se recomienda estudiar la adherencia en función del grupo de edad al que pertenece el paciente (niños dependientes de sus padres, adolescentes, adultos o pacientes de edad avanzada). El género también es otro factor que se ha descrito que puede tener un impacto en la adherencia, comprobándose que las mujeres y los hombres tienen diferentes patrones de comportamiento y diferentes razones para ser no adherentes (36).

En cuanto al **Sistema Sanitario**, los servicios de salud con defectos en su desarrollo, los sistemas de distribución de medicamentos deficientes, la falta de confianza entre los profesionales sanitarios y el paciente, la falta de percepción de la necesidad de tomar la medicación y las preocupaciones acerca de la misma, ejercen un papel importante en la falta de adherencia al tratamiento (18). Es importante que el profesional sanitario se implique de forma activa en la enfermedad del paciente , ya que si el paciente percibe un abandono por parte de su médico o FC es uno de los factores que más impacto tiene en la adherencia (37). Además, los pacientes valoran también muy positivamente la comunicación entre profesionales sanitarios, aunque consideran que es un aspecto a reforzar (38).

En lo que respecta a la **enfermedad**, la severidad de los síntomas, el nivel de discapacidad resultante de la enfermedad, la progresión o la efectividad de los tratamientos existentes son factores que influyen en la adherencia (18). Las patologías crónicas presentan mayor nivel de falta de adherencia que las patologías agudas (39). Existe una falta de adherencia notable en los pacientes con depresión (72%), enfermedades respiratorias como la enfermedad pulmonar obstructiva crónica (EPOC) (59%) o enfermedades cardiovasculares (48%). En contraposición, en patologías como el cáncer o en enfermedad por el VIH el grado de adherencia es alto, con valores superiores al 70% (33). Por ello, en los últimos años, muchos grupos de investigación se han centrado en el estudio de la falta de adherencia al tratamiento crónico y en diseñar estrategias de intervención que logren mejorarla (32,39–41).

Existen diferentes factores referidos al **tratamiento farmacológico,** que afectan a la adherencia, los más característicos son los relacionados con la complejidad del régimen posológico, la duración del tratamiento, la eficacia de los tratamientos previos, los cambios frecuentes en el tratamiento y los efectos secundarios (42). La polimedicación es uno de los principales fenómenos asociados a la falta de adherencia, ya que, cuanto mayor es la complejidad del tratamiento prescrito mayor es la probabilidad de que éste no se siga de forma adecuada.

En los últimos años se ha comprobado que, en la mayoría de los casos, el **paciente** es el único responsable de la administración inadecuada de su tratamiento. En muchas ocasiones esto es debido a problemas comportamentales y conductuales que hacen que la persona sea incapaz de ser adherente a su tratamiento. Por ello, entre los factores relacionados con el **paciente** (figura 6), se engloban las percepciones y expectativas que tiene el paciente acerca del tratamiento, los recursos, conocimientos y creencias. La motivación de un paciente para tomar de manera adecuada una medicación se influencia por el interés y la confianza en seguir la pauta (43).

2.4. *Clasificación de la falta de adherencia*

Los tipos de la falta de adherencia es un aspecto importante a tener en cuenta a la hora de escoger la intervención más adecuada, ya que la estrategia planteada será diferente. La falta de adherencia se puede clasificar de diferente forma en función del criterio que se utilice (23).

- <u>En función de la intencionalidad:</u>
  - Falta de adherencia intencionada: es aquella situación en la que el paciente de forma voluntaria y consciente decide no tomar el medicamento debido a determinadas creencias y comportamientos. Existen diferentes marcos teóricos que explican esta relación como son el modelo de necesidad percibida y preocupaciones (44), creencias en salud (45), información-motivación-estrategia (46), modelo transteórico para el cambio (46) y entrevista motivacional (47).

- Falta de adherencia no intencionada: es aquella situación en la que el paciente no es consciente de que no toma el medicamento, o de que no lo toma de forma adecuada. Las causas de esta falta de adherencia pueden estar relacionadas con el paciente, con el tratamiento o con el sistema sanitario (48), siendo el olvido, la falta de autonomía del paciente o la complejidad de los tratamientos las más habituales.

– En función de la temporalidad:
  - Primaria: Situación en la que el paciente no llega ni a retirar su medicamento tras la prescripción del médico.
  - Secundaria: Situación en la que el paciente, una vez retirado el medicamento, no sigue las pautas prescritas.

– En función del periodo de seguimiento:
  - Incumplimiento parcial: Situación en la que el paciente es adherente al tratamiento en algunos momentos concretos.
  - Incumplimiento secuencial: Situación en la que el paciente es adherente durante unos periodos de tiempo.
  - Cumplimiento de bata blanca: Situación en la que el paciente es adherente cuando tiene cercana una visita médica.
  - Incumplimiento completo: Situación en la que el paciente abandona el tratamiento de forma indefinida.

2.5. *Determinación de la adherencia*

El método ideal para la determinación de la adherencia debería ser rápido, fiable, sensible, específico, barato y reproducible. Sin embargo, ninguno de los métodos habituales cumple todas estas cualidades, por lo que se debe escoger la mejor herramienta o combinación de herramientas para cada momento y tener en cuenta las limitaciones de cada uno de ellos, a la hora de interpretar resultados y sacar conclusiones.

La adherencia a un tratamiento se puede medir mediante métodos directos o indirectos (33). Los métodos directos son aquellos que determinan la concentración de un fármaco en los fluidos corporales (sangre y orina, habitualmente), o los que se basan en la observación directa de la toma del medicamento. Los métodos indirectos son aquellos que, como su propio nombre indica, estiman la toma del medicamento utilizando distintas herramientas como pueden ser los cuestionarios, entre otras. Todos estos métodos tienen diferente precisión y debido a sus ventajas e inconvenientes, también tienen diferente frecuencia de uso (Figura 7).

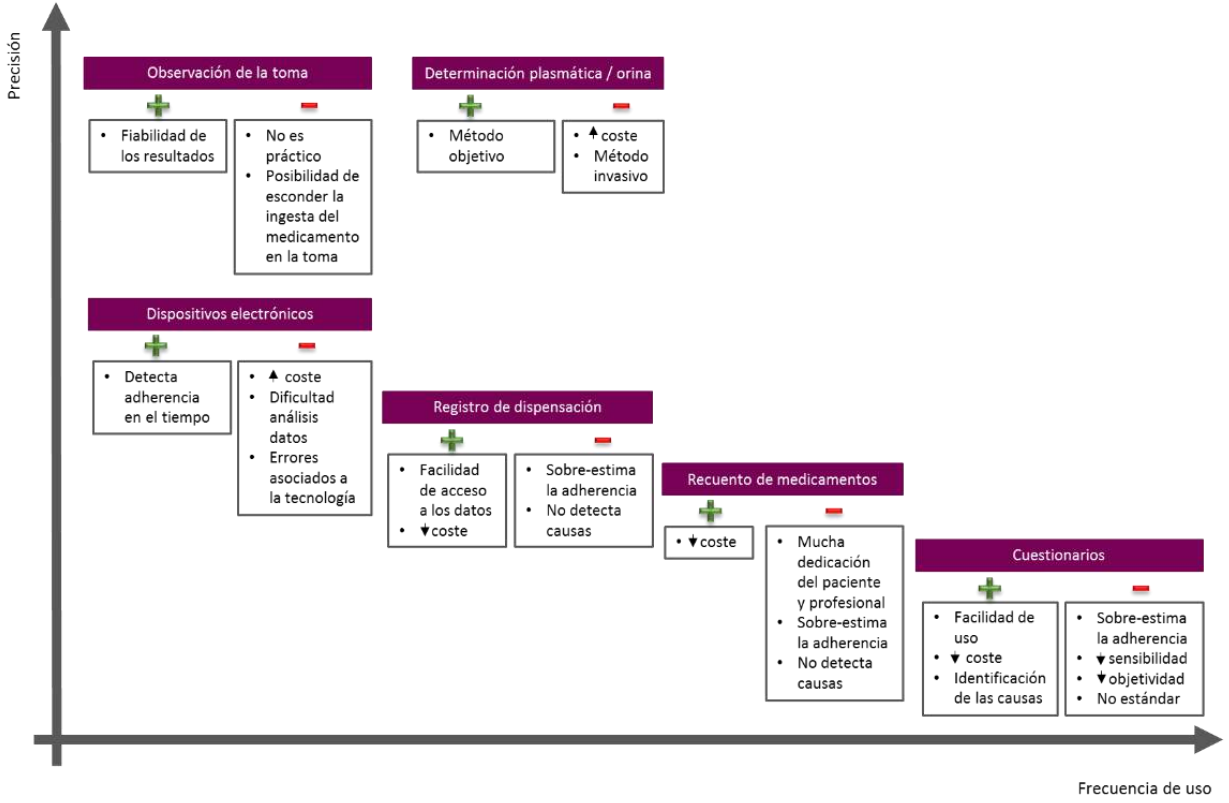

Figura 7. Clasificación de los métodos de determinación de la adherencia en función de la precisión y frecuencia de uso. Ventajas y desventajas de cada uno de ellos (33,49).

El método de determinación en plasma u orina, se basa en determinar la concentración de fármaco o metabolito en estos fluidos. A pesar de presentar desventajas importantes como puede ser el elevado coste, necesidad de personal sanitario e instrumental específico o la escasez de estudios farmacocinéticos poblacionales con los que comparar los resultados obtenidos, puede ser muy útil en determinados medicamentos (ej. inmunosupresores) o en situaciones de toxicidad e interacciones (33,49).

La observación de la toma se basa en supervisar de manera directa y presencial que el paciente ingiere la medicación. El principal problema de este método es la necesidad de que una persona supervise todas las tomas del paciente, lo cual puede no ser viable en todos los ámbitos. Esta es una práctica habitual en residencias y/o hospitales, aunque no hay que descartar que el paciente pueda esconder la medicación ante el supervisor (33,49).

Los dispositivos electrónicos son sistemas informatizados que controlan la apertura de los envases. También registran el momento de esa apertura para un mayor control del cumplimiento de la posología. Para minimizar sesgos de interpretación de los datos, por mal uso del dispositivo (por ejemplo, extraer más de una dosis en una misma apertura), se suele cumplimentar con un diario de administración de las tomas (33,49).

La utilización de los registros de dispensación ha ido en aumento en los últimos años, sobre todo desde la implantación de la receta electrónica en todas las farmacias a nivel nacional. Se basa en cuantificar, en función de la posología, cuánto le dura un envase a un paciente y cruzar este dato con las fechas de recogida de la medicación en la farmacia. Este método es relativamente económico y permite al farmacéutico o al médico establecer de forma rutinaria e informatizada un seguimiento sobre la adherencia (33,49).

El recuento de medicamentos, se basa en contabilizar el número de fármacos que el paciente retorna a la farmacia. Para que el paciente se considere adherente, la cantidad de medicamentos devueltos debería ser acorde a la de medicamentos

teóricos calculados a partir de la posología. El sistema personalizado de dosificación (SPD) permite hacer este recuento de manera rápida y eficaz (33,49).

Los cuestionarios por su parte, son el método más utilizado para la medición de la adherencia. Aunque cada cuestionario puede tener sus peculiaridades, la mayoría consisten en una serie de preguntas sobre la toma de la medicación que el paciente ha de contestar. En función de sus respuestas se le considerará adherente o no adherente al tratamiento. Además, también se podrá cuantificar la adherencia en función de las tomas realizadas. Existe una gran diversidad de cuestionarios por lo que es muy importante que el cuestionario a utilizar esté validado en la enfermedad y población diana del estudio (Tabla 3).

Tabla 3. Cuestionarios de adherencia en función de la patología (50).

Enfermedad	Cuestionario	Número de ítems
Asma	Four Item Questionnaire for Asthma Inhaler Adherence (51)	4 ítems
	Pediatric Inhaler Adherence Questionnaire (52)	6 ítems
Esclerosis múltiple	Multiple Sclerosis Treatment Adherence Questionnaire (MS_TAQ) (53)	30 ítems (en tres grupos: Barreras, Efectos secundarios y Estrategias de afrontamiento)
Hemofilia	Hemophilia Regimen Treatment Adherence Scale (54)	24 ítems
Hipertensión	Brief Adherence Self-Report Questionnaire (ASRQ) (55)	6 ítems
	Hill-Bone Compliance to high blood pressure therapy scale (56)	14 ítems (tres escalas para reducir el sodio, mantener citas y tomar medicamentos)
	Voils Measure of Extent and Reasons for Medication Non-Adherence (57)	3 ítems para grado de adherencia y 21 para las causas
Inmunosupresión	Frazier Noncompliance Inventory (FNI) (58)	11 ítems
	Immunosuppressive Therapy Adherence Scale (ITAS) (59)	5 ítems
	Medication Immunosuppressive Therapy Adherence Scale (ITAS-M) (60)	4 ítems
Osteoporosis	Adherence Evaluation of Osteoporosis Treatment (ADEOS-12) (61)	12 ítems

Tabla 3 (cont.): Cuestionarios de adherencia en función de la patología (50).

Enfermedad	Cuestionario	Número de ítems
Reumatología	Compliance-Questionnaire-Rheumatology (CQR) (62)	19 ítems
Salud mental	Brief Adherence Rating Scale (BARS) (63)	4 ítems
	Tablets Routine Questionnaire (TRQ) (64)	2 ítem sobre dificultad para tomar la medicación + 4 sobre dosis olvidadas
VIH / Sida	AIDS Clinical Trials Group (*ACTG*) *Adherence* Questionnaire (65)	1-5 ítems
	Community Programs for Clinical Research on AIDS (CPCRA) Antiretroviral Medication Self-Report (66)	Recuperación del medicamento de 3 o 7 días y 10 razones posibles para las dosis antirretrovirales perdidas
	Self-Rating Scale Item (SRSI) (67)	1 ítem
	Self-Reported Adherence Questionnaire (SERAD) (68)	Tres componentes (la segunda parte incluye una sección de 13 elementos por motivos de no adherencia)
	Self-Reported Questionnaire Assessing Adherence to Antiretroviral Medication (69)	9 ítems
	Simplified Medication Adherence Questionnaire (SMAQ) (70)	6 ítems
	Visual Analog Scale (VAS) (71)	1 ítem (el paciente marca su grado de adherencia en una escala)
Generales	Morisky Adherence Questionnaire 4 item (MAQ) (72)	4 ítems
	Morisky Adherence Questionnaire 8 item (MAQ) (73)	8 ítems
	Adherence Estimator (74)	3 ítems
	Adherence to Refills and Medication Scale (ARMS) (75)	12 ítems
	Brief Medication Questionnaire (BMQ) (76)	9 ítems
	Medical Outcomes Study (MOS) (77)	5 ítems
	Medication Management Instrument for Deficiencies in the Elderly (MedMaIDE) (78)	20 ítems
	Medical Adherence Measure (79)	Entrevista semi-estructurada

2.6. *Estudios publicados sobre la mejora de la adherencia*

La falta de adherencia es un problema que ha sido estudiado desde hace años. Durante este tiempo se han propuesto diferentes intervenciones para mejorar los resultados. Sin embargo, las dificultades para investigar en adherencia ya sea por la variabilidad existente entre medicamentos, enfermedades o pacientes, o porque los métodos de medición no son los más adecuados, hacen que a día de hoy no exista un procedimiento totalmente consolidado.

Las intervenciones múltiples parecen tener un efecto mayor en la mejora de la adherencia debido, posiblemente, a que existen numerosos puntos de control entre la prescripción de un medicamento y la toma del mismo. Aunque, independientemente de la intervención, hay tres elementos esenciales que deben ser comunes a todas ellas (80): (i) una comunicación efectiva entre todos los profesionales sanitarios, pacientes y/o cuidadores, (ii) facilitar en la medida de lo posible la toma correcta de los medicamentos con estrategias concretas como son, pautas posológicas sencillas, revisiones de la toma de la medicación, uso de SPDs, empleo de recordatorios etc., y (iii) esfuerzo y constancia por parte del personal sanitario apoyando y revisando continuamente la situación.

La farmacia, y por lo tanto el FC, ocupa un lugar privilegiado y desempeña un papel esencial en toda la secuencia de acontecimientos para mejorar el grado de control de la adherencia de los pacientes.

A nivel nacional, se han llevado a cabo varios estudios de investigación en farmacia comunitaria con el objetivo de promover la adherencia al tratamiento. Todos estos estudios, han concluido que la farmacia comunitaria es un establecimiento sanitario muy apropiado para ofrecer un servicio eficaz y de calidad para la mejora de la adherencia de los pacientes (81–87). Fikri-Benbrahim y cols. (81) en 2016, realizaron un estudio de 6 meses en 13 farmacias comunitarias españolas y concluyeron que la intervención educacional aumenta la adherencia en pacientes sometidos a tratamiento antihipertensivo, comparado con la práctica habitual. Desde el CGCOF se puso en marcha el proyecto “AdherenciaMED” con el objetivo del diseñar y evaluar el impacto clínico, económico y social de un servicio enfocado a la mejora de la

adherencia terapéutica (82). En la fase piloto, que tuvo lugar entre octubre de 2017 y abril del 2018, se concluyó que la intervención del farmacéutico, a través del servicio de adherencia terapéutica, es efectiva ya que se aumentó el número de pacientes adherentes y se mejoró el uso de los medicamentos, todo ello con un impacto positivo en el control clínico de las enfermedades y un aumento de la calidad de vida de los pacientes. Además, el servicio se consideró coste-efectivo con un beneficio neto de 38 euros por cada euro invertido por paciente en 6 meses. Por otra parte, Machuca y cols. (83) observaron, en un estudio experimental en pacientes con prescripción antibiótica, una mejor adherencia y percepción de la salud en aquellos pacientes que recibían la información del FC por escrito respecto a aquellos a los que se les proporcionaba de manera verbal.

Por último, varios estudios realizados en farmacias comunitarias avalan la eficacia del SPD en el aumento de la adherencia al tratamiento (84–86). Mediante el programa "Adhiérete", impulsado por el CGCOF con el objetivo principal de mejorar la adherencia a los tratamientos en pacientes mayores, crónicos, polimedicados e incumplidores, se comprobó que la utilización de esta herramienta y de sistemas de recordatorios como las aplicaciones móviles aumentan en un 40,7% la adherencia a los tratamientos y mejoran en 5,5 puntos de media la calidad de vida, además de reducir en un 33,4% los problemas relacionados con los medicamentos (87).

2.7. Importancia de la adherencia a estatinas en el tratamiento de la hipercolesterolemia

La hipercolesterolemia es uno de los principales factores de riesgo de las enfermedades cardiovasculares, causantes de un tercio de las muertes mundiales (88). Según la OMS y el Grupo de Recursos Cardiovasculares, Europa es el continente con mayor prevalencia de hipercolesterolemia en el mundo, donde un 54% de la población europea tiene niveles altos de colesterol (89,90). Esta situación da lugar a 2,6 millones de muertes por año y 29,7 millones de años de vida ajustados por discapacidad (AVAC), en todo el mundo (89).

La actividad física, la dieta y la adherencia al tratamiento son aspectos clave en el control de las dislipemias (91,92), sin embargo, la adherencia a los tratamientos hipolipemiantes es baja (93) y los hábitos de vida poco saludables son habituales en los pacientes que padecen hipercolesterolemia (94).

La falta de adherencia a estatinas es un problema de nivel mundial y se estima que al inicio del tratamiento solamente el 50% de los pacientes es adherente y este porcentaje suele disminuir con el paso del tiempo (95). Esta falta de adherencia está asociada a mayores tasas de hospitalización (96), mayores tasas de morbilidad y mortalidad (97,98) y a un aumento de los costes sanitarios (99,100) superando anualmente los 210 mil millones de euros solamente en Europa (101).

De todo ello, surge la necesidad de estudiar el efecto de la intervención del farmacéutico comunitario en la mejora de la adherencia a medicamentos hipolipemiantes y determinar si esta mejor influye en los resultados clínicos relacionados con la enfermedad. También es importante conocer las causas de la falta de adherencia y determinar si las intervenciones realizadas mejoran la adherencia de la misma forma en función de las diferentes causas y poner en contexto los resultados obtenidos con los estudios previamente publicados, contextualizando así la evidencia científica sobre el tema para evaluar el coste-efectividad de estos servicios y que las políticas sanitarias apoyen y remuneren este tipo de actividades.

3. DETECCIÓN DE DISCREPANCIAS EN EL USO DE MEDICAMENTOS

3.1. Errores de medicación y discrepancias en el uso de medicamentos

Los errores de medicación se encuentran entre las 10 principales causas de muerte en el mundo (102). Estos errores pueden causar incidencias en la seguridad del paciente y están asociados a una mayor tasa de hospitalización y a un aumento de la morbilidad y la mortalidad (103). Así, los errores de medicación constituyen la causa evitable más común de los efectos adversos relacionados con la medicación y suponen una carga importante para la salud pública, con un coste anual estimado de entre 4,5 y 21,8 billones de euros (104). Debido a su impacto, la OMS ha incluido medidas de prevención para disminuir los errores de medicación en el documento *"Global Patient Safety Challenge*" (105). Las medidas adoptadas para reducir la frecuencia y el impacto de los daños prevenibles relacionados con los medicamentos como consecuencia de un error, un accidente o un problema de comunicación, parece que aumentan la seguridad de los pacientes (106). De hecho, las estadísticas muestran que estas estrategias podrían prevenir 95.000 muertes al año en Europa (103). Uno de los SPFA que pretenden reducir la existencia de estos errores es el servicio de *Conciliación de la medicación*.

Penm y cols. (107), en el año 2019, crearon un grupo de trabajo de expertos en la materia a nivel mundial que propuso la siguiente definición para la conciliación de medicamentos: "*El proceso de crear la lista más precisa posible de todos los medicamentos que un paciente está tomando y comparar esa lista con las prescripciones. Así, las alergias, historial de reacciones adversas a medicamentos y las ayudas a los medicamentos se enumeran con el objetivo de proporcionar medicación correcta al paciente en todos los puntos de transición dentro del sistema sanitario*".

Teniendo en cuenta la forma de detección de discrepancias que se hace en el servicio de conciliación, si esto se traslada a un ámbito comunitario, podemos definir el servicio de detección de discrepancias en el entorno comunitario como: "*aquel proceso por el cual se elabora la relación más precisa posible de todos los*

medicamentos que un paciente utiliza y los medicamentos prescritos, sin tener en cuenta una transición asistencial" y será la que se tenga en cuenta a partir de ahora en este documento, refiriéndonos a ella como "detección de discrepancias". Se estima que 24% de las reacciones adversas a medicamentos están relacionadas con alguna discrepancia en los medicamentos, por lo que, debido al impacto económico y sanitario de las discrepancias, actualmente es considerado un problema de salud pública (108,109). Un paciente puede tener errores de medicación de diferentes tipos (Figura 8).

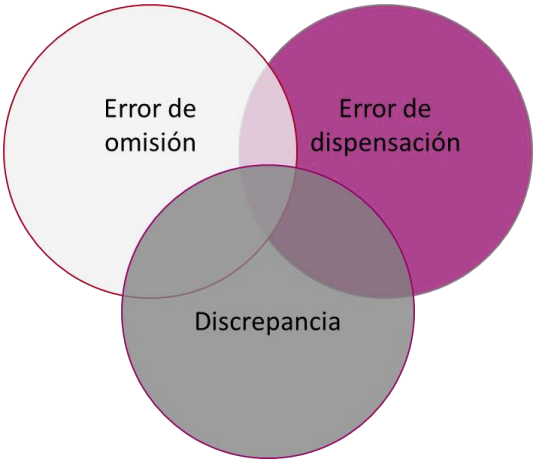

Figura 8: Clasificación de los errores de medicación que puede tener un paciente (108).

El **error de omisión** ocurre cuando el médico prescribe un medicamento, pero éste no se dispensa, el paciente no llega a recoger el medicamento en la farmacia. El **error de dispensación** ocurre cuando el medicamento se dispensa de manera incorrecta; y por su parte las **discrepancias** ocurren cuando existen diferencias entre el medicamento que utiliza el paciente y el que realmente tiene prescrito.

Una reciente revisión sistemática apunta a que la prevalencia de los errores de medicación en la farmacia comunitaria puede ascender hasta el 73% (108), por lo que las estrategias llevadas a cabo a este nivel pueden ser útiles en la prevención, identificación o solución de estos problemas. La detección de discrepancias es

considerada por diferentes organizaciones como un proceso determinante en la detección de errores de medicación y en la mejora de la salud de los pacientes (110,111).

En este sentido, una de las muchas finalidades de los SPFA es la de detectar y disminuir los errores de medicación, y en concreto las discrepancias, mediante lo que se ha denominado como 'conciliación de la medicación'.

3.2. Causas y factores de riesgo de las discrepancias en el uso de medicamentos

Los factores de riesgo desencadenantes de las discrepancias de medicamentos se engloban en tres grupos: (i) relacionados con el paciente, (ii) relacionados con el medicamento, y (iii) relacionados con el sistema sanitario (Figura 9).

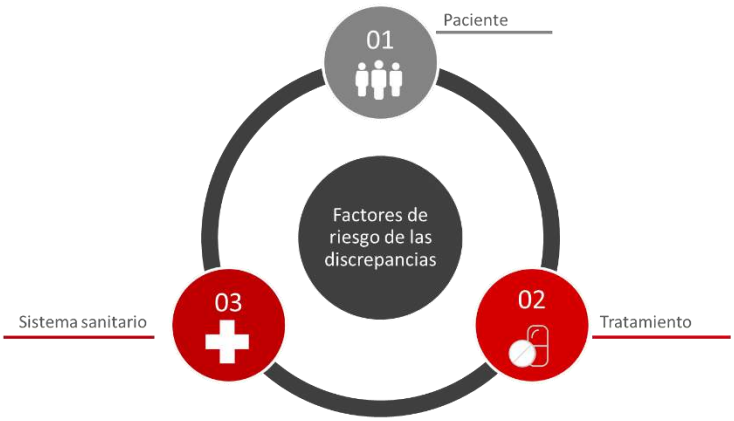

Figura 9. Factores de riesgo en la aparición de discrepancias de medicamentos (108).

Los principales factores de riesgo relacionados con el **paciente** son la polimedicación, la edad avanzada, las comorbilidades, los ingresos hospitalarios, el bajo nivel educativo y los bajos ingresos familiares. De ellos, la polimedicación y la edad avanzada son los factores de riesgo más importantes, aumentando la probabilidad de presentar una discrepancia en la medicación entre un 1,1-11,4 y 1,0-

4,0, respectivamente (112–115). En resumen, cuantos más medicamentos tenga prescrito el paciente, mayor es la probabilidad de que se presente un error de medicación (108).

Respecto a los factores relacionados con el **tratamiento**, la casuística puede ser muy variada. La falta de adherencia, la duplicidad de tratamiento, la utilización de medicamentos caducados o la discontinuidad de la medicación son solo algunos ejemplos (116,117).

Finalmente, los factores de riesgo más comunes relacionados con el **sistema sanitario** son la presencia de más de un médico prescriptor (114,118), la edad del médico prescriptor (113,119) y los cambios frecuentes en la medicación (120).

3.3. Clasificación de las discrepancias de medicamentos

La SEFH clasifica las discrepancias en función de si existe justificación o no para la diferencia encontrada (121).

- Discrepancia justificada:
  - Inicio de medicación justificada por la situación clínica.
  - Decisión médica de no prescribir un medicamento.
  - Decisión médica de cambiar la dosis, frecuencia o vía de administración de un medicamento.
  - Sustitución terapéutica.
- Discrepancia no justificada que requiere aclaración:
  - Omisión de medicamento sin justificación médica.
  - Inicio de medicamento sin justificación médica.
  - Diferente dosis, frecuencia o vía de administración de un medicamento.
  - Medicamento equivocado.
  - Prescripción incompleta.

3.4. Determinación de las discrepancias de medicamentos

El farmacéutico puede identificar las discrepancias de medicamentos en diferentes momentos (122):

- Tras una transición asistencial: es lo que propiamente se denomina *conciliación de la medicación* y consiste en elaborar una lista completa de la medicación previa al ingreso de un paciente, y compararla con la que se le había prescrito en el centro sanitario al ingreso, en los traslados y en el momento del alta (110,123). Es un proceso en el que, hasta estos últimos años, solo ha participado el farmacéutico hospitalario. A nivel nacional ha habido algunos estudios que han demostrado la efectividad del FC en este punto de la cadena terapéutica (124,125), por ello, las autoridades competentes han mostrado un gran interés por que este servicio sea ofertado en la farmacia comunitaria como un servicio profesional.
- En la visita a la farmacia hospitalaria: El farmacéutico hospitalario puede identificar diferencias entre la medicación que el paciente tiene prescrito y la que realmente utiliza en el momento de la dispensación de medicamentos en el hospital a pacientes externos, es lo que se denomina como *detección de discrepancias* desde la farmacia hospitalaria.
- Sin embargo, las discrepancias también se pueden identificar en el día a día del paciente, sin requerir una transición asistencial para su detección: El FC puede identificar diferencias entre la medicación que el paciente tiene prescrito y la que realmente utiliza en el momento de la dispensación, es lo que se denomina como detección de discrepancias desde la farmacia comunitaria.

3.5. Estudios publicados sobre la detección de las discrepancias de los medicamentos

En los últimos años se han propuesto diversas estrategias para reducir los errores de medicación que incluyen servicios de revisión y conciliación de medicamentos, el uso de sistemas automatizados de información, actividades educativas e intervenciones multicomponente (126–128). Se ha demostrado la eficacia de los farmacéuticos hospitalarios para identificar los errores de medicación (129–131)

pero los datos en el entorno comunitario son relativamente escasos y además, pocos estudios han incluido farmacéuticos comunitarios (132). Esta falta de estudios sobre la intervención de los farmacéuticos comunitarios y la experiencia previa que estos profesionales tienen en otros servicios han llevado a la OMS a considerar la participación de los farmacéuticos comunitarios como una de las estrategias prioritarias para reducir los errores de la medicación, y en concreto la detección de discrepancias, en atención primaria (16).

El servicio de detección de discrepancias a nivel comunitario es un nuevo servicio por lo que no hay evidencia sobre estudio previos que evalúen su efectividad ni coste-efectividad, por lo que, parece interesante analizar la intervención del FC en la detección de discrepancias entre lo que el médico prescribe y lo que el paciente realmente utiliza.

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HIPÓTESIS Y
OBJETIVOS

Las proyecciones demográficas mundiales prevén un aumento de la esperanza de vida, y se estima que en 2050 el número de personas mayores de 80 años se triplique. Este aumento de la edad media poblacional está estrechamente relacionado con un aumento de las enfermedades crónicas y, por tanto, con la polimedicación.

El consumo de medicamentos ha crecido durante los últimos años, produciendo un aumento de la falta de adherencia al tratamiento. Esta falta de adherencia es un problema de salud pública que afecta tanto a países desarrollados como en desarrollo y su prevalencia se sitúa en valores del 60% en el caso de las dislipemias. Esta situación da lugar a una disminución de la calidad de vida del paciente y a un aumento de los ingresos hospitalarios y de la morbi-mortalidad, con su consiguiente impacto en el gasto sanitario.

Otra consecuencia del aumento del consumo de los medicamentos es el aumento de los errores de medicación. Estos errores se encuentran entre las 10 principales causas de muerte en el mundo y son la causa evitable más común de los efectos adversos relacionados con la medicación. Prevenir los errores de medicación disminuiría las tasas de hospitalización y de morbi-mortalidad, con la consiguiente contención del gasto sanitario.

Los SPFA han demostrado ser estrategias eficaces para garantizar un uso más seguro, efectivo y eficiente de los medicamentos. Dentro de estos servicios, el servicio de adherencia terapéutica y el servicio de detección de discrepancias pueden ser servicios en los que la intervención farmacéutico comunitario mejore los resultados en salud del paciente.

Por todo ello, se plantea la hipótesis de que “la utilización de los SPFA en la farmacia comunitaria es una buena estrategia para mejorar la adherencia terapéutica e identificar las discrepancias entre los medicamentos prescritos y los que realmente utiliza el paciente”.

El **objetivo principal** de la presente tesis doctoral consiste en:

1. Evaluar el impacto de la intervención del FC en la mejora de adherencia a tratamientos hipolipemiantes y la detección de discrepancias en el uso de medicamentos.

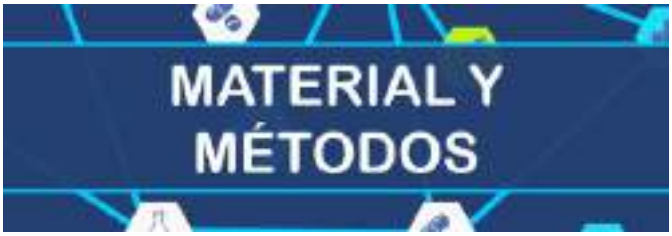
Los **objetivos específicos** de este trabajo son:

1.1 Estudiar el efecto de la intervención del FC en la adherencia a estatinas y el impacto sobre el control de los niveles de colesterol (capítulo I).

1.2 Evaluar el efecto de la intervención del FC en la adherencia a estatinas en función de la causa de la falta de adherencia del paciente (capítulo II).

1.3 Analizar sistemáticamente la evidencia publicada sobre las intervenciones que realiza el FC en la mejora de la adherencia y su relación con las variables clínicas (capítulo III).

1.4 Estudiar el impacto clínico y económico de la intervención del FC en la detección de discrepancias entre la medicación que utiliza el paciente y la que tiene prescrito en la hoja de tratamiento activo (capítulo IV).


MATERIAL Y
MÉTODOS

1. DESCRIPCIÓN DE LOS ARTÍCULOS CIENTÍFICOS

El presente trabajo se articula sobre los resultados publicados en 4 artículos científicos vinculados a una misma línea de investigación. Los artículos completos se incluyen en el apartado de resultados.

I. **Ainhoa Oñatibia-Astibia,** Amaia Malet-Larrea, Belen Larrañaga, Miguel Ángel Gastelurrutia, Begoña Calvo, Dulce Ramírez, Ignacio Cantero, Ángel Garay, Estibaliz Goyenechea. Tailored interventions by community pharmacists and general practitioners improve adherence to statins in a Spanish randomized controlled trial. Health Services Research. 2019;54(3):658-668.

II. **Ainhoa Oñatibia-Astibia,** Amaia Malet-Larrea, Miguel Ángel Gastelurrutia, Begoña Calvo, Dulce Ramírez, Ignacio Cantero, Estibaliz Goyenechea. Effect of health professional intervention on adherence to statin use according to the cause of patient non-adherence. International Journal of Clinical Pharmacy. 2020;42(2):331-335.

III. **Ainhoa Oñatibia-Astibia,** Amaia Malet-Larrea, Miguel Ángel Gastelurrutia, Begoña Calvo, Estibaliz Goyenechea. Community pharmacists' intervention to improve adherence to lipid lowering medication and the influence on clinical outcomes: a systematic review and meta-analysis. Journal of Evaluation in Clinical Practice (en revisión).

IV. **Ainhoa Oñatibia-Astibia**, Amaia Malet-Larrea, Amaia Mendizabal, Elena Valverde, Belen Larrañaga, Miguel Ángel Gastelurrutia, Martín Ezcurra, Leire Arbillaga, Begoña Calvo, Estibaliz Goyenechea. The medication discrepancy detection service: a cost-effective multidisciplinary clinical approach. Atención Primaria. 2020. doi: 10.1016/j.aprim.2020.04.008

Los dos primeros artículos corresponden a un estudio aleatorizado, controlado y multicéntrico. En el primero de ellos se analiza el impacto de la intervención profesional del FC y MAP en la falta de adherencia en pacientes con prescripción de estatinas y su relación con las variables clínicas. En el segundo, por su parte, se estudia la efectividad de la intervención profesional en la falta de adherencia en pacientes con prescripción de estatinas en función de las causas de la misma.

El tercer artículo recoge una revisión sistemática que contextualiza y actualiza la evidencia científica sobre las intervenciones que desempeña el FC para mejorar la adherencia a tratamientos hipolipemiantes y su relación con las variables clínicas.

El cuarto artículo consiste en un estudio experimental que analiza el impacto de un servicio de colaboración entre FC y profesionales de atención primaria para detectar y resolver discrepancias entre la medicación prescrita y la hoja de tratamiento activo.

2. METODOLOGÍA SEGUIDA EN EL DESARROLLO DE LOS ESTUDIOS

2.1. Estudio de adherencia a estatinas

El primer diseño experimental (artículos 1 y 2) consistió en un estudio randomizado y controlado de 6 meses de duración que tenía por objetivo evaluar el impacto de las intervenciones de los profesionales sanitarios (FC y MAP) en la adherencia a las estatinas y su relación con los niveles totales de colesterol, así como analizar el impacto de la intervención profesional en función de la causa de la falta de adherencia (intencionada o no intencionada).

El estudio se llevó a cabo en 46 farmacias comunitarias y 50 centros de salud de diez regiones españolas (Andalucía, Aragón, Asturias, Castilla-La Mancha, Cataluña, Extremadura, Galicia, Madrid, País Vasco y Valencia) entre febrero de 2014 y junio de 2016. Se reclutaron 746 pacientes mayores de edad (con una media de edad de 63,9 ± 11,1 años, siendo el 53,4% mujeres), que tenían prescrita al menos, una estatina en los tres meses anteriores. A continuación, se establecieron los siguientes criterios de exclusión: participación en otros programas de promoción de la adherencia o rehabilitación cardíaca, incapacidad para tomar el medicamento de forma autónoma, ser dependientes, estar residenciados, o haber sufrido algún evento cardiovascular en los 6 meses anteriores al inicio del estudio. El estudio se desarrolló según el diseño experimental recogido en la figura 1.

Tras el reclutamiento, el profesional sanitario evaluó la adherencia de los participantes utilizando el test de Morisky-Green-Levine (1), se midieron los niveles de colesterol total (CT) (mg/dl) y se recogieron datos sociodemográficos. Asimismo, se analizaron hábitos alimenticios y de ejercicio físico, basándose en las recomendaciones generales de la población española (2). Los pacientes clasificados como no adherentes en el test de Morisky-Green-Levine, se asignaron aleatoriamente, acorde con el programa *SAS software program (SAS (r) 9.2; Copyright 2002-2003 by SAS Institute Inc., Cary, NC, USA*) al grupo Intervención (INT) o al grupo No Intervención (NOINT) (Figura1).

Figura 1. Flujograma del estudio.

Los integrantes del grupo INT se sometieron a una intervención co-diseñada por farmacéuticos y médicos de atención primaria expertos en adherencia. Una vez conocida la causa de la falta de adherencia, se definió una estrategia para intentar revertirla. Para ello, los profesionales sanitarios seleccionaron el tipo de intervención dependiendo de la causa de la falta de adherencia y de las características del paciente (Tabla 1).

Tabla 1: Descripción de las intervenciones propuestas para el grupo intervención.

Causa	Tipo de falta de adherencia	Intervenciones propuestas
Falta de adherencia no intencionada		
Olvido	Olvido	- Escribir pictogramas o posología en el cartonaje. - Utilizar sistemas personalizados de dosificación.
Falta de adherencia intencionada		
Consideración inadecuada de la patología o del tratamiento	Formativo	- Proporcionar información oral y escrita estandarizada sobre la enfermedad y los beneficios del tratamiento. - Proporcionar educación sanitaria.
Polimedicación, pautas de tratamiento complicadas o reacciones adversas al medicamento.	Relacionadas con el medicamento	- Derivar al médico para ajuste de dosis o cambio de tratamiento. - Proporcionar información oral y escrita estandarizada sobre el tratamiento y los beneficios de tomarlo.
Razones culturales o creencias	Cultural	- Derivar al médico para cambio de tratamiento.
Dudas sobre la eficacia de los medicamentos genéricos, información contradictoria de los diferentes profesionales sanitarios o dificultades en el acceso al sistema de salud	Estructural	- Proporcionar información oral y escrita estandarizada sobre medicamentos genéricos. - Promover la comunicación entre farmacéutico, médico y miembros familiares.
Coste de medicamentos	Económico	- Estudiar diferentes opciones para disminuir el pago del medicamento.

A los 3 y 6 meses del inicio del estudio se analizó la eficacia de cada estrategia. En la visita realizada en la farmacia o despacho del MAP a los 3 meses se evaluó la adherencia, mientras que en la última visita (6 meses) se analizaron, además de la adherencia, los niveles de CT y se valoró la modificación de los hábitos alimenticios y ejercicio físico de los pacientes (Figura 2).

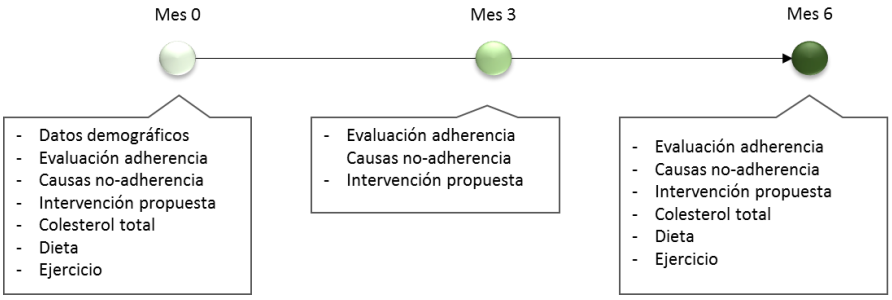


Figura 2. Desarrollo general del estudio.

Todos los participantes del estudio firmaron un consentimiento informado, previo al inicio de la intervención, según el modelo incluido en el Anexo 1. Paralelamente, se les entregó por escrito una hoja con la información detallada sobre el protocolo del programa y las actividades a realizar en cada visita. El estudio fue aprobado por los Comités de Ética para la Investigación Clínica de las 10 comunidades autónomas participantes.

Para detectar una mejora en la adherencia del 50-65% con un 80% de potencia y un valor del estadístico p bilateral de 0,05, se calculó que eran necesarios 160 pacientes por grupo. Los pacientes clasificados como no adherentes se asignaron aleatoriamente en los grupos INT y NOINT manteniendo una distribución de 1 frente a 1, como ya se ha comentado anteriormente.

El análisis estadístico de los resultados se realizó mediante el programa SPSS (versión 18 Windows XP Microsoft, USA). Todos los resultados se realizaron bajo el análisis por intención de tratar basado en el método de imputación múltiple. En primer lugar, se llevaron a cabo las pruebas de Kolmogorov-Smirnov y Shapiro-Wilk para evaluar el

ajuste de los datos a la distribución normal. Para analizar los cambios en las variables clínicas paramétricas se emplearon el test t Student de muestras pareadas o de muestras independientes, ANOVA de un factor; la prueba de Chi-cuadrado (χ^2) para estudiar la frecuencia de distribución de las variables; el análisis de covarianza (ANCOVA) para los cambios de las concentraciones de colesterol durante el estudio y el ajuste respecto a los valores iniciales; el análisis de regresión múltiple para evaluar el impacto de la intervención del profesional sanitario en los niveles de colesterol; y el análisis de la regresión logística binaria para evaluar el impacto del profesional sanitario en la adherencia. Los datos se presentaron como número y porcentaje para las variables categóricas, y como media ± desviación estándar para las variables continuas.

2.2. Revisión sistemática y meta-análisis

El siguiente estudio, plasmado en el tercer artículo científico presentado en esta tesis, consistió en una revisión sistemática de la literatura científica sobre los ensayos clínicos publicados basados en la evaluación del impacto de la intervención del FC en la adherencia al tratamiento hipolipemiante, y su relación con determinadas variables clínicas. Esta revisión se completó con un meta-análisis de los estudios encontrados (Figura 3).

Figura 3. Flujograma de la revisión sistemática

La búsqueda se realizó utilizando los términos MeSH y Emtree, para garantizar la idoneidad de la misma, a través de las bases de datos *MEDLINE, Cochrane Library, Science Direct, Scopus* y *Web of Knowledge*, teniendo en cuenta todas las publicaciones anteriores a diciembre de 2019. En cuanto a los criterios de exclusión, no se tuvieron en cuenta aquellos estudios en los que: (i) no se incluían a personas en tratamiento para hipercolesterolemia o que no tomaban medicamentos hipolipemiantes, (ii) no tenían como objetivo la mejora de la adherencia, (iii) no se determinaba la adherencia, (iv) la intervención no era proporcionada por el FC, (v) no se estudiaban otras variables clínicas y, (vii) no existiese grupo control. Tampoco se incluyeron estudios piloto, revisiones sistemáticas, meta-análisis, resúmenes de conferencias, tesis doctorales o artículos de opinión. El protocolo fue registrado y realizado conforme a los criterios PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) (3). Todos los artículos encontrados fueron importados a un gestor de referencias (Mendeley).

A continuación, dos revisores hicieron la selección de los artículos potencialmente relevantes para el estudio, de manera independiente, de acuerdo con los criterios establecidos y un tercer revisor se encargó de resolver las discrepancias encontradas. Por último, los datos más importantes de cada uno de los artículos fueron tabulados. El riesgo de sesgo se evaluó utilizando la herramienta Cochrane Risk of Bias (ROB 2.0).

Finalmente, los resultados se presentaron como media ± desviación estándar. La relación entre las variables dicotómicas se estableció mediante la estimación de las *odds ratio* (OR) con intervalos de confianza del 95%. Cuando los datos se consideraron suficientes y homogéneos se realizó un meta-análisis con el programa *Review Manager V.5.3 (RevMan 5)* (4) utilizando el método inverso-varianza y el modelo de efectos aleatorios.

2.3. Estudio de las discrepancias de la medicación

El cuarto artículo científico consistió en un estudio experimental, sin grupo control, llevado a cabo en 10 farmacias comunitarias y los 2 centros de salud de la Organización Sanitaria Integrada (OSI) Bidasoa, País Vasco, entre octubre de 2015 y septiembre de 2016. El objetivo del mismo era evaluar el impacto de un servicio de detección de discrepancias de la medicación en el número de medicamentos dispensados y el coste-efectividad del servicio. En dicho estudio participaron farmacéuticos de farmacia comunitaria y profesionales de atención primaria.
Los FC reclutaron un total de 240 pacientes para los que se habían detectado discrepancias de la medicación al no cumplir con el tratamiento especificado en la hoja de tratamiento activo, por ejemplo, no tomar un medicamento recogido en la hoja de tratamiento activo, tomar un medicamento no recogido en la hoja de tratamiento activo, no seguir la pauta de medicación prescrita o tomar el tratamiento por duplicado.

Las discrepancias encontradas por el FC eran trasladadas, a través de su correspondiente informe, a las farmacéuticas de atención primaria responsables de coordinar el programa, derivar los casos al médico de atención primaria o especialista, en función de quien hubiese realizado las prescripciones, y cuantificar

las visitas a urgencias y hospitalizaciones de los pacientes reclutados. Tanto el médico de atención primaria como el especialista analizaban la incidencia y actuaban según correspondiese, una vez recibido el informe del FC (Figura 4).

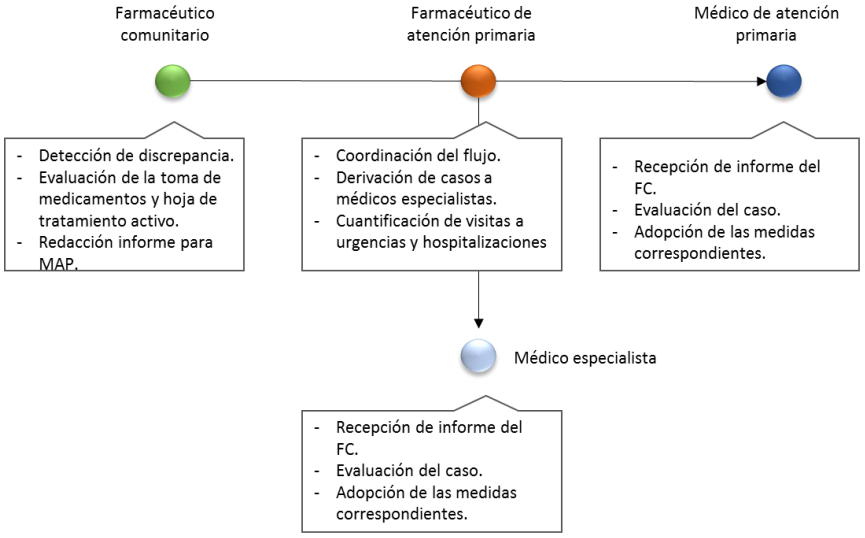


Figura 4. Desarrollo general del estudio. MAP: médico de atención primaria; FC: farmacéutico comunitario.

Todos los participantes del estudio firmaron un consentimiento informado, previo al inicio del estudio, según el modelo recogido en el Anexo 2. Paralelamente, se les entregó por escrito una hoja con la información detallada sobre el protocolo del programa. El estudio se diseñó en base a la declaración de Helsinki y fue aprobado por el Comité de Ética para la Investigación Clínica del País Vasco.

La evaluación económica se realizó desde la perspectiva del Sistema Nacional de Salud, procediendo con un análisis de coste-efectividad del servicio. La relación coste-efectividad incremental (ICER) se calculó para comparar los costes antes y después de la intervención.

El análisis estadístico de los resultados se realizó mediante el programa SPSS (versión 18 Windows XP Microsoft, USA). Los cambios en el número de medicamentos dispensados, visitas a urgencias y los ingresos hospitalarios fueron cuantificados y comparados antes y después de la intervención mediante el test t de Student para muestras independientes. La prueba Chi-cuadrado (χ^2) y el test de Fisher, se emplearon para analizar la frecuencia de distribución de las variables estudiadas. También se realizó un análisis de sensibilidad univariante para evaluar la incidencia de las variables en el coste-efectividad. Los datos se presentaron como número y porcentaje para variables categóricas, y como media ± desviación estándar para variables continuas.

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RESULTADOS

CAPÍTULO 1:

TAILORED INTERVENTIONS BY COMMUNITY PHARMACISTS AND GENERAL PRACTITIONERS IMPROVE ADHERENCE TO STATINS IN A SPANISH RANDOMIZED CONTROLLED TRIAL

1.1 INTRODUCTION

Hypercholesterolemia is one of the most important risk factors in the development of cardiovascular diseases (CVD) which are responsible for more than one-third of all deaths worldwide[1]. Key factors in the management of dyslipidemia include physical activity, diet, and compliance with therapy[2,3]. However, lipid-lowering therapies remain underused[4] and unhealthy lifestyle is common in hypercholesterolemic patient[5].

Currently, non-adherence is a problem of outstanding magnitude that particularly affects those with chronic diseases[6]. Hypercholesterolemia is a symptomless condition, and as a consequence, non-adherence rates are high[7]. While it is difficult to determine the exact magnitude of statin non-adherence, it is estimated to be around 50% during the initial stages of prescription, and has been observed to increase with time [8]. Moreover, non-adherence has been found to be directly related to higher rates of hospitalizations[9], increased morbidity and mortality[10,11], and overall increases in healthcare costs [12,13]. However, the relationship between non-adherence to lipid-lowering drugs and risk of cardiovascular events remains unclear.

Causes of non-adherence, either intentional or non-intentional, may be related to a patient's health care system, community, financial resources, therapy regimen, and other patient-related factors[6]. A wide range of interventions have been studied to improve adherence to lipid-lowering drugs, including simplification of treatment regimens[14,15,16,17] use of reminder systems[18,19,20] and delivery of educational and informational content to patients[21,22.] However, no single intervention has been shown to improve adherence in patients affected by chronic diseases. Rather, a combination of strategies is necessary[23].

Community pharmacists (CPs) and general practitioners (GPs) are ideally positioned to detect non-adherence and to provide patient-centred interventions to those with chronic diseases [24,25]. In the last few years, interventions by several types of health professionals have been reported, and these have focused on improving adherence to lipid-lowering medicines[26,27]. However, only a few of these studies assessed the

impact of adherence on clinical outcomes[28,29]. In a recently published systematic review, patient-centred interventions were found to improve adherence to lipid-lowering drugs and cholesterol levels[7]. However, these interventions were complex, they were composed of multiple components that involved a combination of different types of strategies, and the measures and outcomes that were assessed were not consistent. Thus, direct comparisons among these data are challenging[30]. Services that focus on detecting causes of non-adherence and then delivering the best intervention to address these causes may help clarify the relationship between improved adherence and clinical outcome.

In many cases, lifestyle patterns are related to statin non-adherence[31]. Although, a new prescription of statin usually involves assessment of healthy lifestyle, unhealthy habits are common in patients treated with statins[32]. Apart from adherence to lipid-lowering drugs, physical activity and healthy diet are key factors in the management of hypercholesterolemia[2,3]. CP and GP are the most accessible health professionals who could play a major role in health promoting activities and providing health education to patients[33,34].

In this context, the aim of this study was to evaluate the impact of interventions that were administered by CPs and GPs in Spain to promote adherence to statins. The relationship of these interventions to total cholesterol (TC) levels in patients with hypercholesterolemia and their lifestyle patterns were also examined.

1.2. METHODS

Study design and ethical approval

This study was a six-month randomized controlled trial. It was conducted with the participation of 46 community pharmacies and 50 primary care centres in ten provinces in Spain (Andalusia, Aragon, Asturias, Basque Country, Castile-La Mancha, Catalonia, Extremadura, Galicia, Madrid, and Valencia) between February 2014 and June 2016. This study was not registered in advance but it was classified as a post-authorisation observational prospective study (EPA-SP) by the AEMPS (OAT-HIP-2013-01, 07/05/2013). The study started once the AEMPS issued the authorization and the

research ethic committees gave the approval. (This data can be verified through the promoters of the study: contacto@oatobservatorio.com; cofgipuzkoa@redfarma.org).

The protocol for this study was in agreement with the Helsinki Declaration. All of the participating patients provided informed consent at the time of their enrolment.

Participants

Patients were recruited according to the following criteria: aged 18 years or older, a prescription of at least one statin was received within the previous three months, and an informed consent form was completed. Patients who had participated in other adherence-promotion or cardiac-rehabilitation programs, those who were not able to communicate with the health professionals, those who could not self-administer statins, those who were dependent or living in long-term care facilities, or those who had suffered a stroke in the previous six months were excluded from this study.

Each health professional involved in this study, was responsible for recruiting a minimum of six patients, including two patients who were adherent to treatment (ADH) and four patients who were non-adherent to treatment (Figure 1). If 6 patients (2 adherent and 4 non-adherent) were recruited and a chance to include more patients remained, they were recruited following the sequence of "adherent – non-adherent – non-adherent" or "non-adherent – adherent – non-adherent", in order to preserve proportionality. Initial adherence was assessed at recruitment using Morisky-Green-Levine test. The non-adherent patients were randomly allocated to the intervention group (INT) or the non-intervention group (NOINT), (Figure 1). Randomization was performed by an external researcher according to the SAS software program (*SAS (r) 9.2 -; Copyright 2002-2003 by SAS Institute Inc., Cary, NC, USA*).

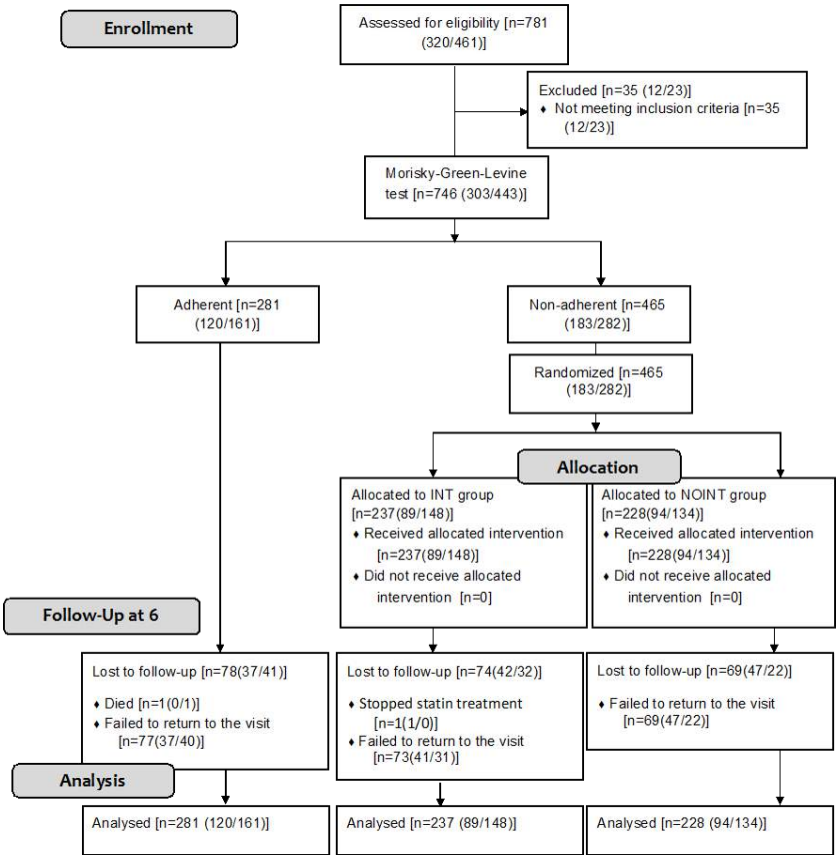

Figure 1. Consort flow diagram of the progress through the phases of the study of three groups (ADH: adherent; INT: intervention group; NOINT: no-intervention group). Data is shown as [total (community pharmacy data/general practitioner data)].

Study procedure

Participants in the INT group received an intervention that was co-designed by pharmacists and primary care doctor experts on adherence for this study. Based on patient feedback and the cause of non-adherence, a multicomponent strategy was proposed (Table 1). Firstly, CP or GP identified the cause of non-adherence. The cause of non-adherence could be intentional or unintentional. The possible causes within the group of unintentional non-adherence were disability and forgetfulness. The possible causes within the group pf intentional non-adherence were lack of

knowledge about the disease or treatment, related to medication, psychological, related to health system and economic. After identifying the cause, the CP or GP chose the most appropriate intervention for the patient. At the subsequent visit, the adherence and therefore effectiveness of each strategy were evaluated using the Morisky-Green-Levine test. Participants in the NOINT and ADH groups received usual care. All data were entered into online electronic case report forms (e-CRF).

Table 1: Description of interventions provided to INT group patients.

Causes of Non-adherence		Proposed Interventions
Non-intentional non-adherence		
Disability Forgetfulness		o Adapt the dose regimen to the patient's situation. o Keep a record of medication intake. o Include pictograms, indication of posology in the box, etc., in the labelling. o Use dispensers, drug packaging, etc. o Other use reminders (alarms, etc.).
Intentional non-adherence		
Knowledge about the disease or treatment	• Not wanting to improve his/her condition • Not adequately considered the information received regarding pathology or treatment • Not aware of the severity of his/her illness • Not aware of the benefits of the treatment • Not aware of the consequences of not following treatment • Believe that generic drugs are less effective than brand name drugs	o Provide written and oral standardized information regarding: - pathology - benefits of treatment - non-pharmacological health education (diet, physical activity, etc.). o Adapt the dose regimen to the patient's situation. ** o Keep a record of medication intake. o Include pictograms, indication of posology in the box, etc., in the labelling.

Table 1 (cont.): Description of interventions provided to INT group patients.

Related to the medication	• Polymedication • Complicated dose régimen • The pharmaceutical form caused problems	o Refer to GP for dose / medication adjustment * o Provide standardized information about treatment.
	• Adverse drug reactions	o Assess the risk-benefit of taking the drug. o Refer to GP for dose / medication adjustment. *
Psychological	• Cultural reasons or beliefs	o Refer to GP for alternative treatment. *
Related to health system	• Contradictory information received from doctor and pharmacist • Difficulties in receiving health care (change of doctor, schedules, distance, etc.)	o Encourage communication with the doctor or pharmacist. o Encourage communication with family members, caregivers, pharmacist, etc.
Economic	• Economic reasons (fees, etc.)	o Evaluate options to reduce the cost of the medicine (request for aid, changes in treatment, etc.)

GP: General Practitioner. * Refers only to community pharmacist intervention. ** Refers only to GP intervention, since in Spain, pharmacists are not allowed to change dose regimens.

Training

CPs and GPs attended a 2-hour workshop that presented and described the study protocol. They also received information regarding hypercholesterolemia, statin treatment, and strategies to detect the cause of non-adherence and possible interventions to increase adherence. For the duration of the study, the CPs and GPs were supported by phone by a lead researcher for this study.

Outcome measures

Adherence to statin therapy was the primary outcome and it was assessed with the Morisky-Green-Levine test[35]. For statistical purposes, patients were classified as adherent (0 questions answered differently) or non-adherent (≥ 1 question answered differently). Causes of non-adherence and intervention provided were registered at each visit. Causes of non-adherence were classified as intentional or unintentional. Since, one patient could receive more than one intervention, for statistical purpose, they were categorized in two groups: (i) interventions to improve unintentional non-adherence (when the cause of non-adherence is forgetfulness) and (ii) interventions to improve intentional non-adherence (when the cause of non-adherence is related to the knowledge about the disease or treatment,or factors related to medication, the patient´s psychological state, the health system, or economic circumstances).

Total cholesterol levels were measured at community pharmacies with Refloton® Plus (Roche) and according to the usual analytical process in the reference hospital laboratory of each primary care centers. The therapeutic objective was dichotomized into achievement of the TC goal (< 200 mg/dl) and not achieving the TC goal (≥ 200 mg/dl).

Physical activity and dietary intake were both evaluated. Based on previous recommendations for populations in Spain [36], patients were dichotomized into those who exercised and those who did not. Dietary intake was also dichotomized into those who followed a diet low in sugar and fats or had healthy eating habits and those who did not, based on previously published criteria[36].

Sample size

Adherence to a statin regimen was previously estimated to be less than 50%[37]. To detect an improvement in adherence from 50% to 65% with 80% power and a two-sided p-value of 0.05, 160 patients were needed for each group. The sample size was estimated to obtain differences in adherence and randomization was done in order to classify non-adherent patients in the INT and NOINT in a 1:1 distribution. The OpenEpi 20 software (http://www.openepi.com/Menu/OpenEpiMenu. htm) was used.

Statistical analyses

Kolmovorov-Smirnov and Shapiro-Wilk tests were used to evaluate data distribution. Changes in clinical characteristics were evaluated and compared between groups with paired t-tests or Student's *t*-test for parametric variables. Non-parametric variables was analysed by ANOVA (Friedman) for repeated measurement analysis. Chi-squared (χ^2) and Fisher's exact tests were used to analyse the frequency distribution of the studied variables and the relationship between groups according to outcome. Changes in cholesterol levels during the study period were analysed and adjusted according to baseline values by factorial analysis of covariance (ANCOVA).

Multiple regression analysis was used to evaluate the impact of professional intervention on cholesterol levels, and was adjusted for variables related to outcome. Binary logistic regression was also performed to evaluate the impact of the studied variables and professional intervention on adherence during this study. The results are expressed as *n* and percentage (%) for the categorical variables and as the mean ± standard deviation (SD) for the continuous variables.

Analyses were performed in the intention-to-treat population [38]. Data were analysed on an intention-to-treat (ITT) and a per-protocol basis. For the ITT analyses, values were calculated based on the multiple imputation system. Information of patients lost to follow-up was imputed for all the variables. The fully conditioned method using a logistic model was used to generate 50 multiple imputation data for each condition. For the per-protocol analyses, patients were considered to have complied the study if they completed the first-month and the sixth-month visit after the baseline visit.

Statistical analyses were performed with the SPSS 18.0 program for Windows XP (Microsoft, USA). A two-tailed p-value less than 0.05 was designated as the level of statistical significance.

1.3. RESULTS

Participant recruitment

A total of 746 patients were recruited for the study, with 303 patients recruited by CPs and 443 patients recruited by GPs. Figure 1 lists the number of patients in each group. There were 281 patients (37.6%) enrolled in the ADH group (CP: 120; GP: 161) and 465 non-adherent patients who were randomly assigned to the INT group or the NOINT group 237 patients (31.8%; CP: 148; GP: 237) and 228 patients (30.6%; CP: 94; GP: 134), respectively. There were 221 patients who did not complete a follow-up visit. When demographic data of the patients who dropped out of the study were compared with the patients who remained in the study, no significant differences were found ($p > 0.05$). Moreover, the proportions of patients enrolled from community pharmacies and primary health centres were similar (Fig. 1).

Baseline analyses shows that adherent patients had lower values of total cholesterol (ADH: 200.3mg/dl vs NOADH: 216.72mg/dl; $p<0.001$) than non-adherent patients. Patients´ age and time since diagnosis also differed significantly between groups (Table 2).

Table 2. Baseline characteristics of the patients studied^.

	ADH	NO ADH		p *	p #
		NOINT	*INT*		
Total (n = 746)	**(n = 281)**	**(n = 228)**	**(n = 237)**		
Age, years	65.8 (10.6)	61.9 (11.8)	63.7 (11.3)	<0.001	0.833
Females	148 (52.7)	128 (56.1)	122 (51.5)	0.636	0.426
Total cholesterol (mg/dl) [□(SD)]	200.3 (42.8)	219.3 (46.3)	211.7 (52.7)	<0.001	0.862
Time since diagnosis, y [□ (SD)]	7.6 (7.1)	6.3 (6.1)	6.1 (5.6)	0.023	0.986
Phytosterol intake, yes	15 (5.3)	12 (5.2)	16 (6.8)	0.720	0.423
Dieting, yes	132 (47.0)	103 (45.2)	99 (41.8)	0.482	0.216
Exercising, yes	196 (70.0)	147 (64.5)	149 (62.9)	0.488	0.188

Table 2 (cont): Baseline characteristics of the patients studied^.

Recruited by CPs (n=303)	(n = 120)	(n = 94)	(n = 89)		
Age, years	65.2 (11.9)	61.5 (12.7)	63.9 (12.9)	0.098	0.898
Females	66 (55.0)	62 (66.0)	54 (60.7)	0.299	0.327
Total cholesterol (mg/dl) [□(SD)]	207.2 (41.7)	222.1 (44.8)	217.0 (48.9)	0.052	0.415
Time since diagnosis, y [□ (SD)]	8.2 (8.4)	6.1 (5.5)	5.2 (4.8)	0.018	0.605
Phytosterol intake, yes	7.0 (5.8)	6 (6.3)	5 (5.6)	0.984	0.554
Dieting, yes	43 (35.8)	29 (30.9)	33 (37.1)	0.431	0.268
Exercising, yes	82 (68.3)	54 (57.4)	53 (59.6)	0.408	0.844
Recruited by GPs (n=443)	**(n = 161)**	**(n = 134)**	**(n = 148)**		
Age, years	66.3 (9.6)	62.2 (11.2)	61.8 (10.5)	<0.001	0.478
Females	82 (50.9)	66 (49.3)	68 (45.9)	0.685	0.351
Total cholesterol (mg/dl) [□(SD)]	196.0 (40.7)	218.9 (44.0)	214.4 (46.9)	<0.001	0.480
Time since diagnosis, y [□ (SD)]	7.3 (6.2)	6.3 (6.4)	6.6 (6.0)	0.397	0.678
Phytosterol intake, yes	8 (5.0)	6 (4.5)	11 (7.4)	0.494	0.212
Dieting, yes	89 (55.3)	74 (55.2)	66 (44.6)	0.314	0.884
Exercising, yes	114 (70.8)	93 (69.4)	96 (64.9)	0.709	0.576

^Data is reported as n (%) except where indicated as mean [□(SD)].
ADH: Adherent group; INT: Intervention group; NOINT: No intervention group; □: mean; SD: standard deviation.
* Analysis of ADH, INT, and NOINT groups was performed by using ANOVA or the Chi-squared test.
# Analysis of INT and NOINT groups was performed by using Student´s *t*-test or Fisher´s exact test.

Health professional intervention

Adherence throughout the study was analysed at 0, 3, and 6 months after the start of the study. The Friedman test for repeated measures showed a significant increase in the percentage of patients who became adherent during the period analysed, and this percentage was significantly higher in the INT group (Figure 2). The proportion

of adherent patients was 9.5% higher after six months of intervention (χ^2=22.87, p < 0.001) in the INT group compared with the NOINT group (Figure 2A). Logistic regression analysis was performed to evaluate the impact of baseline characteristics on adherence (ADH group vs. INT and NOINT groups) firstly and to analyse the impact of different variables and professional intervention on adherence secondly. Interventions provided by the health professionals improved adherence to statins throughout the six months of study [OR = 1.49 (95% CI: 1.30–1.76; p < 0.001)] (Table S1). Age and gender were slightly significantly associated with adherence at follow-up. Per-protocol analysis results did not differ qualitatively from those in the ITT analysis (see supplementary data).

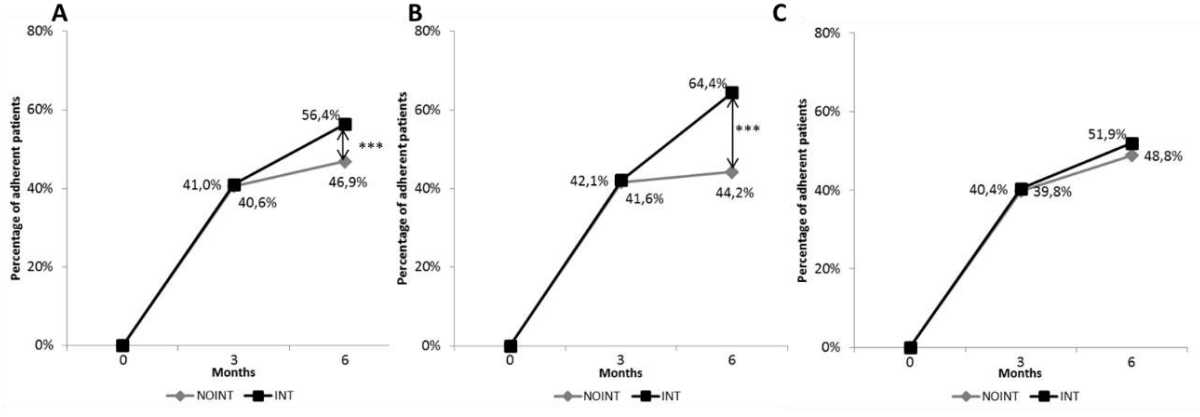

Figure 2. Variation in adherence to statins in patients who were non-adherent at baseline. A) Total (CP and GP), B) CP, and C) GP groups were analysed. The Friedman test for repeated measures was used to evaluate the evolution of adherence with time and intervention-related effects according to group.NOINT: Non-adherent patients with usual care; INT: Non-adherent patients with intervention. *: $p < 0.05$; **:$p<0.01$. Analysis of adherent patients of INT and NOINT groups was performed by using Chi-squared test

Causes of non-adherence were analysed at baseline. Unintentional non-adherence (55.7%, n=132) was more prevalent than intentional non-adherence (44.3%, n=105) among the studied patients. The most provided intervention for unintentional non-adherence (80.7% of the unintentional non-adherence causes), was directed towards forgetfulness like using drug packaging (74.6%), including the posology in the box (59.8%) and using reminders (31.2%). The most frequently provided intervention for intentional non-adherence was directed towards improving knowledge about the disease or treatment (60.9% of the intentional non-adherence causes) providing written and oral standardized information (92.6%).

Cholesterol levels decreased in both groups over the course of the study (INT: -11.06mg/dl, $p < 0.001$; NOINT:-10.4mg/dl, $p < 0.001$). Per-protocol analysis also showed a decrease in both groups, yet a statistically significant decrease was only observed in the INT group (INT: 210.18 mg/dl vs. 197.59 mg/dl, $p = 0.028$; NOINT: 223.32 mg/dl vs. 214.42 mg/dl, $p = 0.127$). In order to evaluate relationship between adherence and clinical outcome, data was stratified in patients that achieved adherence at the end of the study, and patients who remain non-adherent. Adherent patients at endpoint showed lower values of total cholesterol compared with non-adherent patients (Adherent: 197.33±35.32mg/dl vs non-adherent: 212.23± 40.68mg/dl; $p<0.001$) (Figure 3). When a factorial ANCOVA was adjusted for baseline cholesterol levels, the effect of professional intervention on the decrease in cholesterol levels during the six-month period exhibit statistical significance as well ($p < 0.001$).

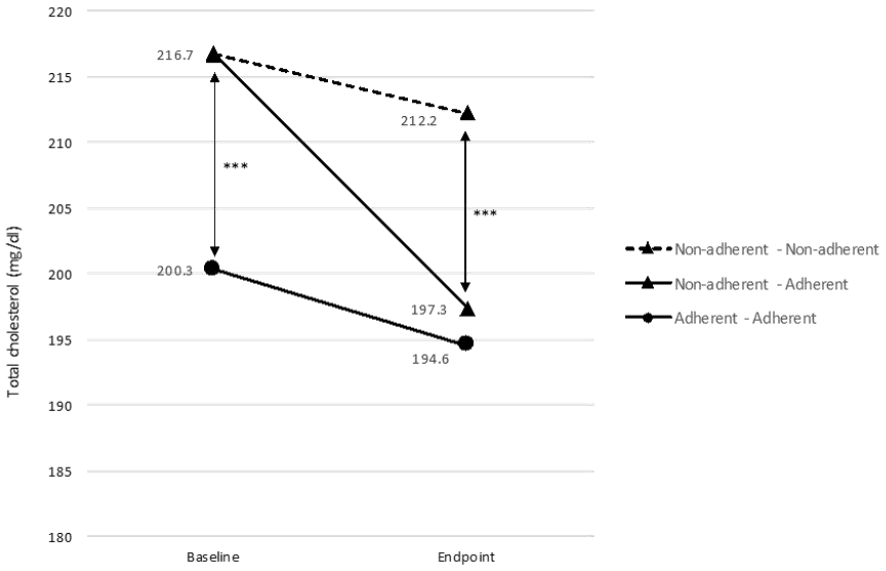

Figure 3: Total cholesterol variation between baseline (0 months) and endpoint (6 months) based on patients´ adherence variation. Analysis was performed using Student´s t-test. Statistical differences between baseline and endpoint were only observed in non-adherent – adherent group ($p<0.001$). ***: $p<0.001$

Between the INT and NOINT groups, there were no differences in the proportion of patients showing normal cholesterol levels at baseline (Table 2). However, this proportion was significantly higher ($\chi^2 = 21.78$, $p < 0.001$) in the INT group (52.1%) compared to the NOINT group (45.0%) at the endpoint of the study. Per-protocol analysis results did not differ qualitatively from those in the ITT analysis (see supplementary data).

No differences were observed in the physical activity or dietary intake of the three studied groups at baseline (Table 2). However, patients in the INT group had a significant increase in their overall amount of exercise over the six-month study period (baseline: 62.9% vs. endpoint: 93.1%, $p < 0.001$) compared with the patients in the NOINT group (baseline: 64.5% vs. endpoint: 65.7% min, $p = 0.998$) and ADH group (baseline: 70.0% vs. endpoint: 69.7%, $p=0.985$) who did not have an increase in their overall amount of exercise. Regarding dietary intake, a greater proportion of

the patients in the INT group stated that they were following a diet to reduce cholesterol levels (baseline: 41.8% vs. endpoint: 68.4%; $\chi^2 = 5.45$, p = 0.002), while the proportion of patients who stated that they were following a diet to reduce cholesterol levels in the NOINT group (baseline: 45.2% vs. endpoint: 51.3%, $\chi^2 = 0.47$, p = 0.627) and ADH group (baseline: 47.0% vs. endpoint 48.2%, $\chi^2 = 0.73$, p=0.712) remained unchanged. Per-protocol analysis results did not differ qualitatively from those in the ITT analysis (see supplementary data).

Community pharmacists' and general practitioners´ intervention

CP INT group exhibited a 20.1% increase in the proportion of adherent patients at the endpoint of the study (χ^2=40.27, p < 0.001; Figure 2B), compared with the NOINT group showing that CP´s intervention improved adherence to statins throughout the six months of study [OR = 2.34 (95% CI: 1.87–3.03; p < 0.001) (Table S1). Although the intervention provided by CP did not reach statistical significance in cholesterol levels decrease between groups (INT: -5.1mg/dl vs NOINT: -4.7mg/dl; p = 0.571), at endpoint, adherent patients (209.7±29.50mg/dl) showed lower values of total cholesterol compared with non-adherent patients (221.7±45.14mg/dl) patients (p<0.001).

In GP group, the proportion of patients adherent after GPs´ intervention did not reach significance (p<0.05) (Figure 2C), and total cholesterol decrease did not show differences between INT and NOINT groups (INT: -12.7mg/dl; p < 0.001; NOINT: -15.2mg/dl; p=0.303). However, adherent patients (191.05±36.38mg/dl) at endpoint showed lower values of total cholesterol compared with non-adherent (207.9±37.71mg/dl) patients (p = 0.047).

Unintentional non-adherence was more prevalent than intentional non-adherence in CP and GP groups. Drug packaging was the most frequent intervention used in CP to improve unintentional non-adherence, whereas adapting the dose regimen to the patient´s situation was the most provided intervention in GP. Providing written and oral information was the most used intervention to improve intentional non-adherence in both centres.

Percentage of patients that followed a diet to reduce cholesterol and that increased their overall amount of exercise at endpoint compared to baseline, improved in both groups showing the same trend as in the global analysed (FC+GP).

1.4. DISCUSSION

This six-month interventional program with CPs and GPs, studied variation in adherence to statins in hypercholesterolemia patients and its relationship with total cholesterol levels and lifestyle patterns. The present research shows that CPs intervention improved adherence to statin in patients who were non-adherent at baseline. Moreover, it suggests that adherence could be related with total cholesterol reduction and with an improvement on the studied lifestyle patterns.

After health professional intervention, percentage of patients that finished the study being adherent to statins was higher compared with patients that did not receive the intervention, concluding that intervention provided by CP and GP throughout the 6-months period was effective. When adherent patients were studied independently to the intervention group, a total cholesterol reduction was determined. These findings are in accordance with previously published reports, which analysed the impact of adherence on lipid profiles[7,39]. Some authors state that total cholesterol level decrease could be greater in longer studies[7,40] so, a longer intervention period could also provide greater reduction than those observed in the study. Moreover, patients who were adherent at baseline showed lower values of total cholesterol compared with non-adherent patients, reinforcing that adherence to statins could be related with improvement in clinical values, in total cholesterol in this case. Considering that high total cholesterol levels have been related to an increased rate of major cardiovascular events and mortality, a total cholesterol level reduction would probably lead to a reduction in cardiovascular risk for these patients[41]. Our study also suggests that CP and GP intervention increases the number of patients that reach total cholesterol level objective. Reaching total cholesterol level under 200mg/ml is considered to have normal level of total cholesterol decreasing as well, cardiovascular risk in those patients[41].

Among previously published works studying interventions delivered by health professionals to improve adherence and clinical outcomes, only a few focused on hypercholesterolemia patients. For example, Aslani et al.[42] analysed adherence to lipid-lowering drugs and total cholesterol levels using two validated questionnaires, and no changes due to intervention were observed. In a study performed by Faulkner et al.[43], the intervention was focused on adherence in patients who underwent cardiac surgery, and improvements in adherence to treatment and lipid profiles were observed after two years. In another study, improvements in adherence and lipid profiles were observed when a calendar reminder-based intervention was conducted[44]. The results of the present study are consistent with those of a recently published Cochrane review that analysed adherence to a lipid-lowering medication in the context of various types of interventions[7]. The interventions delivered in our study were based on an identification of the causes of non-adherence and selection of the best intervention in each situation. Therefore, customizing interventions depending on the cause of the non-adherence and situation of the patient could be an effective way to reduce non-adherence in chronic diseases.

To the best of our knowledge, this study represents the first major hypercholesterolemia adherence trial to evaluate interventions delivered by CPs and GPs. In fact, the intervention was co-designed by community pharmacists and primary care doctors with the goal of establishing a standard intervention that would be able to be implemented in both of these health professional fields. In the case of interventions where reminders were used, there are studies where adherence improves after intervention in the community pharmacy[42,19] and in the hospital setting [45,46]. On the other hand, when the intervention is about providing education on the importance of adherence to treatment and other issues related to the disease, there are studies that do not find improvement at the end of the study in community pharmacy[21] neither in the hospital environment[22,26]. Data suggest that in order to obtain the improvement in adherence, identifying the cause of non-adherence and choosing the most appropriate intervention for the patient's situation should be part of the intervention.

In the present study, intervention provided by CPs showed a greater improvement on adherence compared to GPs group. It is worth highlighting that in our study, the

patients enrolled in the non-intervention group in both settings, especially those recruited by the GPs, showed an unexpected enhancement in adherence. This result may be attributed to different factors, including a Hawthorne effect by which a simple observation modifies patients' behaviour[47]. However, when the type of interventions provided were studied, our data shows that drug packaging and including the posology in the box were the most used intervention to improve unintentional non-adherence, while providing written and oral standardized information was the one to improve intentional non-adherence. Those interventions have been classically offered in the CP and has already showed their effectiveness, reinforcing the idea that CP could be one of the most appropriate health professional in improving adherence [48,49].

Among baseline data of recruited patients, ADH group patients were older at baseline. Although, several studies have reported that non-adherence rates increase with time[50], a systematic review of 102 studies found that elderly people might have higher compliance [51]. This could show that although non-adherence has been usually related to elderly, in middle-age patients other factors like priorities on life or lack of time, can influence on non-adherence and become less likely to be compliant to therapy. For these patients the CP could be an accessible health centre and the actions toward implementing this type of services in the CP could be in this way also justified.

Dietary and exercise habits were also modified at the end of the study. Number of patients following a diet and doing exercise was higher in the INT group compared with the NOINT group. Our results are in accordance to other previous studies since the relationship between a healthy diet and adherence has previously been described[52,53]. It has been established that changes in lifestyle, in addition to pharmacological treatment, are related to a decrease in the prevalence and progression of chronic diseases[54]. Thus, the intervention proposed in the present study could potentially improve both clinical and lifestyle patterns.

There were some limitations associated with the present study. For example, there were a substantial number of patients who did not complete the study and follow-up. This rate is comparable to other intervention trials which analysed adherence outcome for various chronic diseases[55,56], and to the rates reported for lipid-lowering

interventional trials [42] and a multiple imputation analysis was used to take into account the uncertainty of the imputed values. It may be worth considering that if participating health professionals had received reimbursement, may have provided better patient recruitment and the number of drop-outs could be reduced [44]. Being a non-clustered randomized controlled trial, the risk of concealment of an allocation is major. Knowledge of treatment group assignment may influence the professionals' way of acting or may behave in a compensatory way to the non-intervention group patients that may diminish differences between the intervention and the control groups. Finally, adherence and lifestyle outcomes were measured using patient-reported information. However, all available adherence measures have their limitations[12] and Morisky-Green test is one of the most accepted self-report measures for identifying non-adherence[57] .

Considering that adherence to statins may change over time, the impact of an intervention should be re-evaluated at different time points. Studies evaluating other variables such as morbidity, mortality, quality of life, and/or cost-effectiveness could also be useful in providing guidance for healthcare systems and establishing cost-effectiveness of the intervention.

In summary, the findings of this study show that intervention delivered by health professionals, increased adherence to statins after six months, especially among patients who were enrolled in the community pharmacy group, and this improvement on adherence was related to a decrease in total cholesterol levels and a healthier lifestyle.

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Supplementary material

Table S1. Logistic regression analysis was performed to determine the impact of professional intervention on non-adherent patients who became adherent by the end of the study (n=465). (The dependent variable was dichotomized as 0: non-adherent at baseline and non-adherent at endpoint; or 1: non-adherent at baseline and adherent at endpoint).

Model and characteristics	*OR*	*95% CI*	p-value
Total (n = 465)			
Professional intervention (CP and GP)	1.49	1.30-1.76	<0.001
Gender	1.19	1.02-1.39	0.031
Age	1.01	1.00-1.02	0.003
Center	0.86	0.78-1.02	0.078
Community pharmacy (n=183)			
CP intervention	2.34	1.87-3.03	<0.001
Gender	1.21	0.94-1.58	0.146
Age	1.01	0.99-1.01	0.248
General practitioner (n=282)			
GP intervention	1.14	0.95-1.39	0.192
Gender	1.20	0.98-1.47	0.773
Age	1.06	1.01-1.03	0.003

OR: odds ratio; CI: confidence interval; CP: community pharmacist; GP: general practitioner.

Table S2. Baseline characteristics of the patients studied (per protocol).

	ADH	NO ADH		p *	p #
		NOINT	*INT*		
Total (n = 525)	**(n = 203)**	**(n = 159)**	**(n = 163)**		
Age, years	65.8 (10.4)	62.5 (11.9)	63.1 (11.0)	0.010	0.663
Females	105 (51.7)	93 (58.5)	87 (53.7)	0.416	0.368
Total cholesterol (mg/dl) [□(SD)]	199.7 (40.7)	219.9 (42.7)	215.1 (46.3)	< 0.001	0.343
Total cholesterol < 200 mg/dl	110 (54.2)	53 (33.3)	59 (36.2)	< 0.001	0.640
Time since diagnosis, y [□(SD)]	7.4 (6.9)	6.0 (5.6)	5.8 (5.0)	0.039	0.705
Phytosterol intake, yes	7 (3.4)	5 (3.1)	8 (5.0)	0.653	0.573
Dieting, yes	122 (60.1)	93 (58.5)	88 (54.0)	0.487	0.416
Exercising, yes	163 (80.3)	126 (79.2)	124 (76.1)	0.542	0.507
Recruited by CPs	**(n = 86)**	**(n = 56)**	**(n = 61)**		
Age, years	65.6 (11.2)	63.2 (12.6)	65.8 (11.1)	0.393	0.276
Females	46 (53.5)	41 (73.2)	36 (64.3)	0.175	0.841
Total cholesterol (mg/dl) [□(SD)]	205.6 (41.4)	222.9 (45.8)	219.1 (48.2)	0.054	0.669
Total cholesterol < 200 mg/dl	41 (47.7)	18 (39.5)	21 (36.2)	0.074	0.558
Time since diagnosis, y [□(SD)]	7.8 (7.9)	6.0 (5.3)	4.7 (4.7)	0.053	0.222
Phytosterol intake, yes	5 (5.8)	3 (4.9)	3 (5.4)	0.978	0.998
Dieting, yes	38 (44.2)	30 (49.2)	22 (39.3)	0.431	0.216
Exercising, yes	66 (76.7)	43 (76.8)	39 (63.9)	0.642	0.838
Recruited by GPs	**(n = 115)**	**(n = 98)**	**(n = 107)**		
Age, years	65.9 (9.9)	62.1 (11.6)	61.8 (10.8)	0.060	0.819
Females	59 (51.3)	52 (53.1)	49 (46.7)	0.656	0.396
Total cholesterol (mg/dl) [□(SD)]	195.4 (39.7)	218.1 (40.9)	212.9 (45.3)	< 0.001	0.403
Total cholesterol < 200 mg/dl	69 (59.0)	35 (35.7)	38 (36.2)	< 0.001	1.000
Time since diagnosis, y [□(SD)]	7.2 (6.3)	6.1 (5.8)	6.3 (5.1)	0.345	0.756
Phytosterol intake, yes	2 (1.7)	2 (2.0)	5 (4.8)	0.330	0.446
Dieting, yes	83 (72.2)	63 (64.3)	66 (62.9)	0.314	0.833
Exercising, yes	97 (84.3)	83 (84.7)	85 (79.4)	0.756	0.452

^Data is reported as n (%) except where indicated as mean [□ (SD)]. ADH: Adherent group; INT: Intervention group; NOINT: No intervention group.* Analysis of ADH, INT, and NOINT groups was performed by using ANOVA or the Chi-squared test.# Analysis of INT and NOINT groups was performed by using Student´s *t*-test or Fisher´s exact test.

Table S3 - Summary results of adherence, physical activity and diet (per-protocol analysis).

	Number (%)			Risk ratio* (95% CI)	Risk difference* (95% CI)
	INT (n=163)	NOINT (n=159)	ADH (n=203)		
Baseline					
Adherent, yes	0 (0)	0 (0)	203 (100)	0.98 (0.02 - 48.87)	0.0 (-1.2 – 1.2)
Diet, yes	88 (54.0)	93 (58.5)	122 (60.1)	0.92 (0.76 – 1.12)	-4.5 (-6.3 – 15.3)
Physical activity, yes	124 (76.1)	126 (79.2)	163 (80.3)	0.96 (0.85 – 1.08)	-3.1 (-5.9 – 12.3)
TC goal achievement, yes	59 (36.2)	53 (33.3)	110 (54.2)	1.09 (0.80 – 1.47)	2.9 (-7.1 – 13.7)
Third month					
Adherent, yes	84 (51.5)	48 (30.3)	203 (100)	1.17 (1.30 – 2.26)	21.2 (10.9 – 31.8)
Endpoint					
Adherent, yes	104 (63.6)	73 (45.9)	203 (100)	1.39 (1.13 – 1.71)	17.4 (7.2 – 28.6)
Diet, yes	117 (72.2)	103 (64.5)	131 (64.5)	1.11 (0.95 – 1.29)	7.7 (-3.1 – 17.1)
Physical activity, yes	161 (98.6)	131 (82.4)	165 (81.3)	1.19 (1.11 – 1.28)	16.2 (10.2 – 22.5)
TC goal achievement, yes	97 (59.7)	64 (40.3)	112 (55.2)	1.48 (1.18 – 1.86)	19.4 (8.5 – 30.0)

* Risk calculated between INT and NOINT groups.

Table S4 - Summary results of total cholesterol (per-protocol analysis).

	INT		NOINT		ADH		Adjusted difference* (95%CI) at endpoint
	Baseline (mean (SD))	Endpoint (mean (SD))	Baseline (mean (SD))	Endpoint (mean (SD))	Baseline (mean (SD))	Endpoint (mean (SD))	
Total cholesterol (mg/dl)	211.7 (52.7)	201.7 (40.6)	219.9 (42.7)	205.4 (37.3)	199.7 (40.7)	188.4 (40.1)	4.5 (-6.64 – 14.54) n.s.

*Adjusted for baseline, age, and time since diagnosis calculated between INT and NOINT groups.
n.s.: not significant.

CAPÍTULO 2:

EFFECT OF HEALTH PROFESSIONAL INTERVENTION ON ADHERENCE TO STATIN USE ACCORDING TO THE CAUSE OF PATIENT NON-ADHERENCE

2.1 INTRODUCTION

Non-adherence to medication is a complex, multicomponent problem that particularly affects the patient's response to chronic disease. Non-adherence to medication is considered a public health problem due to its high prevalence and consequences such as increased morbidity, mortality and health care costs [1].

Patients' failure to follow treatment plans may be intentional or unintentional. With intentional non-adherence, a patient actively decides not to follow the recommendations for a prescribed treatment. With unintentional non-adherence, the patient passively forgets to follow the prescribed treatment (i.e., take medication) [2]. Interventions addressing non-adherence differ, depending on the cause [2, 3].

The literature on patient adherence is extensive; various types of intervention have been proposed in recent decades [3]. A recent systematic review showed that the variability in the methods used to improve adherence to chronic medication regimes remains high, and the effectiveness of the applied methods remains to be elucidated [4]. Previous research [5] has shown that an intervention based on identifying the cause of non-adherence and providing the most appropriate intervention improved adherence to statins and reduced total cholesterol levels of hypercholesterolemic patients.

Thus, the objective of the present study was to analyze the effects of an intervention by community pharmacists (CPs) and general practitioners (GPs) on the adherence to statin regimes among patients with hypercholesterolemia, depending on the cause of patient non-adherence.

Ethics Approval

The protocol for this study was in agreement with the Helsinki Declaration and was approved by the Clinical Research Ethics Committees. All of the participants provided informed consent at the time of their enrolment.

2.2 MATERIALS AND METHODS

Study design, participants and procedure

The study was a 6-month randomized controlled trial that included 46 community pharmacies and 50 primary care centers in 10 Spanish provinces.

The selection of patients and the methodology used in this study, have been described in detail elsewhere [5]. Briefly, each CP or GP recruited at least six patients receiving statin treatment, including two adherent patients and four non-adherent patients. When a patient was recruited, adherence was assessed using the four-item Morisky-Green-Levine test [6]. Non-adherent patients were assigned randomly to the intervention (INT) and non-intervention (NOINT) groups. Participants in the nonintervention and adherent groups received the usual care, and those in the intervention group received an intervention based on the identification of the cause of non-adherence and selection of the most appropriate intervention for each patient. Depending on the cause, patients were categorized as having intentional or unintentional non-adherence (Table 1).

At the subsequent visits (3rd month and 6th month), adherence, and the effectiveness of each intervention for patients in the INT group were evaluated. If necessary, another intervention was proposed.

The CPs and GPs attended a 2-hour workshop to learn the study procedure and for the duration of the study, they were supported by telephone by a lead researcher.

Table 1. Description of interventions provided to the INT group patients.

Cause	Type of non-adherence	Proposed interventions
Unintentional non-adherence		
Forgetfulness	Forgetfulness	- Display of pictograms or posology on the medicine box. - Use of a dispenser or use of a reminders.
Intentional non-adherence		
Inadequate consideration of pathology or treatment information	Formative	- Provision of standardized written and oral information about the pathology and benefits of treatment, non-pharmacological health education.
Polymedication, complication of dose regimen or adverse drug reaction	Medication related	- Referral to GP for adjustment of dose or medication or for alternative treatment. - Provision of standardized information about the treatment and risks and benefits of taking the drug.
Cultural reasons or beliefs	Psychological	- Referral to GP for alternative treatment.
Doubt regarding the effectiveness of generic drugs, receipt of contradictory information from the CP and GP, or difficulty in receiving health care	Structural	- Provision of standardized written and oral information about generic drugs. - Communication between the GP or CP and family members.
Fees or medication cost	Economic	- Exploration of options to reduce the cost of medicines.

GP: General practitioner; CP: Community pharmacists.

Outcome measures

The primary outcome in this study was adherence to statin therapy, assessed at each visit by CP or GP using the Morisky-Green-Levine test. Demographic data were collected at baseline.

Statistical analyses

Data were assessed using per-protocol analysis, as this approach produced results similar to an intention-to-treat analysis with respect to significant findings [5]. Paired t tests or Student's tests were used for parametric variables and ANOVA was used for repeated-measurement analysis for nonparametric variables. Chi-square ($\chi 2$) and Fisher's exact tests were used to analyze the frequency distribution and the relationship between groups according to the outcome. Statistical analyses were performed with SPSS 18.0 software. The level of statistical significance was designated as a two-tailed p value <0.05.

2.3. RESULTS

A total of 746 patients were recruited for the study (CP=303; GP=443). A total of 237 of non-adherent patients were randomly assigned to the INT group and 228 to the NOINT group. At baseline, adherent (n=281, 37,6%) and non-adherent (n=465, 62,3%) patients differed in terms of mean age (65.8±10.4 vs. 62.3±11.6 years respectively, p<0.001), total cholesterol level (199.7±40.7 vs. 215.5±49.8 mg/dL respectively, p<0.001) and time since diagnosis (7.4±6.9 vs. 6.1±5.8 years respectively, p=0.028). Unintentionally non-adherent individuals were older than intentionally non-adherent individuals (64.0±11.6 vs. 61.1±10.9 years respectively, p=0.035). No difference was observed between the patients who visited GPs and CPs.

At baseline, more patients were classified as having unintentional non-adherence (56.6%) than intentional non-adherence (43.4%). The most prevalent cause of intentional non-adherence was formative (42.6%), followed by medication related (25.2%) and structural (22.8%) causes. Psychological (5.0%) and economic (4.5%) causes were less prevalent.

When comparing patients in the INT and NOINT groups of unintentional and intentional non-adherence, there were more adherent patients in the INT group compared with the NOINT group at the 3rd month (INT intentional 49.5% vs NOINT intentional 35.3%, p<0.001 and INT unintentional 59.1% vs NOINT unintentional 35.6%, p<0.001) and at the 6th month (INT intentional 55.3% vs NOINT intentional 36.1%, p<0.001 and INT unintentional 66.4% vs NOINT unintentional 39.0%, p<0.001) (figure 1). Among patients with unintentional non-adherence, only the INT group increased the percentage of adherent patients at the 3rd month (INT unintentional: 59.1% vs. INT intentional: 49.5%, p<0.001) and at the end of the study (INT unintentional: 66.4% vs. INT intentional:55.3%, p<0.001) (Figure 1). All of the groups increased their percentage of adherent patients at the end of the study compared with the 3rd month visit. However, this increase was only significant in the INT group.

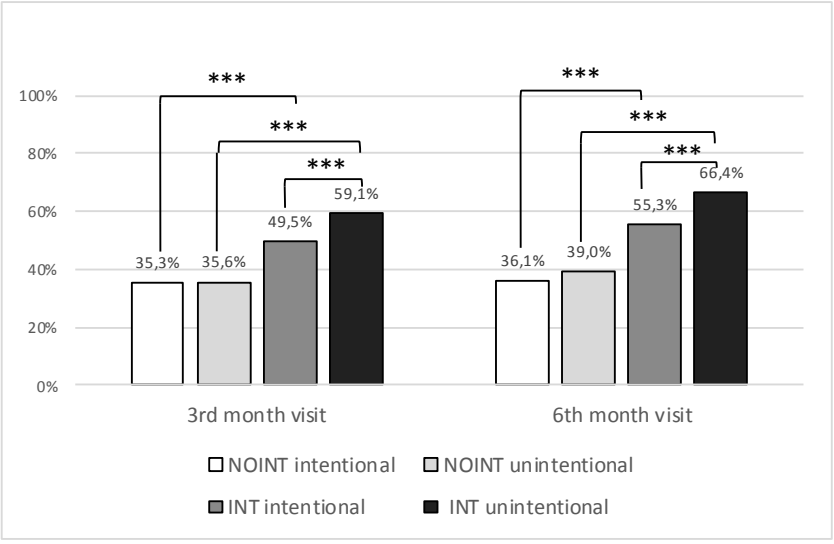

Figure 1: Variation during 6-month intervention in adherence to statins among non-adherent patients at baseline, according to the intentionality of non-adherence and intervention.
INT: Intervention group; NOINT: No intervention group;
***: p<0.001.

Patients with medication-related non-adherence showed greater adherence (59.4% change;n=1]) at the end of the study period than did patients with non-adherence due to formative (41.6% change;n=20) and structural (53.7% change;n=14) causes (χ^2=1.35, p=0.472). No differences was observed between the CPs and GPs.

2.4. DISCUSSION

The present study showed that professional intervention to reduce non-adherence to statin regimens was more effective for patients with unintentional non-adherence than for those with intentional non-adherence. Various cognitive and behavioral models have demonstrated that a patient´s attitude toward treatment is a determining factor for treatment adherence [7, 8]. When a patient with unintentional non-adherence is identified, the CP and GP may use tools to remind the patient to conform to the treatment, which does not necessitate alteration of the patient's attitude toward the treatment.

At baseline, there were more patients classified as having unintentional non-adherence than intentional non-adherence. The distribution of patients in the present study is consistent with previous published research [9].

To our knowledge, no previous study has compared intervention efficacy based on these causes of non-adherence. Several authors have concluded that a tailored approach based on the cause of non-adherence is necessary to effectively improve adherence [10]. Since interventions are more effective in patients with unintentional non-adherence, providing remunerated intervention guidelines to health professionals could establish cost-effective professional services.

The present study has some limitations. Reporting bias is common in studies based on self-reported measures of adherence. All available adherence measures have limitations, and the Morisky-Green-Levine test, a questionnaire that provides information about medication-taking behaviour and barriers to adherence, was used in this study. The methodology of the present study relies only on CP and GP opinion for classifying intentional and. unintentional non-adherence. However, all health

professionals groups were formed before the beginning of the study and were advised by a lead researcher in case of any methodological doubt. Patients enrolled in the NOINT group showed an unexpected increase in adherence. This result may be attributed to different factors, including the Hawthorne effect, by which a simple observation modifies patients´ behavior. However, the increase in adherence was only statistically significant in the INT group. This study evaluates adherence at 6 months. Adherence is a state that can change over time so adherence improvement should be reassessed in subsequent months. Finally, the small number of patients with psychological and/or economic causes of non-adherence precluded drawing conclusions about whether interventions designed to address these factors were effective.

In summary, this study examined the effectiveness of adherence-directed interventions according to non-adherent causes. These findings suggest that interventions provided to patients with unintentional non-adherence are more effective than those provided to patients with intentional non-adherence, having important implications for researchers, educators, and policy makers. Further studies are needed to evaluate the effects of interventions in patients with intentional non-adherence with economic and psychological causes, and to find interventions that could improve intentional non-adherence to the same extent.

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Conflicts of Interest

The authors declare that they have no conflict of interest.

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CAPÍTULO 3:

COMMUNITY PHARMACISTS' INTERVENTION TO IMPROVE ADHERENCE TO LIPID LOWERING MEDICATION AND THE INFLUENCE ON CLINICAL OUTCOMES: A SYSTEMATIC REVIEW AND META-ANALYSIS

3.1. INTRODUCTION

Dyslipidemia, defined as high plasma levels of triglycerides, low-density lipoprotein cholesterol (LDL-c) and total cholesterol (TC) or low plasma levels of high-density lipoprotein cholesterol (HDL-c), has been determined as a major risk factor for cardiovascular diseases [1,2].

According to the World Health Organisation and Cardiovascular Resource Group, Europe is the continent with the highest prevalence of high cholesterol in the world where a 54% of European population has high cholesterol levels [3,4]. This situation contributes to 2.6 million deaths per year and 29.7 million disability adjusted life years (DALYS), worldwide. The overall costs of cardiovascular diseases in developed and developing countries, rising annually to €210 billion in European Union and to $317 billion in Unites States [5,6].

Non-adherence to medicines is the extent to which a person's taking medication, do not corresponds with agreed recommendations from a health care provider [7–10]. It is a current worldwide problem of outstanding magnitude that affects particularly to developed and in developing countries [7]. It is assumed that a patient is non-adherent when they take fewer than 80% of the medicines as prescribed. Prevalence is higher in chronic diseases, where reaches values around 50% [7] such as, Chronic Obstructive Pulmonary Disease (COPD) (33%) [11], schizophrenia (52%) [12], asthma (67%) [13], Diabetes Mellitus (DM) (78%) [14] or dyslipidemia (60%) [15]. This situation leads to a decrease of the quality of life, increased hospitalizations or morbi-mortality and economic burden due to personal, health and social costs [16]. It is estimated that non-adherence represents approximately the 60% of the suboptimal medicines use [17] and improving adherence would save great amount of money to health systems [18].
Non-adherence could be intentional, when the patient makes a rational decision of not taking the treatment or follow as recommended, or unintentional, when unplanned behaviour such as forgetfulness or lack of awareness causes the situation, or mixed [19,20]. Interventions towards improving non-adherence are proposed depending on the cause of non-adherence [21–24], among others. Adherence evaluates the process of using medication. However, the measurement of Economic, Clinical and Humanistic Outcomes (ECHO) are necessary to evaluate the impact of the

intervention [25]. Determination of clinical outcomes includes measuring the medical events that occurs as a result of the disease or treatment and it justifies the improvement on patients´ care [26].

Community pharmacists, in the context of the transition of a medication-centered to a patient-centered practice, are one of the most accessible professionals, are the last link on the dispensing chain, have experience on detecting drug adverse events and have demonstrated to have a useful role on managing chronic conditions [27,28]. Different type of interventions have been proposed to identify the best strategy to improve patient´s medication taking [29]. Some systematic reviews studied the improvement on adherence level or on clinical outcomes due to the health care professionals´ intervention [30–34], but none of them was focused on both, the impact of community pharmacists´ interventions on adherence to chronic treatment and clinical outcomes.

Therefore, the objective of this systematic review was to determine whether community pharmacists´ interventions improve patients´ adherence to lipid-lowering medication and if this modification involves changes on health outcomes compared with usual care.

3.2. MATERIAL AND METHODS

Selection criteria and literature search

A systematic review of randomized clinical trials (RCT) assessing the impact of community pharmacists' intervention on patients´ adherence to lipid lowering medication and on clinical outcomes was conducted The protocol was previously registered online (CRD42016037213) and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [35] were followed (Additional file 1). RCT studying adherence as the degree to which a patient's behaviour, in relation to taking medication, corresponds with agreed recommendations from a health care provider, were considered. Based on the method of adhesion assessment, no exclusion was made and all forms of measure were considered. Statins are the mainstay treatment for hyperlipidemia, but studies with other lipid lowering drugs

were also considered. The clinical outcome that must have a study for its inclusion was any blood lipid level measurement (total cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides). Other clinical outcomes related with dyslipidemias like blood pressure, glucose levels, or IBM index were also recorded.

The exclusion criteria were: (i) studies not including patients diagnosed for hypercholesterolemia or taking lipid-lowering drugs; (ii) studies in which the improvement of the adherence to treatment was not one of the aims of the study; (iii) studies in which adherence was not measured; (iv) studies in which the intervention was not carried out by a community pharmacist; (v) studies in which the clinical variables were not measured; (vi) pilot studies, reviews, systematic reviews, meta-analysis, conference abstracts, doctoral thesis and commentaries and (vii) studies without control group.

A systematic search was conducted in bibliographic databases (MEDLINE, Cochrane Library, Science Direct, Scopus and Web of Knowledge) to look for relevant publications until December of 2019 [36]. A search strategy was developed using MeSH and Emtree terms and previous published filters were also checked to ensure the suitability of the search [29,37] (Additional file 2).
Moreover, other published systematic reviews and articles of similar areas were consulted and bibliographies of the included articles were reviewed to ensure the inclusion of cited articles [15,26,29,38].

Study selection
All the retrieved articles were imported to a reference manager (Mendeley) and two independent reviewers (AOA and AML) made the selection of the potentially relevant articles according to the stablished criteria. A third reviewer (EG) was involved to resolve the discrepancies. Firstly, articles were excluded based on the information obtained from the title and abstract. Full text of the remaining articles were obtained and excluded if any exclusion criteria were detected.

Data extraction
A standardized table (table 1) that included data on article (principal author, title, year of publication and setting), study (objective, setting, study design, method or

randomization and recruitment, follow-up, sample size calculation, chronic disease, inclusion criteria of participants, population characteristics and professional implicated), the pharmacy service (name of the service, description of the intervention, timeline, remuneration and training), clinical and humanistic outcomes (sample size, tools to measure clinical and humanistic outcomes and results obtained), adherence (method of measurement, description of the method, general and specific results and additional information) and miscellaneous (conclusions, limitations, funding source and other relevant studies) was used to extract relevant data. Data extraction was carried out by two reviewers (AOA and AML) and discrepancies were settled by a third expert (EG). A positive result was considered if statistical differences were found between control group (CG) and intervention group (IG) at the end of the study on the studied variable. If this data was not available, changes from baseline was taken into account, accepting that these results could be less relevant. If the results were analysed by subgroups in both primary variables (adherence and clinical outcome) the results of the non-adherence patients at baseline were chosen. Studies were classified as being "Interventions that improve adherence", if they found any positive result in adherence after CP´s intervention, or "Interventions that could not demonstrate an improvement on adherence" if they could not demonstrate any positive result in adherence after intervention.

Intervention effect measurement

Continuous data were reported using mean difference and the standard deviation. Dichotomous data were reported using odds ratios (OR) with 95% confident intervals. A two-tailored p-value <0.05 was designated as the level of statistical significance. Serum cholesterol levels were reported as mg/ml. Cholesterol values reported as mmol/l were converted to mg/dl [39].

Missing data

If necessary data for inclusion in the meta-analysis was not provided in any of the studies, the corresponding author was contacted to request this information. If necessary data was not obtained, the study was excluded from the quantitative analysis (meta-analysis).

Data synthesis

Studies were classified depending on the method of adherence measurement (i) using a validated test or (ii) using medication-possession ratios (e.g. medication refill data); and the duration of follow-up.

Risk of bias

The risk of bias was assessed using the Cochrane risk of bias (ROB 2.0) tool [40]. The criteria applied to assess methodological quality, encompassed five areas: (i) bias arising from the randomization process, (ii) bias due to deviations from intended interventions, (iii) bias due to missing outcome data, (iv) bias in measurement of the outcome, and (v) bias in selection of the reported result. Each area was assessed and rated as "high risk", "low risk" or "some concerns". Studies were graded as: "low risk of bias" when a low risk of bias was determined for all domains; "some concerns" if at least one domain was assessed as raising some concerns, but not to be at high risk of bias for any single domain; or "high risk of bias" when high risk of bias was reached for at least one domain or the study judgement included some concerns in multiple domains.

Meta-analysis

A meta-analysis was performed for outcomes when enough data were available. Meta-analyses were performed in the Review Manager V.5.3 (RevMan 5) [41] using the inverse-variance method and the random effects model. Adherence was measured as dichotomous variable. The OR and 95% CI were calculated to generate the forest plot. Total cholesterol was measured as a continuous variable and expressed in mg/dl. The mean difference and standard deviation were calculated to generate the forest plot. Only data from the intervention provided by community pharmacists were included.

A Z-test with a two-tailed p value of <0.05 was used to assess the statistical significance of the meta-analysis result. Clinical heterogeneity was assessed studying the comparability of the included studies in term of type of intervention. Statistical heterogeneity was assessed using the Cochran's Q test and was measured by the I^2 statistic. An I^2 value between 40-60% indicated moderate heterogeneity, whereas an I^2 value exceeding 60% indicated substantial statistical heterogeneity[36].

When different approaches of analysis are included in the same study, the most pragmatic method (i.e. intention-to-treat analysis instead of per-protocol analysis or validated questionnaire instead of electronic dispensing data) and the longest duration data (i.e. 12-month data vs. 6-mont data) was chosen.

3.3. RESULTS

Study description

A total of 1918 potential articles were yielded through the search in bibliographic databases (MEDLINE: n=476; Cochrane Library: n=43; Science Direct: n=17; Scopus: n=1011; Web of Knowledge: n=371). 42 additional records were identified through hand search. After removing duplicates (n=1217) and screening titles and abstracts, 104 publications were assessed for eligibility. 98 were excluded due to any of the following situations: not include patients treated with lipid-lowering drugs (n=7), the improvement of adherence was not one of the objectives of the study (n=57), not having a control group (n=2), not measuring adherence (n=11), the intervention was not carried out by a community pharmacist (n=9) and the clinical variable was not measured (n=12). Finally, 5 articles were included for the qualitative synthesis (Figure 1) [42–46].

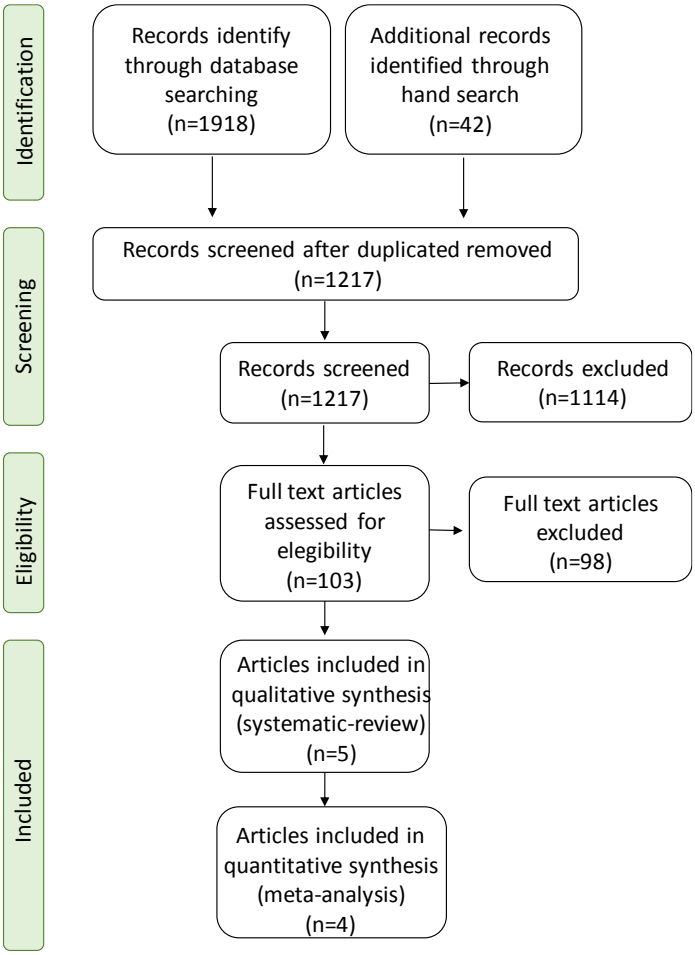


Figure 1: Flow diagram of the different phases of the study selection (Moher et al., 2009).

General study characteristics

The publication year of selected studies ranged from 2010 up to 2019 and the location was mostly in Europe. In particular, 4 studies were performed in Europe [43-45],1 in Australia [42] and 1 in North America [46]. Regarding type of study, 3 were randomized controlled trials (RCT) [43–45] whereas 2 studies were cluster-randomized controlled trials (c-RCT) [42,46].

All studies described the intervention in detail and were face to face interventions [42,43,45,46] in exception of one study that intervention was telephone based [44]. The follow-up period was more than 6 months for 3 studies [42,43,46] and of 6 months for the other two [44,45]. The frequency of the visits was two-monthly for 2 studies [45,46], three-monthly for 1 study [42] and variable for 2 studies [43,44]. One of the studies included physicians in the intervention [46], whereas in the other ones, the intervention provided was exclusive of community pharmacists [42–44]. One of the included studies reported data of community pharmacists and general practitioners but data were given separately [45].

In relation to studied chronic disease, 4 studies included patients with dyslipidaemias [42,43,45,46]. The other study included dyslipidaemias within other chronic diseases [44] but it was considered suitable for the qualitative synthesis since the 95.9% of the recruited patients had hyperlipidaemia (table 1).

Regarding the method of adherence measurement, 2 studies used validated questionnaires [42,45], 2 studies used medication-possession ratios [43,46] and one study used both of them [44]. Total cholesterol levels were measured using fasting finger prick methods in all studies [42–45], except in one where TC levels were measured in hospital laboratory [46] (table 1).

Two of the included 5 studies, remunerated the service with AUD$100 and 25 for each completed patient of the IG and CG respectively [42] and with $50/$104 for each recruited and intervention provided [46]

Table 1. Characteristics and results of selected studies.

Author	Title, year, country	Type of study / Sample size / Loss reason / Chronic disease	Intervention and control description / Professional implicated / Follow up / Frequency / Remuneration	Method of measurement of adherence	Adherence reported data	Clinical outcome reported data	Other reported data
Alsani, P., et al. (Aslani et al., 2011)	A community pharmacist delivered adherence support service for dyslipidemia 2011 Australia	Cluster randomized controlled trial n=142 n CG= 70 n IG=97 Loss reason: withdraw (n=45). Dyslipidemia	IG: Assessment of adherence to therapy, clinical outcomes, barriers and facilitators of adherence, delivery intervention to promote adherence CG: Measurement of blood lipid levels. Community pharmacists 9 months Three monthly Remuneration: Yes	BMQ and MARS Measured at baseline, on the middle of the study and at final.	No differences in non-adherence. IG were less likely to take less than the prescribed dose after the 1st time interval ($p<0.05$). IG were more liable to alter the dose at the 3rd reading compared to the 2nd ($p<0.05$).	Total cholesterol (mmol/l): CG (49) / IG (48) 0mo: 4.81 / 5.10 Med: 4.73 / 4.95 Final: 4.80 / 4.63 * *	Exercise: Differences between CG and IG at time 2, not at the endpoint. Skim milk consumption: IG patients consumed slightly more skim milk at time 2 and endpoint.

Table 1 (cont.). Characteristics and results of selected studies.

Author	Title, year, country	Type of study / Sample size / Loss reason / Chronic disease	Intervention and control description / Professional implicated / Follow up / Frequency / Remuneration	Method of measurement of adherence	Adherence reported data	Clinical outcome reported data	Other data
Eussen S et al. (Eussen et al., 2010)	A pharma-ceutical care program to improve adherence to statin therapy: RCT 2010 Netherland	Randomized controlled trial n=899: CG= 460 n IG=439 Loss reason: Withdrew (n=3) Died (n=1) Did not attend final evaluation (n=9) New users of statin	IG: Initial visit: Counselling structured education of indication, effects and adverse effects, dosage, importance of adherence and duration of the treatment. On the following visits information about problems with statins were recorded and total cholesterol, HDL-cholesterol and triglyceride level measurement. CG: Verbal and oral drug information. CP 12 months: Baseline, 15 days, 3, 6, 12 months, Remuneration: No	Medication possession ratio Adherent if the amount of medication dispensed > 80% of the days. Persistent if medication was dispensed within 60 days before the 12-month evaluation	Discontinuation of treatment (%): 6 mo. * CG 16 IG 1 12 mo. CG 26 IG 2 3 $HR_{6mo.}$=0.66, 95%CI 0.46-0.96; p=0.026 $HR_{12mo.}$=0.84, 95%CI 0.65-1.10; p=0.21 Medication possession ratio (%): Mean CG 99.2 IG 99.5	Total cholesterol reduction: IG: -17.2mg/dl LDL cholesterol reduction: IG: -9.47mg/dl Target LDL-c level (%): 3 months: 65% 6 months: 72% 12 months: 77% 3 mo. * Adh 67% Non-adh 45% 6 mo. * Adh 74% Non-adh 50% Sperarman´s correlation: MPR and TC: r=-016, p=0.002MPR and LDL-c: r=-0.10, p=0.08	NA

Table 1 (cont.). Characteristics and results of selected studies.

Author	Title, year, country	Type of study / Sample size / Loss reason / Chronic disease	Intervention and control description / Professional implicated / Follow up / Frequency / Remuneration	Method of measurement of adherence	Adherence reported data	Clinical outcome reported data	Other data
Lyons I et al. (Lyons et al., 2016)	The Medicines Advice Service Evaluation (MASE): a randomised controlled trial of a pharmacist-led telephone based intervention designed to improve medication adherence. 2016 United Kingdom	Randomized controlled trial n=677; CG= 337; IG=340 Loss reason: Withdrew (n=32) Ineligible (n=19) Could not contacted (n=40) Prescription of at least one oral medication for DM2 and/or lipid regulation.	IG: MAS two telephone consultation with pharmacist, a written summary of the discussion and reminder charts. Measurement of blood lipid levels. The pharmacists tailor the information and advice taking account patients´ personal beliefs and preferences. CG: Usual care. CP 6 months-Variable Remuneration: Yes	Diagnostic Adherence to Medication Scale (DAMS) and Medication Possession Ratio (MPR) Measured at baseline, at the 4th week and endpoint.	Non-Adherent patients (<90% of medication taken in the previous 7 days) (%): DAMS CG IG 0 mo. 13.1 13.3 4 mo. 20.2 11.5 6 mo. 19.6 10.6 OR=1.54 (1.11-2.15, 0.010) MPR CG IG 6 mo. 40.6 29.9 OR=1.60 (1.14-2.24, 0.006)	Total cholesterol (mmol/l): Patients meeting guidelines targets (<5mmol/l) (%): Total CG IG 0 mo. 62.6 56.2 6 mo. 55.1 65.3	Reduction of HbA1c levels in the IG compared with CG (p=0.061). Satisfaction with the service.

Table 1 (cont.). Characteristics and results of selected studies.

Author	Title, year, country	Type of study / Sample size / Loss reason / Chronic disease	Intervention and control description / Professional implicated / Follow up / Frequency / Remuneration	Method of measurement of adherence	Adherence reported data	Clinical outcome reported data	Other data
Oñatibia – Astibia A et al. (Oñatibia-Astibia et al., 2019)	Tailored interventions by community pharmacists and general practitioners improve adherence to statins in a Spanish randomized controlled trial. 2019 Spain	Randomized controlled trial n=746 n CG1= 228 n CG2=281 n IG=237 Loss reason: Died and failed to return to the visit Statin prescription within the previous three months.	IG: Non-adherent with intervention. Identification of the cause of non-adherence and selection of the most appropriate intervention. At the subsequent visits, the effectiveness of the intervention was evaluated. CG1: Non-adherent with usual care. CG2: Adherent with usual care. CP+GP 6 months2monthly Remuneration: No	Morisky Green Levine test Measured at each visit	Adherent patients (%): CP / CG / IG 0 mo. / 0% / 0% 3 mo. / 41.6% / 42.1% 6 mo.* / 44.2% / 64.4% OR=2.34 (1.87-3.03); p=0<001	Total cholesterol (mg/dl): Total / CG / IG 0 mo.* / 223.3 / 210.2 6 mo. / 214.4 / 197.6 * Total cholesterol (mg/dl): Total / NO-ADH / ADH 0 mo. / 216.7 / 6 mo.* / 212.2 / 197.3	Dietary intake: increase over the study period in the INT group. Exercise increase over the study period in the INT group.

Table 1 (cont.). Characteristics and results of selected studies.

Author	Title, year, country	Type of study / Sample size / Loss reason / Chronic disease	Intervention and control description Professional implicated / Follow up / Frequency / Remuneration	Method of measurement of adherence	Adherence reported data	Clinical outcome reported data	Other data
Villeneuve et al. (Villeneuve et al. 2010)	A cluster randomized controlled Trial to Evaluate an Ambulatory primary care Management program for patient with dyslipidemia : The TEAM study. 2010 Canada.	Cluster randomized controlled trial n=225: CG= 108; IG=117 Loss reason: Withdrew (n=3) Died (n=1) Did not attend final evaluation (n=9) Statin monotherapy +inadequate lipid control	IG: Initial visit: Counselling and a treatment plan using a patient decision aid. On the following visits evaluation of lifestyle changes, adherence and drug´s efficacy. CG: Measurement of laboratory tests and adjustment of lipid lowering medication CP+GP Two monthly. Remuneration: Yes	Medication possession ratio Adherent if the amount of medication dispensed covered at least 80% of the days. Persistent if medication was dispensed within 60 days before the 12 month evaluation. Each visit	No differences in non-adherence. <u>Adherent patients (%):</u> ns <u>Persistent patients (%):</u> ns	LDL cholesterol (mmol/l): Total: 0 mo.* CG 3.2 IG 3.5; 12 mo. CG 2.3 IG 2.4 High risk: 0 mo.* CG 3.2 IG 3.5; 12 mo.* -0.15 Mod risk: 0 mo.* CG 3.2 IG 3.5; 12 mo. 0.14 Total cholesterol (mmol/l): 0 mo.* CG 5.4 IG 5.7; 12 mo. CG 4.4 IG 4.4 LDL target levels: <u>12mo.</u> RR=1.16 (1.01-1.34)	No differences between CG and IG at baseline or final: Blood pressure. Fasting blood glucose. Body mass index. Waist circumference. Visits to physician.

NA: Not applicable; CG: Control group; IG: Intervention group; Guidel: Guidelines. RR: Relative Risk; OR: Odds Ratio; CP: Community pharmacists; GP: General practitioners; RCT: Randomized controlled trial.

Risk of bias

A total of 5 randomized clinical trials were assessed for bias risk using the RoB 2.0 [40]. From them, 2 studies showed a low risk of bias [44,45], 2 studies uncertain risk of bias [43,46] and 1 study showed high risk of bias [42] (Figure 2).

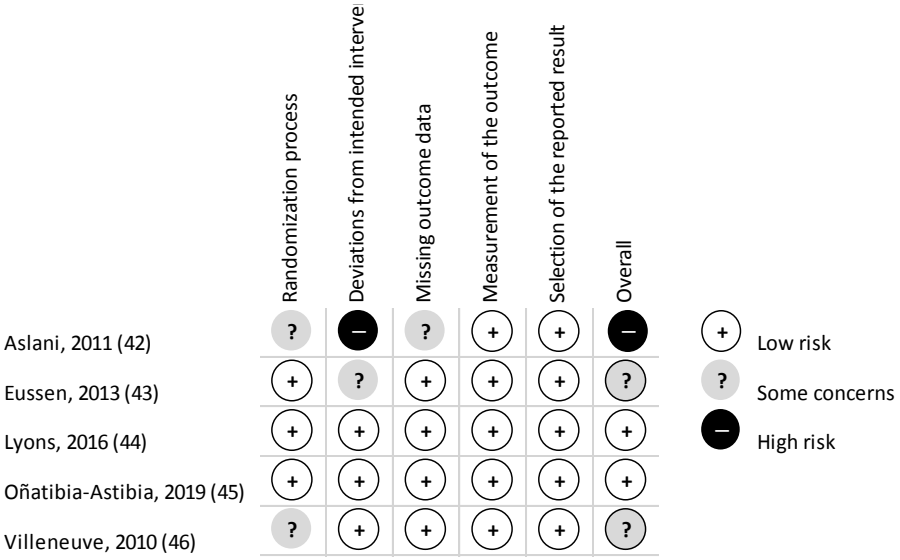


Figure 2. Methodological quality summary about each methodological quality item.

The risk of bias in the randomization process was low [43–45] for three studies and unclear for two [42,46]; the risk of deviations from intended interventions was low for three studies [44–46], unclear for one[43] and high for other one[42]; the risk of bias of missing outcome data was low for four studies[43–46] and unclear for one[42]; the risk of measurement of the outcome, was low for all the studies[42–46] and the risk of bias in selection of the reported result was low for two studies4[4,45], unclear for other two[43,46] and high for the other one [42] (Figure 3).

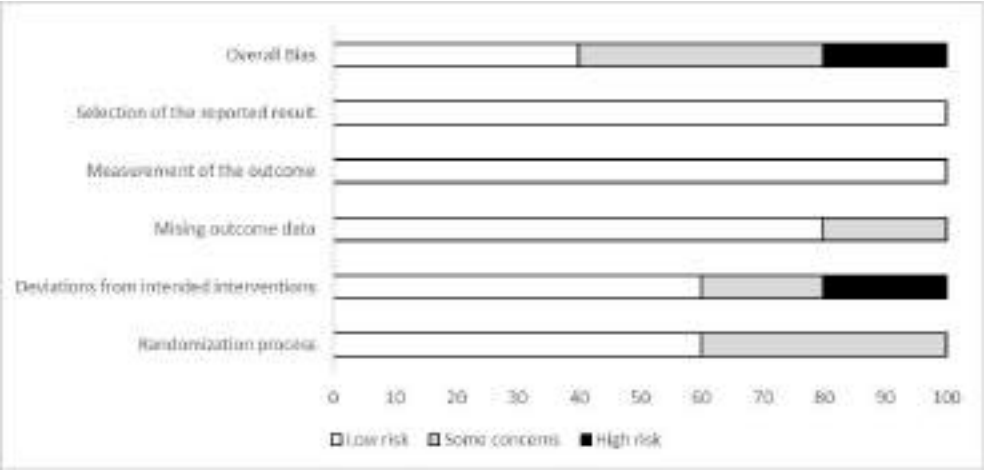


Figure 3. Risk of bias graph presented as percentages across all included studies.

Effects of interventions

Interventions that improve adherence

Adherence was improved in three studies [43–45] and two of them showed an improvement on clinical outcomes [43,45].

Eussen S et al., [43] undertook a study in which pharmacist intervention was provided to 439 new statin users during 12 months. The intervention was based on educational counselling and consisted of a face to face interview in which a structured education on indication, adverse events of statin therapy, posology and importance of adherence was given to the patient. Simultaneously, a drug information letter summarizing the visit was given. After the first counselling visit, subsequent refill visit were scheduled 3, 6 and 12 months later. Adherence was measured by medication possession ratio (MPR) and the clinical outcome, total cholesterol and LDL-cholesterol, were measured with a Cholestech LDX Analyzer using finger blood sample. Differences were observed on discontinuation of statin treatment between CG (16.0%) and IG (11.0%) after 6 months after the start of the treatment (HR=0.66; 95% CI 0.46-0.96; p=0.026). This difference in discontinuation rate was not statistically significant at twelve months (HR=0.84; 95% CI 0.65-1.10; p>0.05). MPR

did not show significant differences between groups (IG: 99.5% vs CG: 99.2%; p>0.05). Patients of the IG reduced total and LDL-cholesterol levels at the endpoint of the study (TC: -17.2mg/dl; LDL-cholesterol: -9.5mg/dl) and increased the percentage of patients that targeted LDL-c levels, being this percentage greater in adherent patients compared with non-adherent patients (3 month: 67% vs 45%; p=0.010 and 6 month: 74% vs 50%; p=0.010) (Table 1).

Oñatibia-Astibia A et al., [45] reported an intervention that improved adherence and the studied clinical outcomes. The intervention was provided two-monthly to 237 patients with a statin prescription within the previous three months, during six months. Based on patient feedback and the cause of non-adherence, a multicomponent strategy was proposed. Adherence was measured by Morisky-Green-Levine test. Non-adherent patients on the IG finished the study being more adherent than patients on the CG (OR=2.34; 95% CI 1.87–3.03; p<0.001). The indirect clinical outcome was total cholesterol measured at community pharmacies with Reflotron® Plus (Roche). Non-adherent patients that finished adherent after the intervention of 6 months, presented lower total cholesterol level compared with those who remains non-adherent (197.3mg/dl vs 212.2mg/dl; p<0.001). (Table 1).

Lyons I et al., [44] carried out a trial in which pharmacist intervention was provided to 340 patients with at least one oral medication for type 2 diabetes mellitus and/or lipid regulation during 6 months. The intervention was provided by telephone twice following a semi structured interview guide and was reinforced by postal information after the first telephone consultation. The objective of the telephone consultation was to identify any medication related problem and provide an intervention. Additionally, if no problem was detected, the pharmacist reinforced the importance of adherence and offered healthy lifestyle advices. Adherence was measured using the self-reported Diagnostic Adherence to Medication Scale (DAMS) and MPR calculated from electronic pharmacy dispensing data. Total cholesterol levels were collected using a self-administered finger pick test. Differences with DAMS and MPR, were observed on adherence between CG and IG at 6 months of the study. Self-reported adherence using the DAMS showed that the IG had increased odds of being adherent (OR=1.54; 95% CI 1.11-2.15; p=0.010) compared with CG respectively. Analyses of MPR also showed an increased odds of being classified as adherent was 60% greater for the IG

compared with the CG (OR=1.60; 95% CI 1.14-2.24; p<0.01). More patients of the IG reached targets for total cholesterol comparing with patients of the CG, but this difference was not statistically significant (65.3% vs 55.1%; p=0.24) (Table 1).

Interventions that could not demonstrate an improvement on adherence

Adherence was not improved in two studies [42,46] and one of them did not show improvement on clinical outcomes [46].

Aslani P et al. [42], undertook an study in which pharmacist intervention was provided to 72 patients taking a lipid-lowering medicine for at least 1 month prior to enrolment during 9 months (34). The intervention was based on delivering an individualised strategy to address patients´ barriers to adherence to therapy, to clinical outcomes and to barriers and facilitators of adherence and follow up the patient. Using a reminder to assist patients in taking the medication regularly and providing information about individual needs were the most common interventions. Adherence was measured by Brief Medication Questionnaire (BMQ) and Medication Adherence Report Scale (MARS) and total blood cholesterol was measured by pharmacists using the Accutrend GC (Roche diagnostics) test. No differences were observed in adherence at 9 months of the study. IG patients reduced their total cholesterol levels during the studied period (Baseline: 5.10mmol/l; Intermediate: 4.95mmol/l; Final: 4.63mmol/l; p<0.05), but there was no significant difference between IG and CG across the study (Middle of the study: IG 4.95mmol/L vs CG 4.73mmol/L; End of the study: IG 4.63mmol/L vs CG 4.80mmol/L; p>0,05) (Table 1).

Villeneuve J et al.,[46] carried out a trial in which pharmacist intervention was provided for 12 months to 108 patients with a new prescription of a statin or already receiving statin treatment with inadequate control. The intervention was provided by the pharmacist who provided counselling and drew up a treatment plan using a patient decision aid. The decision aid provides information on patient risk factors, personal estimation of cardiovascular diseases and treatment options. The treatment plan, included lifestyle changes and pharmacotherapy and it was evaluated during the titration visits [47,48]. Adherence was measured by MPR. Clinical outcomes, including LDL-c, HDL-c total cholesterol and triglycerides, were obtained through blood analysis

in the hospital. No differences were observed on adherence (OR=1.04 95% IC 0.90-1.27; p>0.05), neither on lipid levels (LDL-cholesterol: Adjusted reduction of -0.05 95% IC -0.3 to 0.2; p>0.05; HDL-cholesterol: Adjusted reduction of 0.02 95% IC -0.03 to 0.07; p>0.05; total cholesterol: Adjusted reduction of -0.03 95% IC -0.3 to 0.2; p>0.05; triglycerides: Adjusted reduction of -0.03 95% IC -0.2 to 0.1; p>0.05) between CG and IG at 12 months of the study (Table 1).

Pooling the results

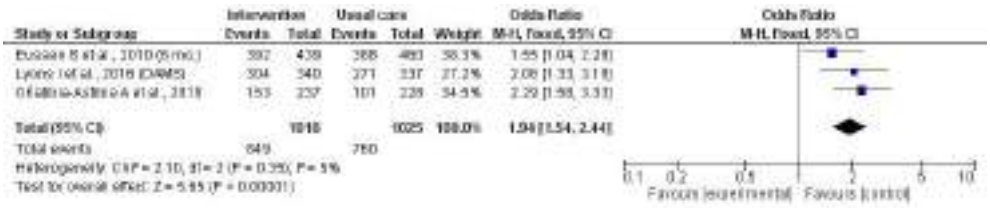
Medication adherence

Pooling data for medication adherence included 4 studies since one study [42] was excluded from the analysis due to not having enough data. This analysis included 2266 patients (1124 intervention + 1142 control). Meta-analysis using a random effects model estimated an OR of 1.67; 95%CI 1.38-2.02; p<0.001, favouring intervention with a moderate statistical heterogeneity (I^2=54 %) (Forest plot 1.1).

Forest plot 1.1: Forest plot diagram of OR for correlation between intervention and usual care in adherence.

Results were grouped into follow-up period (6 months and longer than 6 months) and into adherence measurement method (validated questionnaires or medication-possession ratios).

Pooling data for medication adherence into the follow-up period of 6 months included 3 studies. This analysis included 2041 patients (1016 intervention + 1025 control). Meta-analysis using a random effects model estimated an OR of 1.94; 95%CI 1.54-2.44; p<0.001, favouring intervention. There was low statistical heterogeneity (I^2=5%) (Forest plot 1.2).



Forest plot 1.2: Forest plot diagram of OR for correlation between intervention and usual care in adherence at 6 months.

Pooling data for medication adherence into the follow-up period longer than 6 months included 2 studies. This analysis included 1124 patients (547 intervention + 577 control). Meta-analysis using a random effects model estimated an OR of 1.34; 95%CI 1.04-1.73; p=0.020, favouring intervention. There was not statistical heterogeneity (I^2=0%) (Forest plot 1.3).

Forest plot 1.3: Forest plot diagram of OR for correlation between intervention and usual care in adherence at ≥6 months.

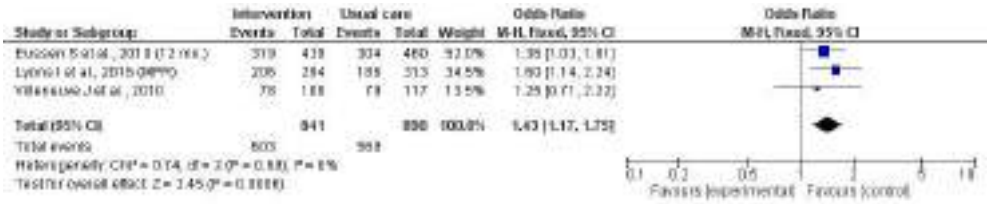
Medication adherence with validated questionnaires

Pooling data for medication adherence into using validated questionnaires for the measurement included 2 studies. This analysis included 1142 patients (577 intervention + 565 control). Meta-analysis using a random effects model estimated an OR of 2.19; 95%CI 1.65-2.91; p<0.001, favouring intervention. There was not statistical heterogeneity (I^2=0%) (Forest plot 1.4).

Forest plot 1.4: Forest plot diagram of OR for correlation between intervention and usual care in adherence measured by validates questionnaires.

Medication adherence with medication possession ratio

Pooling data for medication adherence into using medication refill data for the measurement included 3 studies. This analysis included 1731 patients (841 intervention + 890 control). Meta-analysis using a random effects model estimated an OR of 1.43; 95%CI 1.17-1.75; p<0.001, favouring intervention. There was not statistical heterogeneity (I^2=0%) (Forest plot 1.5).



Forest plot 1.5: Forest plot diagram of OR for correlation between intervention and usual care in adherence measured by medication refill data.

Total cholesterol: The meta-analysis cannot be proceed due to the variability in quantifying total cholesterol variation

3.4. DISCUSSION

This review found that community pharmacist-led interventions can improve adherence to statins but its contribution in the cholesterol management could not be demonstrated.

All the included studies evaluated the impact of community pharmacist intervention on patients' adherence to statins and although the qualitative analysis shows results of all sorts, a statistically significant result favoring the intervention group was observed in the meta-analysis. In particular, the meta-analysis showed that the odds of becoming adherent after the intervention was 1.67 higher in the intervention group compared to usual care. Although the included studies were different in terms of method used, the overall result was that an intervention provided by a community pharmacist might improve patients´ adherence to statins. This result is similar to other previous systematic reviews that evaluated adherence to lipid-lowering medication after different health professional intervention [15] or evaluated adherence to medication after community pharmacist-led intervention [49].

Different methods were used to evaluate adherence. Some studies used validated questionnaires whereas others, used medication dispensing data. Although the number of studies included was limited, studies that uses validated questionnaires get more favorable results than studies that use medication-dispensing data. In particular, the first ones had an odd of becoming adherent after the intervention 0.76 higher than the second ones. This could be one of the reasons why Villeneuve et al did not find improvement on adherence after community pharmacists´ intervention [46] since overestimated adherence values are found while using this method [50]. Different authors recommends multimeasure approach in measuring adherence to medication. Previous data showed that using both, an objective and a subjective measures will, therefore, provide higher reliability [51]. In this sense, Lyons et al used two different methods founding similar values and reinforcing the conclusion [44]. It is worth lighting that any of the included studies used direct methods of measurement that include plasma or urinary determination of the drug. Those methods have the advantage that are objective and reliable methods, but the cost of the method, the need of specialized professional and the fact that it is an invasive method, make that this method is not used in the community pharmacy.

Short-term studies and long-term studies were included in the review. The meta-analysis showed that adherence levels increase over both groups, getting better results in the short-term studies. Previous studies found that adherence to statins decreases over the time. For example, Benner et al [52] found that it decreases from 79% to 56% from the 3rd to the 12th month. Adherence is not a static condition and is known to vary over time, resulting in periods of adherence followed by periods of non-adherence [53,54] and variation of the results over the time could be justified. However, the low number of studies, especially in the long-length group, may complicate drafting a conclusion. Eussen et al [43] suggested that pharmacist-led intervention may be most effective in patients newly starting statin treatment since adherence decreases after several months.

Due to the variability in the method used for quantifying the clinical variable and the variability of the variable measured, it is difficult to evaluate the relationship between community pharmacists' intervention and its impact on patients´ lipid levels. Two recent systematic reviews [15,49] found positive benefits from health professional-led interventions. Van Driel et col [15], stated that any type of intervention intended to increase adherence, improves medication adherence and in long-term studies also imrpoves lipid levels, in patients taking lipid lowering medication. Milosavljevic et col. [49], with a very small number of included studies, suggested that community pharmacist-led interventions improved adherence and among other diseases improves also cholesterol control.

The results of the meta-analysis of this review shows that the most effective interventions to improve adherence to lipid lowering medications are those that provide a specific intervention taking into account patients´ situation. Lyons et al [44] proposed an intervention where each pharmacist were able to tailor the information and provide the information based on patients´ needs, personal beliefs and preferences. Similarly, Oñatibia-Astibia et al study [45] was based on choosing the most appropriate intervention after identifying the cause of non-adherence.

These findings are in line with other studies where a combination of different type of interventions proved to be effective [55,56]. Apart from using more than one intervention, teamwork between different health professionals has been identified as one of the

key factors for success in implementing adherence programs [57]. The present review did not study this point since only community pharmacist-led interventions were included and collaboration with other health professionals was poorly described. Other reviews that included different health professionals neither found interventions provided in a collaborative way [15]. However, studies evaluating adherence after interventions at different levels and by different professionals, may give an idea of the importance of multidisciplinary work.

The risk of bias indicated that some of the included studies were biased in the bias due to deviations from intended interventions. In most of the studies, patients rather than professionals were randomized. Therefore, the control group patients could receive the intervention ideally. Only studies that were clustered should have been included in the review, but due to the low number of published articles with inclusion characteristics, all types of randomized controlled trials were accepted. Regardless, the meta-analysis shows a positive result between interventions of CP and adherence, so if contamination resulted real, and some participants of the CG received intervention, the likely effect of this would be smaller, strengthen in this way the effectiveness of the intervention.

Another domain biased in the included studies was the risk of bias in relation to blinding of outcome assessment. Adherence was measured using questionnaires in some of the studies where the risk of bias detection is higher. However, the reproducibility and reliability of the questionnaires was studied and therefore, the overall result of the area has been classified as having low risk of bias. When interpreting the results from this review, several limitations need to be considered. Firstly, there is a low number of studies that evaluate the impact of community pharmacists' intervention on patients´ adherence to lipid lowering medication and on clinical outcomes. Many of the studies that evaluated the impact of the intervention of the community pharmacist in adherence to the hypercholesterolemic treatment did not evaluate the implication that this intervention had in the clinical variables. Moreover, those who did, used different variables that makes difficult to draw a conclusion. Therefore, more studies are needed to evaluate adherence and its relationship to the clinical variable. Secondly, adherence is not a static condition and can vary over time. In the studies included in the review, they evaluate adherence at

a specific point. Studying adherence a few years after the end of the study is not easy from a methodological point of view, but it is necessary to conclude the long-term effectiveness of the intervention of the pharmacist. Finally, control group defined as usual care can englobe a wide diversity of control interventions since usual care is different in some settings. However, if in many settings usual care can include some extra interventions, the observed differences will be underestimated, and the results could be even greater than those obtained in the meta-analysis.

Community pharmacists have demonstrated to be key agents in improving adherence to treatment. More research is needed on providing interventions in evaluating adherence to lipid-lowering medication and its relation with clinical outcomes and investigating the best intervention to improve adherence in order to implement pharmaceutical services.

Conclusion

This meta-analysis provides further evidence to support community pharmacist-led intervention in improving adherence to lipid-lowering medication. Due to the limited comparability and low number of studies, the variation in adherence could not be related to the variation in clinical variables. Future research should attempt to better understand which is the implication of adherence in clinical outcomes.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

3.6. REFERENCE

Ainhoa Oñatibia-Astibia, Amaia Malet-Larrea, Miguel Ángel Gastelurrutia, Begoña Calvo, Estibaliz Goyenechea. Community pharmacists' intervention to improve adherence to lipid lowering medication and the influence on clinical outcomes: a systematic review and meta-analysis. Journal of Evaluation in Clinical Practice (en revision)

CAPÍTULO 4:

THE MEDICATION DISCREPANCY DETECTION SERVICE: A COST-EFFECTIVE MULTIDISCIPLINARY CLINICAL APPROACH

4.1. INTRODUCTION

Medication errors (ME) are among the top 10 causes of death worldwide (1). Such errors can cause patient safety incidents, which are associated with a higher rate of hospitalisation and increased morbidity and mortality, accounting for more than 1% of total global health expenditures (2). ME is the single most common preventable cause of adverse events in medication practice and a major public health burden, with an estimated annual cost in Europe of €4.5 billion to €21.8 billion (3). Due to the health and economic impact of ME, the World Health Organization (WHO) has included the reduction of ME in the Global Patient Safety Challenge (4).

ME has been defined as 'any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer' (5). Contributing factors may be associated with health care professionals, patients, the work environment, medicines, computerised information systems, and/or primary–secondary care communication (6). Reducing the frequency and impact of preventable harm related to medicines as the consequence of error, accident, or communication problem will contribute to the achievement of medication safety for patients (7). Statistics show that these strategies will lead to 95,000 fewer deaths per year in Europe (2).

Various strategies to reduce ME in the community setting have been proposed in recent years; they include medication review and reconciliation services, the use of automated information systems, education, and multicomponent interventions (8–10). The effectiveness of clinical pharmacists in identifying ME has been demonstrated, but data from primary care are relatively scarce and few studies have included community pharmacists (CPs) (11–13). This lack of research among CPs and the previous experience that these professionals have in other services (14) have led the WHO to consider the involvement of CPs in the prioritisation of strategies to reduce ME in primary care (6).

In this context, to meet the need for high-quality and cost-effective identification of medication discrepancies, a medication discrepancy detection service (MDDS) was designed. To ensure patient-centred care, collaboration among different health

professionals is needed (15). The MDDS is offered by a multidisciplinary team including CPs and general practitioners (GPs) in collaboration with primary care pharmacists and primary care nurses. The identification of medication discrepancies is a way to detect ME, and CPs in Spain are ideally positioned to do so, as they have access to electronic medical records and are responsible for dispensing medicines. Therefore, the aim of the present study was to evaluate the impact on the number of medicine intake and the cost effectiveness of the MDDS as implemented collaboratively in the community pharmacy and primary care services settings.

4.2. METHODS

Study design and ethical approval

This non-controlled before-and-after study was undertaken between October 2015 and September 2016 in the Bidasoa Integrated Healthcare Organisation, Spain, which is comprised of one regional hospital and three primary care units. The multidisciplinary professional group that provided the MDDS consisted of CPs, primary care pharmacists, GPs, and hospital specialists. All the CPs of the pharmacies located in the municipalities attended by the Integrated Healthcare Organisation, were invited to participate in the project. CPs and GPs attended a 2-hour workshop that presented and described the study protocol. The protocol for this study was approved by the Ethics Committee for Clinical Research of the Basque Country (PI2015080 EPA-SP) and was in line with the Helsinki Declaration. All participants provided written informed consent at the time of their enrolment, and CPs delivered information sheets explaining the study to patients who met the study criteria.

Patients

Patients were recruited according the following criteria: patients that had a discrepancy between their active medical charts and the medicines they were actually taking. CP identified this patients with discrepancies like (i) patients not taking medications that appeared in their charts, (ii) taking medications that did not appear in their charts, (iii) not following the prescribed dosage regime, (iv) not following the prescribed posology and (v) duplicated treatment.

Study procedure and health outcomes

CPs offered the MDDS service to patients in whom at the time of dispensing they identified a discrepancy between their active medical chart and the medicines they were taking. CPs registered each participating patient's name, health identification number, willingness to participate in the study, and date of first appointment (record 1). Patients were asked to bring all current medications, including dietary and other products, to the pharmacy. The CPs performed a clinical interviews and checked brown bags For the interview, the pharmacist used a guide consisting of structured questions that allowed to collect as much information as possible about taking prescribed medications, other medications, supplements, creams or other products. The brown bag checking consisted of checking an inventory of the medications taken by each patient based on the medication packages. At the time of the clinical interview, each patient provided written informed consent .If a patient did not return for the scheduled appointment, it was recorded as "rejected". After the clinical interview, the information was compared with the patient's medical chart and the CP prepared a report in which all detected discrepancies were registered. Once the CP evaluated the patient's situation, the CP completed the report and sent it to the primary care pharmacist. Time invested in the clinical interview and report preparation was also registered.

Upon receiving the report, the primary care pharmacist contacted the corresponding primary care nurse, who cited the patient with the GP. The GP conducted a clinical interview and was responsible for making any necessary changes to the medical chart in the electronic prescribing system. If a medical specialist was responsible for the prescription, the primary care pharmacist contacted directly by telephone to solve the problem. Pharmacotherapeutic changes were made in agreement with the patient, and the GP made sure that the patient understood the new treatment (Figure 1). Discrepant medications were classified using the Anatomical Therapeutic Chemical system.

Primary care pharmacists compiled and recorded all data, and were responsible for registering discrepancies and for ensuring that the flowchart was followed correctly. Emergency department (ED) visits and hospital admissions 6 months before and after the intervention were registered at the end of the study period using hospital records.

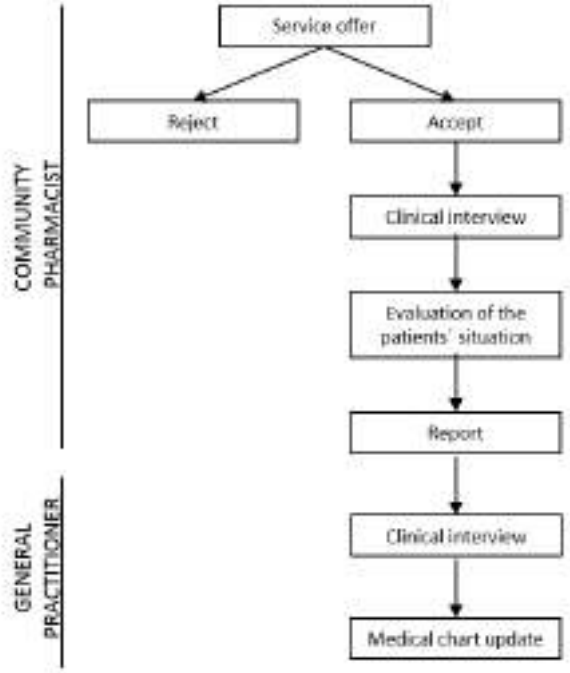


Figure 1. Flowchart of the study procedure.

Economic outcomes

An economic evaluation was conducted from the National Health System (NHS) perspective. The cost and effectiveness of the service was analysed. The direct costs of medications (including discrepant medications), ED visits and hospital admissions 6 months before and after the intervention, and interventions costs were included. The numbers of medicines, ED visits, and hospital admissions served as effectiveness variables. Costs were estimated using posology and the prices of the medicines. The costs associated with ED visits were estimated based on the Basque Health Service (BHS) rates (16–18). The diagnosis-related group (DRG) was identified for each hospital admission. DRGs make up an established payment system for groups of patients with similar clinical characteristics who are expected to have similar health resource consumption (4). The cost for each DRG was determined using BHS rates (16–19). The total cost of each intervention included costs associated with: (i) the time spent by the CP on the clinical interview, (ii) the time spent by the CP to complete the report, (iii) the cost of GP consultation (iv) the cost of hospital telephone specialist

consultation and (v) the cost of the time spent by primary care pharmacists. Costs (i) and (ii) were estimated using collective CP bargaining data. Costs (iii) and (iv) were estimated using BHS rates (16). All costs were expressed in euros and updated to 2017 using the Spanish Retail Price Index. The incremental cost-effectiveness ratio (ICER) was calculated to compare costs before and after the intervention.

Statistical analysis

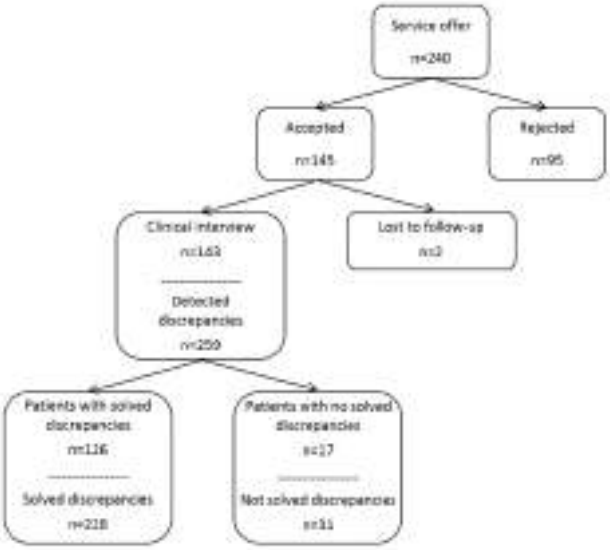
Changes in the numbers of medicines, ED visits, and hospital admissions were evaluated and compared before and after MDDS implementation with the paired *t* test or Student's *t* test for parametric variables. The chi-squared test and Fisher's exact test were used to analyse the frequency distributions of the study variables. A one-way sensitivity analysis was conducted to examine the impacts of the study variables on the results of the economic evaluation. General data are expressed as means ± standard deviations. Statistical analyses were performed using the SPSS software (version 18.0 for Windows XP; Microsoft Corporation, Armonk, NY, USA). Two-tailed p values < 0.05 were considered to be statistically significant.

4.3. RESULTS

Ten of the 30 community pharmacies located in the municipalities attended by the Integrated Healthcare Organisation participated in the project and offered the MDDS to a total of 240 patients. CPs identified 259 discrepancies in 143 patients, leading to 228 medication reconciliations for 126 patients by GPs and other medical specialists. The majority (72.3%) of participants were women and the mean age was 72.3 ± 13.1 years. The mean number of prescribed medicines take was 9.1 ± 3.8 per patient and the mean number of medication interventions was 1.8 ± 1.3 per patient (Study diagram figure).

The main type of discrepancy registered by CPs was that patients were not taking medicines listed on their active medical charts (58.7%, n = 152). In more than half (54.8%, n = 125) of discrepancy cases, GPs decided to withdraw the treatment. In

other cases, the treatment was not modified (24.6%, *n* = 56), it was modified (13.6%, *n* = 31), or new treatment was initiated (7.0%, *n* = 16).



Study diagram figure: Flowchart of patients during the study.

The groups of medicines with the most discrepancies were drugs for obstructive airway diseases (R03; 8.3%, *n* = 19), psycholeptics (N05; 8.3%, *n* = 18), and non-steroidal anti-inflammatory and antirheumatic products (M01A; 7.5%, *n* = 17).

After the intervention, a significant reduction in the number of medicines in patients' active medical charts (-0.92 ± 1.09, $p < 0.0001$) was seen. CPs invested an average of 11.8 ± 4.1 minutes performing each initial patient interview and 13.8 ± 5.0 minutes drafting the report. They thus spent a mean total of 25.5 ± 7.4 minutes per patient providing the service. Thirteen cases were transferred to medical specialists who had prescribed discrepant medicines.

The number of hospital admissions decreased (-0.17 ± 0.68, $p = 0.007$) after MDDS implementation compared with baseline (Table 1). The number of ED visits also decreased, but this difference was not significant.

Table 1. Numbers of medicines, emergency department visits, and hospital admissions 6 months before and after the resolution of medication discrepancies.

Variable	*n*	$\bar{x}$(SD)	Difference: $\bar{x}$(SD)	*p* value
Number of medicines				
Before	1149	9.12 (3.82)	−0.92 (1.09)	<0.001
After	1033	8.20 (3.81)		
Number of ED visits				
Before	77	0.61 (1.13)	−0.10 (1.28)	0.405
After	65	0.52 (0.91)		
Number of hospital admissions				
Before	41	0.33 (0.66)	−0.17 (0.68)	0.007
After	20	0.16 (0.42)		

$\bar{x}$: mean; SD, standard deviation; ED, emergency department.

Economic outcomes

The mean cost of the intervention was €71.5 ± 15.8. GP consultations were the costliest components (€55 each) followed by the telephone specialist consultation (50€ each); the average costs of CP and specialist consultations were €11.3 ± 3.3 and €5.2 ± 15.3, respectively. The costs of medication, ED visits, and hospital admissions were lower after the intervention (Table 2). Even taking into account the cost of the intervention, all costs were lower thereafter ($p < 0.05$).

Table 2. Mean costs per patient (€, 2017; $n = 126$).

Item	$\bar{x}$ (SD)	Difference: $\bar{x}$ (SD)	*p* value
Medication			
Before	1.4 (3.0)	−0.77 (2.5)	<0.001
After	0.6 (2.1)		
ED visits			
Before	92.3 (171.9)	−14.4 (193.3)	0.007
After	77.9 (138.7)		
Hospital admissions			
Before	909.7 (2079.8)	−501.2 (2001.9)	<0.001
After	408.4 (1229.6)		
Intervention			
Before	-	71.5 (15.8)	-
After	71.5 (15.8)		
Total			
Before	1003.3 (2165.3)	−444.9 (2089.8)	0.018
After	558.4 (1273.0)		

$\bar{x}$, mean; SD, standard deviation; ED, emergency department.

For all three cost-economic variables, the intervention was cost effective because health outcomes were better and costs were lower. The sensitivity analysis showed that the variable with the greatest impact was the number of hospital admissions, as it was the only variable that could invert the qaly cost. All other variables analysed slightly increased or decreased the benefits obtained with the service (Figure 2).

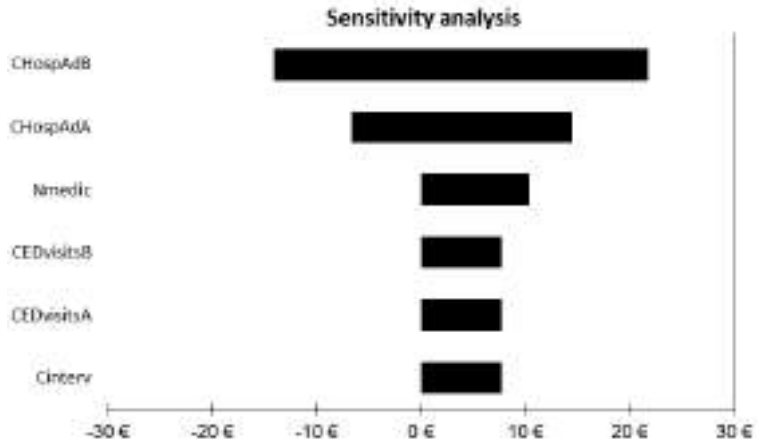


Figure 2. Results of one-way sensitivity analysis including variables critical to the economic evaluation.
CHospAdB, cost of hospital admission before intervention; CHospAAB, cost of hospital admission after intervention; Nmedic, number of medications; CEDvisitsB, cost of emergency department visits before intervention; CEDvisitsA, cost of emergency department visits after intervention; Cinterv, cost of intervention.

4.4. DISCUSSION

This study showed that the MDDS is an effective and innovative way to detect medication discrepancies in community pharmacies and to resolve them with the collaboration of diverse health professionals, such as CPs, GPs, other medical specialists and primary care pharmacists. The high percentage (88%) of resolved discrepancies and the reduction in the number of drugs taken (by almost one per patient) suggest a significant improvement in patient safety.

CPs identified 240 patients with medication discrepancies, of whom 143 accepted study participation. The majority of these 143 patients had single discrepancies, and

the rest had discrepancies in more than one medication. Medication discrepancies can be detected at different levels. Several systematic reviews have shown that pharmacist-based interventions are effective in the community setting (20,21). The MDDS identifies and reduces discrepancies being the particularity of this study the involvement of all health agents, especially community pharmacists, in the control of medication errors. Our data suggest that CPs are ideally positioned to detect medication discrepancies, in agreement with the WHO´s strategy to include CP in plans to detect ME (6).

Removing a medication from the medical chart was the most common intervention performed by the GP. It has been demonstrated that after the MDDS intervention, each patient in this study used, on average, almost one fewer medication than at baseline. Polypharmacy is related to poor adherence, interactions and ME (22), and reducing this condition is included in the WHO´s third Global Patient Safety Challenge (7). Thus, the MDDS could provide a strategy for the reduction of polypharmacy-related problems. Furthermore, this service represents that it could be an efficient way of improving patients' medication-related safety and a strategy to prevent and manage patients´ frailty (23).

One problem associated with medication reconciliation interventions for CPs is the difficulty of contacting physicians (24). Several authors have stated that future initiatives should focus on collaboration between health care professionals, and such collaboration is also essential when designing services (25,26). Therefore, CPs and primary care pharmacists participated in the design of the MDDS. Primary care pharmacists served as intermediaries between CPs and GPs, and this strategy was effective.

The numbers of hospital admissions and ED visits were 45% and 16% lower, respectively, after the intervention than at baseline. Similar reductions have been observed after clinical pharmacists-based interventions (27,28). Due to the use of a wide range of methods to calculate the cost of ME, calculation of the worldwide health care expenditure associated with hospital admissions and ED visits due to such error is difficult (29). However, authors agree that this cost is high (30). A study conducted in the Netherlands showed that the cost of hospital admission due to preventable

medication-related events increased to €3,171 per patient, and ED visits accounted for €30,896, or 5.3% of the total health costs, during the study period (31). One objective of the Organisation for Economic Co-operation and Development in 2014 was to identify good practices in managing health care budgets (32). Therefore, reducing hospital admissions and ED visits with the MDDS could contribute to improving the sustainability of the health system.

Our analysis supports the hypothesis that the MDDS is a dominant intervention, as it improves clinical outcomes with lower costs than usual care, regardless of the cost of the intervention itself. The sensitivity analysis showed that only the cost related to hospital admissions could invert the ICER. The variability in the cost of such admissions is greater than variabilities for other health outcomes. Some authors have stated that use of the DRG system may lead to inequities in associated costs (26). To reduce this variability, the identification of hospital admissions related to medicines and exclusion of unrelated admission from analysis could be useful (33). Previous economic evaluations have focused on transitional care programmes that included interventions to prevent ME among settings, and they have produced variable results (34–37). Recent evaluations have shown that the services provided by CPs tend to be cost effective (38,39). The implementation of professional pharmacy services like the MDDSmay be an efficient way to improve patient safety.

The groups of medicaments with the most discrepancies in this study were drugs for obstructive airway diseases (R03), psycholeptics (N05), and non-steroidal anti-inflammatory and antirheumatic products (M01A). Considering that most discrepancies detected in this study were due to patients not taking medicines included in their medical charts we could state that patients´ more frequently have adherent problems. Patients with medicines prescribed for obstructive airway diseases, psycholeptics and non-steroidal anti-inflammatory and antirheumatic products are one of the most prevalent groups of patients to have adherent problems (40). Although CPs should be aware of discrepancies in all types of medication, special attention must be given to these medication groups when providing the MDDS.

The present study has several limitations. Firstly, it was conducted within the Bidasoa Integrated Healthcare Organisation, and a relatively small number of patients participated. To increase the external validity of our findings, the study should be replicated in other regions. Sencondly, only patients in the NHS are eligible for the MDDS, as they are the only ones for whom CPs receive electronic prescription information. However, the authors do not believe that the inclusion of the entire target population would alter the results. Thirdly, the present study included no random assignment or control group, and the modifications observed could be attributed to factors other than the intervention. To increase the reliability of the MDDS and our finding that it is cost effective compared with usual care, the results of this study should be compared in studies conducted with control groups. Finally, all hospital admissions and ED visits were included in analysis, with no evaluation of cause. To minimise possible bias, future analyses should include only hospital admissions and ED visits associated with ME. Future health policies must provide support for the development and implementation of evidence-based services to prevent ME and improve patient safety.

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DISCUSIÓN

El presente trabajo evidencia la importancia del rol del FC en los SPFA y concretamente en la promoción de la adherencia al tratamiento y la detección de discrepancias en el uso de los medicamentos.

En una sociedad cada vez más concienciada, informada y formada en los aspectos relacionados con la salud y el bienestar, la figura del FC debe responder a unas demandas cuyas exigencias van en aumento. En este contexto, la principal misión de este profesional sanitario es la de garantizar el uso seguro, efectivo y eficiente que hacen los pacientes de los medicamentos. De esta manera, el FC responde con actuaciones que van más allá de la propia entrega de los medicamentos, ofreciendo a los pacientes y al ciudadano en general unos servicios específicos, los SPFA, con el objetivo de reducir tanto la aparición de los problemas relacionados con los medicamentos (PRM), como los resultados negativos asociados a los medicamentos (RNM) (1).

Esta tesis doctoral se centra en evaluar el papel del FC en dos SPFA de atención farmacéutica, el servicio de adherencia terapéutica y el servicio de detección de discrepancias de los medicamentos. Para ello, contempla el diseño de dos estudios experimentales, uno de evaluación del impacto de la intervención del FC en la adherencia al tratamiento con estatinas, que se completa con el análisis de una revisión sistemática y posterior meta-análisis, y un segundo diseño experimental que consiste en el análisis de la identificación de discrepancias en el uso de los medicamentos detectadas por el FC y trasmitidas al médico de atención primaria.

En cuanto a la adherencia al tratamiento, los resultados de nuestros estudios (capítulos I y III) han demostrado que la intervención del FC es crucial en la detección de la falta de adherencia y en la promoción de la misma. Así, en el capítulo I se muestra que la intervención del FC mejora la adherencia al tratamiento con estatinas en pacientes con hipercolesterolemia. De hecho, alrededor de un 65% pacientes, que no estaban siguiendo de manera correcta su tratamiento hipolipemiante al inicio del estudio, tras 6 meses de intervención del FC, terminan el estudio siendo adherentes al tratamiento farmacológico. Los datos obtenidos en el meta-análisis incluido en el

capítulo III, corroboran esta mejora en la adherencia a los tratamientos farmacológicos hipolipeminantes gracias a la intervención del FC.

Estos hallazgos van en consonancia con los observados por otros autores en revisiones sistemáticas previamente publicadas, en las que se estudió la adherencia a los tratamientos hipolipemiantes tras la intervención de diferentes profesionales de la salud (2), o en las que se estudió la adherencia al tratamiento tras la intervención del FC (3). Así, Van Driel y cols. llevaron a cabo una revisión sistemática y un posterior meta-análisis con el objetivo de analizar el impacto de las intervenciones de los profesionales sanitarios en la adherencia a medicamentos hipolipemiantes y sobre los resultados clínicos. Incluyeron un total de 35 estudios de los cuales 7 fueron llevados a cabos en farmacias comunitarias. Como resultado más relevante, los ratios de adherencia demostraron ser mayores tras intervenciones complejas que incluían recordatorios electrónicos, la educación sanitaria, ofrecimiento de información acerca de la importancia de la toma del medicamento, y jornadas formativas que tenían como destinatarios a los pacientes (OR = 1,93; IC del 95%: 1,29-2,88; $p < 0,001$) (2).

Por su parte, Milosavljevic y cols. llevaron a cabo una revisión sistemática relacionada con las intervenciones que realiza el FC con el objetivo de mejorar la adherencia y el resultado clínico de los pacientes. En dicha revisión se incluyeron 22 estudios y se observó que la intervención del FC mejora la adherencia a los tratamientos de elección de diferentes enfermedades crónicas como la hipertensión, enfermedades cardiovasculares, enfermedad pulmonar obstructiva crónica (EPOC) y asma. El número limitado de estudios por patología, la diversidad de las intervenciones y los diferentes métodos utilizados a la hora de determinar la adherencia hizo que no fuera viable realizar un meta-análisis y obtener resultados más concluyentes (3).

Todo lo mencionado anteriormente pone de manifiesto que el FC está situado en un lugar privilegiado dentro de la cadena terapéutica, desde donde se puede identificar la falta de adherencia e intervenir para conseguir que los pacientes cumplimenten los tratamientos de manera adecuada.

La necesidad de abordar la falta de adherencia resulta evidente a tenor de los resultados clínicos y su impacto en el sistema socio-sanitario. Sin embargo, y ya que es un hecho sobre el que influyen varios factores, no existe una estrategia única a la hora de mejorar la adherencia en pacientes no adherentes al tratamiento hipolipemiante (2,3). En este sentido, uno de los planteamientos más eficaces, es proporcionar una intervención personalizada en función de la situación y características del paciente (revisión sistemática de la presente tesis doctoral, recogido en el capítulo III). Los resultados obtenidos en el capítulo I de esta tesis, corroboran esta afirmación, ya que se demuestran la eficacia de una estrategia basada tanto en la detección de la causa de la falta de adherencia, como en el ofrecimiento de una intervención personalizada durante 6 meses. Así, aproximadamente un 65% de pacientes no adherentes al tratamiento al inicio del estudio acaban siendo adherentes tras 6 meses de intervención del FC.

Resultados similares fueron obtenidos por Lyons I y col. en un estudio basado en una intervención diseñada en función de las necesidades y creencias del paciente, en el que se observó un descenso del número de pacientes no adherentes tras la actuación del FC (4). Esta mejora en el nivel de adherencia se observa con dos métodos de determinación de adherencia utilizados. Tras la utilización del cuestionario DAMS se demuestra que los pacientes que reciben la intervención presentan mayores probabilidades de ser adherentes al final del estudio (OR = 1,54; IC del 95%: 1,11-2,15; p = 0,010) respecto a los pacientes del grupo control. Resultados similares se obtienen tras la determinación de la adherencia con los registros de dispensación (OR = 1,60; IC del 95%: 1,14-2,24; p <0,01) (4), lo que permite concluir que, la intervención sobre la casusa de la falta de adherencia con el seguimiento de una estrategia personalizada, es la manera más sencilla, eficaz y directa de tratar el problema de la falta de adherencia.

Otro parámetro a tener en cuenta, es el tiempo de intervención necesario para que se produzcan cambios significativos en el grado de adherencia. Como conclusión de la revisión sistemática del capítulo III, se observan mejoras tanto tras intervenciones cortas (6 meses o menos de duración), como después de intervenciones largas (más de 6 meses de duración). De hecho, estas observaciones permiten concluir que una intervención del FC durante 6 meses es suficiente para lograr cambios en la

adherencia de los pacientes no adherentes a tratamientos hipolipemiantes (capítulo I). Por otra parte, los datos obtenidos en el meta-análisis (capítulo III) corroboran este resultado y demuestran que tanto los estudios de corta como de larga duración aumentan los niveles de adherencia en pacientes tratados con medicamentos hipolipemiantes. En este sentido, se debe tener en cuenta que la adherencia no es una condición estática y que puede modificarse a lo largo del tiempo, existiendo periodos en los que un paciente es adherente y otros en los que no lo es (5,6).

Algunos autores como Benner y col. en un estudio en el que siguieron durante 9 años a 34.501 pacientes mayores de 65 años con una primera prescripción de estatinas, describieron que la adherencia a tratamientos hipolipemiantes disminuía en pacientes de avanzada edad conforme transcurría el tiempo. Así obtuvieron que la adherencia a los 3 meses era del 79% y estos valores disminuían al 56% a los 6 meses y al 42% tras los diez años de tratamiento (7). Otros autores diseñaron un estudio con el objetivo de analizar la efectividad de la intervención del FC en la adherencia a las estatinas. Incluyeron un total de 899 pacientes con una nueva prescripción de estatinas y los pacientes del grupo intervención recibieron educación en adherencia al tratamiento insistiendo en la importancia de tomar la medicación según lo prescrito. Tras 12 meses de estudio observaron que los pacientes del grupo intervención eran más adherentes a los 6 meses de estudio respecto al grupo que recibió la atención habitual (HR= 0,66; IC del 95%: 0,46-0,96; p <0,05) pero no a los 12 meses (HR= 0,84; IC del 95%: 0,65-1,10; p >0,05). Por todo ello, algunos autores sugieren que las intervenciones del FC son más efectivas en el momento en el que el paciente comienza con el tratamiento con medicamentos hipolipemiantes (8). A este respecto, nuestro estudio muestra que, una intervención de 6 meses del FC es suficiente para encontrar mejoras en la adherencia a los tratamientos hipolipemiantes. Serían necesarios más estudios a largo plazo y con un número elevado de pacientes, para poder analizar cómo evoluciona la adherencia a lo largo del tiempo.

Por lo expuesto anteriormente, para la puesta en marcha del servicio de adherencia terapéutica por parte del FC, es importante conocer la estrategia de intervención y el método a utilizar para calcular el grado de adherencia. En el presente trabajo, se ha demostrado que los estudios que utilizan cuestionarios validados para determinar la

adherencia, obtienen resultados más acordes a la realidad (encuentran diferencias en mayor medida tras la intervención del FC) que aquellos que utilizan registros de dispensación de la medicación (capítulo III). Los cuestionarios son uno de los métodos más utilizados debido a su facilidad de uso, bajo coste y capacidad de identificar las causas de la falta de adherencia. De hecho, se ha descrito que los registros de dispensación sobreestiman los valores de adherencia, desde el inicio del estudio, dificultando la interpretación de los resultados (9). El test de Morisky-Green-Levine, utilizado en los estudios recogidos en los capítulos I y II, es uno de los cuestionarios más extendido en la práctica a nivel mundial (10). Muchos autores proponen que la determinación de la adherencia se lleve a cabo mediante diferentes métodos, de manera paralela, en un intento de compensar las carencias que pueda tener cada técnica y dar más robustez a los resultados (4,11,12).

Una de las formas de medir el impacto de una intervención sobre la adherencia al tratamiento, es evaluar algunas variables clínicas de relevancia en la enfermedad a tratar. Por lo que respecta a los tratamientos hipolipemiantes, los resultados de esta tesis sugieren que existe una relación entre la adherencia y los niveles de colesterol total (CT), ya que los pacientes adherentes al tratamiento prescrito al inicio del estudio presentan menores niveles de CT que aquellos que no eran adherentes al tratamiento (capítulo I). Sin embargo, en el estudio recogido en el capítulo III, la falta de homogeneidad en la medición de las variables clínicas impide la determinación de forma cualitativa (revisión sistemática) y cuantitativa (meta-análisis), para poder establecer la relación entre adherencia y CT.

La mayoría de las revisiones sistemáticas publicadas hasta la fecha, han estudiado la mejora de la adherencia o de las variables clínicas de manera independiente tras la intervención del profesional sanitario (13–17); sin embargo, muy pocos autores han analizado la relación entre las dos variables (2,3). En algunas de estas publicaciones se demuestra que las intervenciones de diferentes profesionales sanitarios tienen una influencia positiva en la adherencia a tratamientos hipolipemiantes, lo que se acompaña de una reducción en los niveles de CT y LDL-colesterol. Así, en el estudio de Van Driel y col., se comprobó que la intervención del profesional sanitario mejora la adherencia logrando disminuciones de colesterol total de 17,15mg/dl tras 6 meses de intervención y de 17,57mg/dl tras 12 meses (2). Otros grupos de investigación,

por su parte, postulan que la intervención del FC favorece una mayor adherencia a la medicación en pacientes con hipertensión, hipercolesterolemia, EPOC y asma, junto con una mejora de algunas de las variables clínicas características de estas enfermedades (3). Sin embargo, estas publicaciones presentan la limitación de contar con pocos estudios realizados en farmacia comunitaria sobre medicamentos hipolipemiantes por lo que se requieren más estudios que permitan concluir esta relación.

Por último, destacar que el éxito de la implantación del servicio de adherencia, puede estar condicionado por el tipo de la falta de adherencia y de su causa. Los resultados de esta tesis doctoral muestran que la prevalencia de pacientes con falta de adherencia no intencionada es mayor al inicio del estudio. Además, se observa que, tras la intervención del FC, la falta de adherencia intencionada es más fácil de revertir (capítulo II). En este sentido, varios modelos cognitivos y conductuales han demostrado que la actitud que muestra el paciente hacia el tratamiento, es determinante para que sea adherente o no, por lo que conocer la intencionalidad de la falta de adherencia se considera importante a la hora de proponer una intervención u otra (18,19).

Otro SPFA de atención farmacéutica evaluado en este trabajo, en el que la intervención del FC resulta de vital importancia es el de detección de discrepancias en el entorno comunitario. En el capítulo IV se describe cómo el FC es un profesional perfectamente posicionado para detectar discrepancias entre la medicación que el paciente tiene prescrito y la que verdaderamente toma, y reducir su incidencia. Nuestro análisis muestra, que dos de cada tres pacientes identificados en el estudio presentan más de una discrepancia entre la medicación que toma y la que figura en su hoja de tratamiento activo y que éstas se solucionan tras la intervención del farmacéutico en un 90% de los casos.

Estudios previos han demostrado que la intervención del farmacéutico hospitalario disminuye las discrepancias al tratamiento (20,21). Así Sholihat y col., evaluaron la efectividad de la detección de discrepancias en un estudio observacional que incluyeron 224 pacientes. Sus resultaron demostraron que el 62% de los pacientes a los que el farmacéutico hospitalario revisa la medicación, presentan una o varias

discrepancias y el 78% de las mismas se resuelven con la intervención del farmacéutico (20). En esta misma línea, Hassan y col., estudiaron la efectividad de la intervención del farmacéutico hospitalario en la reducción de las discrepancias en el momento del alta del paciente. De un total de 591 pacientes, hallaron que en 278 casos (47%) se requería la intervención del farmacéutico debido a una discrepancia u otro error de medicación (21).

La conciliación de la medicación por parte del farmacéutico comunitario, consistente en la detección de discrepancias tras una transición asistencial (22,23), se ha descrito como una intervención eficaz para disminuir las discrepancias en el uso de la medicación. El CGCOF en colaboración con Foro de AF-FC, la SEFH y otras entidades, pilotó un estudio de investigación bajo el nombre de "Concilia Medicamentos", en el que participaron 70 farmacias comunitarias, 17 farmacéuticos de hospital y 3 farmacéuticos de atención primaria de las provincias de Asturias, Granada y Salamanca. El estudio incluyó 120 pacientes que habían sido dados de alta tras un ingreso hospitalario, observándose un 87,5% de pacientes con discrepancias en la medicación. Tras la finalización del estudio, el 91,8% de las discrepancias se solucionaron. Como ocurrió a nivel hospitalario, en la farmacia comunitaria la causa más frecuente del error también fue que el paciente no tomara la medicación prescrita (22).

Un estudio desarrollado en 6 farmacias comunitarias analizó el tratamiento farmacológico del paciente tras el alta hospitalaria o visita al especialista con la medicación habitual, durante 3 meses, observando que tras conciliar la medicación de 29 pacientes, el 37,9% presentaba discrepancias en la medicación (36,4% tras el alta hospitalaria y 45,5% tras la visita al especialista) y el 81,2% de estos pacientes fueron derivados al médico (23).

Los datos publicados hasta la fecha muestran que el farmacéutico en sus diferentes ámbitos de ejercicio, es un profesional capaz de detectar y disminuir las discrepancias de los medicamentos. Sin embargo, no se han encontrado estudios que utilizando la metodología que se usa en el servicio de conciliación, tengan como objetivo comparar la lista de medicamentos prescritos en la hoja de tratamiento activo y la lista de medicamentos que realmente utiliza el paciente. Nuestro estudio

arroja unos resultados muy prometedores tanto en el porcentaje de discrepancias identificadas como en el éxito obtenido tras la intervención del FC. Además, nuestro estudio ha puesto en práctica un trabajo colaborativo entre profesionales sanitarios y todo esto, está además en concordancia con la estrategia de la OMS de incluir los FC en la detección de los errores de medicación (24).

La función del FC en la detección de discrepancias y su disminución tiene, además, un impacto directo sobre los recursos del sistema sanitario, debido al ahorro económico que supone la reducción de los medicamentos prescritos, tal y como se desprende de nuestra investigación (capítulo IV). Así, nuestro estudio muestra que, tras la comunicación de discrepancias por parte de los farmacéuticos a los médicos del estudio, la deprescripción de medicamentos era la intervención más realizada por estos últimos. Al finalizar el estudio, cada paciente, presentaba de media un medicamento prescrito menos que al inicio del estudio en la hoja de tratamiento activo y, por tanto, un menor riesgo de polifarmacia. La reducción del número de medicamentos que toma el paciente, se ha asociado a su vez con una mejor adherencia y una menor tasa de interacciones y errores de medicación (25,26). Todo esto se traduce, en que la detección de discrepancias por parte del FC puede ser una manera eficaz de garantizar un uso más seguro, efectivo y eficiente de los medicamentos, evitando la polimedicación, lo cual también está en línea con la estrategia de la OMS en su *Global Patient Safety Challenge* (27).

Los datos presentados en esta tesis doctoral, ponen de manifiesto que el servicio de detección de discrepancias de los medicamentos en el ámbito comunitario por parte del FC es coste-efectivo, como previamente había sido apuntado por diversas revisiones sistemáticas (30,31), y sugieren que su implantación puede ser una forma de garantizar la seguridad del paciente. Además, los costes asociados a los procedimientos hospitalarios son elevados (32–34), por lo que la detección de discrepancias por parte del FC, podría aportar un importante valor y contribuir de manera significativa a la sostenibilidad del sistema sanitario.

A pesar de que varios SPFA han mostrado mejoras a nivel clínico, económico y humanístico, la remuneración de estos servicios, constituye un punto crítico para asegurar la sostenibilidad de los mismos, así como la transición hacia el nivel

asistencial que está experimentando la farmacia comunitaria desde hace unos años (35). Los FC indican habitualmente que la falta de remuneración es una de las principales barreras para el desarrollo de los servicios, sin embargo, es insuficiente para garantizar su implantación. Algunos estudios realizados en las últimas décadas han demostrado que la participación del FC en los SPFA, aunque sean remunerados varía considerablemente; algunos programas reportan un número muy bajo de farmacias participantes (36,37), mientras que otros estudios encuentran un alto interés inicial por parte de los FC, pero una persistencia corta en el tiempo (38,39). Para asegurar la completa implantación de los SPFA se deben tener en cuenta, además de la remuneración, otras barreras como la excesiva carga burocrática, las limitaciones de tiempo, baja conciencia de los beneficios que conllevan los SPFA y la falta de motivación (37). Por ello, la participación de los FC en el diseño de los programas en los que van a estar implicados, es fundamental ya que así se proponen procedimientos que encajan en el día a día del trabajo de los profesionales (40,41).

Los proyectos de investigación incluidos en esta tesis doctoral, se han diseñado conjuntamente con representantes de todos los profesionales sanitarios implicados (profesionales de la medicina, enfermería, farmacia de atención primaria y comunitaria). Este co-diseño ha permitido elaborar protocolos consensuados, para su aplicabilidad en el día a día de estos profesionales. Los investigadores que han participado en el reclutamiento e intervención profesional, farmacéuticos, médicos y demás participantes, han podido aportar su experiencia y valoración sobre el diseño y procedimiento del estudio y han conocido en todo momento la evolución del proyecto.

En cuanto a las limitaciones de los estudios, cabe destacar que el primer diseño experimental (capítulos I y II) tuvo un elevado ratio de pacientes que abandonaron sin terminar. Estos datos, similares a los que tuvieron otros autores con objetivos parejos (42–44), muestran la dificultad que conlleva lograr la continuidad de los pacientes en los estudios de adherencia. Sin embargo, este estudio ha sido controlado y aleatorizado y es robusto por el cálculo del tamaño muestral, lo que permite obtener conclusiones sólidas. Además, el análisis estadístico se hizo

mediante el análisis de imputación de casos, para que los valores perdidos se tuvieron en cuenta a la hora de interpretar los resultados.

La revisión sistemática (capítulo III), incluye pocos estudios, ya que la mayoría de los autores que han estudiado la adherencia a los medicamentos hipolipemiantes, no han analizado el impacto sobre las variables clínicas. Además, aquellos que han analizado ambas variables, han utilizado diferentes metodologías y diferentes variables clínicas (CT, LDL-colesterol, HDL-colesterol, triglicéridos, etc.), suponiendo una complicación en el análisis y comparabilidad de los datos, lo que manifiesta la necesidad de más estudios para la obtención de conclusiones más sólidas.

Por último, el estudio de la detección de discrepancias en el entorno comunitario (capítulo IV), es un estudio llevado a cabo en una región concreta, con un número de participantes limitado y sin grupo control, por lo que sería interesante contar con más estudios para confirmar los hallazgos. Además, este capítulo describe un servicio innovador, co-diseñado por varios profesionales sanitarios y que presenta resultados prometedores.

En definitiva, la implantación de estrategias orientadas a promover un uso seguro, efectivo y eficiente de los medicamentos constituye una de las principales líneas de actuación de las organizaciones e instituciones que velan por la salud de la población, como es el caso de la OMS. La promoción de la adherencia y la detección de discrepancias encajan dentro de estos objetivos prioritarios y ponen en valor la participación del FC como agente de salud. En los últimos años, la evolución de la farmacia comunitaria hacia una farmacia más asistencial ha creado el entorno ideal para la implantación de los SPFA. No obstante, que esta transición se complete de manera exitosa dependerá del beneficio que aporten estos servicios a nivel clínico, económico y/o humanístico, para lo cual es indispensable la puesta en marcha de más estudios controlados, multicéntricos y reproducibles, como los que este trabajo engloba.

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CONCLUSIONES

1. La intervención del farmacéutico comunitario basada en la detección de las causas de la falta de adherencia terapéutica en el tratamiento con estatinas, es una estrategia efectiva que logra aumentar el número de pacientes adherentes trascurridos los 6 meses de intervención, frente al grupo de pacientes que no reciben este servicio.

2. La adherencia al tratamiento con estatinas se asocia con niveles menores de colesterol total tanto al inicio del estudio, como trascurridos los 6 meses de duración de la intervención del farmacéutico comunitario.

3. La intervención del farmacéutico comunitario es más efectiva al abordar la falta de adherencia no intencionada, logrando que, trascurridos los 6 meses del estudio, un mayor número de pacientes con adherencia no intencionada consigan ser adherentes al tratamiento, frente a pacientes con falta de adherencia intencionada.

4. El meta-análisis de la revisión sistemática de ensayos controlados y aleatorizados permite concluir que las intervenciones del farmacéutico comunitario mejoran la adherencia al tratamiento hipolipemiante. El aumento en la adherencia se relaciona con la mejora en las variables clínicas, sin embargo, debido a una elevada variabilidad de las variables estudiadas de los artículos incluidos, se requieren más estudios para establecer esta conclusión.

5. La intervención del farmacéutico comunitario sobre las discrepancias detectadas entre la medicación que toma el paciente y la que tiene prescrita en su hoja de tratamiento activo, disminuye el número de medicamentos prescritos y se asocia con una reducción en el número de ingresos hospitalarios.

6. El servicio de detección de discrepancias en el uso de medicamentos llevado a cabo en la farmacia comunitaria es un servicio que presenta un resultado de coste-efectividad positivo. El coste de los tratamientos farmacológicos, ingresos hospitalarios y visitas a urgencias disminuye tras la intervención del farmacéutico comunitario, produciendo un ahorro superior al coste que conlleva la intervención del farmacéutico.


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ANEXOS

ANEXO 1: Consentimiento informado del estudio de adherencia al tratamiento en pacientes con hipercolesterolemia en España.

CONSENTIMIENTO INFORMADO POR ESCRITO

Yo *(nombre y apellidos)*

.....

He leído la información que se me ha entregado.
He podido hacer preguntas sobre el estudio.
He recibido suficiente información sobre el estudio.
He hablado con *(nombre del investigador)*

.....

Comprendo que mi participación es voluntaria.
Comprendo que puedo retirarme del estudio:

- Cuando quiera
- Sin tener que dar explicaciones.
- Sin que esto repercuta en mis cuidados médicos.
-

Presto libremente mi conformidad para participar en el estudio y doy mi consentimiento para el acceso y utilización de mis datos en las condiciones detalladas en la hoja de información.

_____ _____

Fecha Nombre en letras mayúsculas

Firma del paciente

_____ _____

Fecha Nombre en letras mayúsculas

Firma del investigador

ANEXO 2: Consentimiento informado del programa de conciliación y adherencia al tratamiento.

CONSENTIMIENTO PARA EL PROGRAMA DE CONCILIACION Y ADHERENCIA AL TRATAMIENTO. COORDINACIÓN ATENCIÓN PRIMARIA-FARMACIA COMUNITARIA

Yo…….con DNI …… declaro bajo mi responsabilidad que he sido informado sobre el programa y acepto participar en el mismo.

Se me han explicado las características y el objetivo del programa. Se me ha dado tiempo y oportunidad para realizar preguntas. Todas las preguntas han sido respondidas a mi entera satisfacción.

Sé que se mantendrá en secreto mi identidad, respetando la Ley de Protección de Datos (LOPD).

Soy libre de rechazar la participación en cualquier momento por cualquier motivo, sin tener que dar explicación y sin que repercuta negativamente sobre cualquier tratamiento médico/farmacéutico presente o futuro.

Yo doy mi consentimiento para que se utilicen los resultados de éste programa y renuncio a reclamar cualquier beneficio económico por mi participación.

Yo **DOY** mi consentimiento □
Yo **NO DOY** mi consentimiento □

Fecha …… Firma del paciente ……

Firma representante legal (si procede)……

Nombre representante legal:……

Relación con el paciente:……

Farmacéutico/a responsable: Constato que he explicado las características del proyecto y el procedimiento a seguir con los datos registrados según LOPD.

Fecha …… Firma del farmacéutico/a ……

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mié 29/04/2020 8:36

ALONSO, JOSE (ELS-BCL) <J.Alonso@elsevier.com>

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Para anhoaonrubia@redfarma.org

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Respondió a este mensaje el 29/04/2020 8:44.

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RESUMEN

Las proyecciones demográficas mundiales prevén un aumento de la esperanza de vida, que conlleva un aumento de enfermedades crónicas y por lo tanto un aumento en el consumo de medicamentos. La falta de adherencia al tratamiento y la presencia de discrepancias en el uso de medicamentos está relacionada con un aumento de la morbi-mortalidad y disminución de la calidad de vida. Los farmacéuticos comunitarios están en el último eslabón de la cadena terapéutica y tienen por lo tanto un papel esencial para la garantizar un uso más seguro, efectivo y eficiente de los medicamentos. Por todo ello, el objetivo principal de este trabajo se ha centrado en evaluar el impacto de la intervención del farmacéutico comunitario en la mejora de la adherencia terapéutica, y en concreto en los tratamientos hipolipemiantes, así como en la detección de discrepancias en el uso de medicamentos.

Para ello, se han llevado a cabo los siguientes estudios: (i) estudio randomizado, controlado y multicéntrico donde se analiza el impacto de la intervención profesional en la falta de adherencia en pacientes con prescripción de estatinas y su relación con las variables clínicas y las causas de la falta de adherencia; (ii) revisión sistemática que contextualiza y actualiza la evidencia científica sobre las intervenciones del farmacéutico comunitario para mejorar la adherencia a tratamientos hipolipemiantes y su relación con las variables clínicas y (iii) estudio experimental que analiza el impacto de un servicio profesional farmacéutico asistencial para detectar y resolver discrepancias entre la medicación prescrita a los pacientes y la hoja de tratamiento activo.

Como resultados principales se obtuvo que la intervención del farmacéutico comunitario aumenta la probabilidad de ser adherente en pacientes en tratamientos con estatinas (OR = 2,34; IC del 95%; 1,87-3,03; p <0,001), resultado que se confirmó en el meta-análisis de la revisión sistemática (OR=1,67; IC del 95%; 1,38-2,02; p<0,001; I^2=54%).; los pacientes adherentes mostraron valores más bajos de colesterol total en comparación con los pacientes no adherentes tanto al inicio (200,3mg/dl *vs* 216,7mg/dl; p <0,001) como al final del estudio (197,3mg/dl *vs* 212,2 mg/dl; p <0,001). El porcentaje de pacientes en el grupo de intervención que completaron el estudio como adherentes fue mayor entre aquellos que previamente presentaron una falta de adherencia no intencionada (66.4%) en comparación con aquellos con falta de adherencia intencionada (55,3%) (p <0,001). Tras el servicio de detección de discrepancias en el uso de los medicamentos, el número de medicamentos prescritos por paciente, las visitas al servicio de urgencias y los ingresos hospitalarios tuvieron una reducción media de 0,92 (9,12±3,82 *vs* 8,20±3,81; p<0,0001), 0,10 (0,61 ± 0,13 *vs* 0,52 ± 0,91; p = 0,405) y 0,17 (0,33 ± 0,66 *vs* 0,16 ± 0,42; p = 0,007), respectivamente. El coste por paciente se redujo en 444,9 € (Inicio: 1003,3€ ± 2165,3€ vs. Final: 558,4€ ± 1273,0€; p = 0,018).

Por todo ello, se concluye que la intervención del farmacéutico comunitario mejora la adherencia al tratamiento con estatinas y esta mejora se asocia con niveles menores de colesterol total tanto al inicio del estudio como trascurridos los 6 meses de duración de la intervención del farmacéutico. El aumento en la adherencia parece estar relacionada con la mejora en las variables clínicas, sin embargo, se requieren más estudios para reforzar esta relación. Asimismo, se observa que la intervención es más efectiva si la falta de adherencia es no intencionada. Por último, se observa que el servicio de detección de discrepancias llevado a cabo en la farmacia comunitaria disminuye el número de medicamentos prescritos, las visitas a urgencias y los ingresos hospitalarios, presentando un resultado de coste-efectividad positivo.