Universidad de Granada

Facultad de Ciencias Económicas y Empresariales

Departamento de Economía Aplicada

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Evaluación Económica de experiencias de Telemedicina y programas de Atención Farmacéutica en Andalucía

Tesis doctoral

Francisco Jódar Sánchez

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A Caldera y Tramontana

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ÍNDICE

RESUMEN

Esta tesis doctoral está constituida por cuatro estudios recientes cuyo hilo conductor es la evaluación económica de tecnologías sanitarias orientadas a mejorar la salud y calidad de vida de las personas mayores de 65 años. En concreto, se han evaluado dos tecnologías sanitarias: un programa de telemonitorización (capítulo I) y un servicio de seguimiento farmacoterapéutico (capítulo II). Tres de estos estudios han sido publicados en revistas indexadas en el *Journal Citation Report* y el cuarto está previsto enviarlo próximamente para su publicación.

El primer artículo de esta tesis, titulado *"Implementation of a telehealth programme for patients with severe chronic obstructive pulmonary disease treated with long-term oxygen therapy"*, tiene como objetivo analizar la efectividad de un servicio integral de telemonitorización aplicado a pacientes con enfermedad pulmonar obstructiva crónica (EPOC) muy evolucionada y con indicación de oxigenoterapia domiciliaria. Se realizó un ensayo controlado aleatorizado con 45 pacientes, 24 en el grupo intervención y 21 en el grupo control, durante cuatro meses de seguimiento. No se ha observado mejoras significativas en calidad de vida ni en el consumo de recursos sanitarios, si bien se aprecia una reducción en las visitas a urgencias. Se ha obtenido un elevado nivel de satisfacción en los pacientes telemonitorizados y los profesionales clínicos.

El segundo artículo de esta tesis doctoral, titulado *"Cost-utility analysis of a telehealth programme for patients with severe chronic obstructive pulmonary disease treated with long-term oxygen therapy"*, tiene como objetivo realizar un análisis coste-utilidad del servicio integral de telemonitorización presentado en el primer artículo. El análisis tuvo en cuenta si el grado de comorbilidad implicó diferencias relevantes en los costes y/o en el año de vida ajustado por calidad. El servicio integral de telemonitorización no resultó una intervención coste-efectiva comparada con la alternativa de recibir asistencia sanitaria habitual. Aunque esta estrategia de intervención podría considerarse coste-efectiva para los pacientes sin comorbilidad, se obtuvo una considerable incertidumbre en los resultados.

El tercer artículo de esta tesis doctoral, titulado *"Cost-utility analysis of a pharmacotherapy follow-up for elderly nursing home residents in Spain"*, tiene como objetivo realizar un análisis coste-utilidad de un servicio de seguimiento farmacoterapéutico en personas mayores de 65 años institucionalizadas de Andalucía. Se realizó un estudio observacional prospectivo con 332 sujetos, 210 en el grupo intervención y 122 en el grupo control, en quince residencias de ancianos de Andalucía durante doce meses de seguimiento. El

seguimiento farmacoterapéutico resultó una intervención coste-efectiva comparada con la alternativa de recibir atención sanitaria habitual.

El informe de evaluación económica, titulado *"Cost-utility analysis of a pharmacotherapy follow-up for polypharmacy older people in community pharmacies in Spain"*, tiene como objetivo realizar un análisis coste-utilidad de un servicio de seguimiento farmacoterapéutico en personas mayores de 65 años polimedicadas. Se realizó un ensayo longitudinal controlado aleatorizado por conglomerados con 1.403 sujetos, 688 en el grupo intervención y 715 en el grupo control, en 178 farmacias comunitarias de cuatro provincias españolas durante seis meses de seguimiento. El seguimiento farmacoterapéutico resultó una intervención coste-efectiva comparada con la alternativa de recibir una dispensación farmacéutica habitual.

INTRODUCCIÓN

El mercado es un complejo mecanismo institucional, que utilizan las sociedades modernas para resolver el problema de asignar recursos escasos a fines alternativos. Teóricamente estas asignaciones son eficientes si se cumplen todo un conjunto de exigencias técnicas, instituciones y de comportamiento de los agentes. Lamentablemente desde la obra seminal de Arrow,[1] sabemos que los mercados sanitarios no cumplen las expectativas de la "mano invisible" de Adam Smith,[2] aquejados de graves problemas de incertidumbre y asimetrías de información.

Por otro lado, la eficiencia no es el único criterio colectivo que las sociedades tienen o deben tener en cuenta a la hora de asignar recursos. La justicia importa, y el acceso universal a la asistencia sanitaria, con independencia de la posición social y económica que las personas ocupan en la sociedad, es considerado un valor relevante en la mayoría de las sociedades desarrolladas. Un signo distintivo de una sociedad civilizada.

Dado que los precios del mercado sanitario no son señales fiables del coste de oportunidad social, y que determinados criterios de justicia pueden entrar a formar parte del proceso de toma decisiones colectivas, el papel de los mercados es necesariamente limitado en las sociedades desarrolladas actuales, siendo los Estados los principales agentes que deciden que tecnologías sanitarias se incorporan y ofrecen a los ciudadanos.

Que los mercados sanitarios no funcionen para asignar eficientemente los recursos, no implica que el problema desaparezca. Al contrario, vuelve más necesario e imprescindible el desarrollo de metodologías que sustituyan el papel que tienen los precios en los mercados de competencia perfecta. Es decir ayuden en el proceso de toma de decisiones estableciendo que tecnologías sanitarias son eficientes, y cuál es su coste de oportunidad social. El intenso desarrollo metodológico de la evaluación económica de tecnologías sanitarias durante las últimas décadas es una repuesta a este desafío. Esta tesis es un modesto intento de aplicar de forma rigurosa los recientes desarrollos técnicos de la evaluación económica a tecnologías sanitarias, no evaluadas previamente y con un importante potencial de mejorar la salud y calidad de vida de las personas mayores. El conjunto de estudios aquí presentados aspira a conseguir simultáneamente el rigor académico y la utilidad para la sociedad.

El concepto de tecnología sanitaria engloba a medicamentos, instrumentos y procedimientos médicos y quirúrgicos utilizados en la atención sanitaria, así como los

sistemas organizativos y de soporte en los que se provee dicha atención.[3] En este contexto, el término tecnología sanitaria no se refiere únicamente a nuevos medicamentos o a dispositivos sanitarios sofisticados, sino que incluye además intervenciones que tengan un posible impacto sobre la salud de las poblaciones o de grupos concretos de personas.

La incorporación de las tecnologías sanitarias en el sistema sanitario deber realizarse en base a unos criterios de calidad, necesarios para garantizar la equidad y la accesibilidad por parte de todos los ciudadanos. Por lo tanto, la incorporación de nuevas tecnologías sanitarias y/o revisión de las ya existentes, es un proceso fundamental para la sostenibilidad y eficiencia del sistema sanitario, y la evaluación económica de tecnologías sanitarias es uno de los instrumentos disponibles para poder conseguirlo. Con este fin, la evaluación económica se ha convertido en una herramienta de gran utilidad para los agentes sanitarios en la toma de decisiones sobre la incorporación de tecnologías sanitarias y la asignación racional de los recursos sanitarios disponibles, al realizar un análisis comparativo de dos o más alternativas en el que se consideran sus costes y sus consecuencias.[4]

Aunque la incorporación de la evaluación económica al proceso de toma de decisiones es todavía una tarea pendiente en el sistema sanitario de nuestro país, no son pocos los avances alcanzados, aunque insuficientes si los comparamos con los obtenidos por otros países. En el caso de España, destaca la propuesta de guía para la evaluación económica aplicada a las tecnologías sanitarias,[5] que ha tomado en consideración, como punto de partida, una propuesta anterior de guía española[6-8] y las principales guías internacionales: Australia,[9] Canadá,[10] Holanda,[11] Inglaterra y Gales,[12] y Suecia.[13]

Uno de los factores con mayor relevancia en el elevado gasto sanitario público de un país es el progresivo envejecimiento poblacional, con el consiguiente aumento de enfermedades crónicas asociadas a un elevado consumo de medicamentos. Por tanto, el colectivo de ancianos se presenta como uno de los grupos de pacientes clave sobre los que las administraciones públicas deben actuar.

La presente tesis doctoral está constituida por cuatro estudios recientes cuyo hilo conductor es la evaluación económica de tecnologías sanitarias orientadas a mejorar la salud y calidad de vida de las personas mayores de 65 años, realizados en los últimos años de mi carrera profesional. En concreto, se han evaluado dos tecnologías sanitarias: un programa de telemonitorización (capítulo I) y un servicio de seguimiento farmacoterapéutico (capítulo II). Tres de estos estudios han sido publicados en revistas indexadas en el *Journal Citation Report* y el cuarto está previsto enviarlo próximamente para su publicación.

La telemedicina se define como el suministro de servicios de salud, donde la distancia es un factor crítico, por cualquier profesional de la salud, usando las nuevas tecnologías de la comunicación para el intercambio válido de información en el diagnóstico, el tratamiento y la prevención de enfermedades o lesiones, investigación y evaluación, y educación continuada de los proveedores de salud, todo con el interés de mejorar la salud de los individuos y sus comunidades.[14]

La atención farmacéutica engloba diferentes servicios profesionales farmacéuticos orientados al paciente que utiliza medicamentos. Una de las actividades derivadas de la atención farmacéutica es el seguimiento farmacoterapéutico, un servicio en el que el farmacéutico evalúa la farmacoterapia de los pacientes e interviene, conjuntamente con el médico y el propio paciente, para conseguir que se cumplan sus objetivos terapéuticos.[15]

En ambos casos, la realización de estos estudios está justificada por la limitada evidencia de eficiencia de este tipo de intervenciones en personas mayores de 65 años, las cuales se caracterizan por la presencia de enfermedades crónicas, polimedicación o comorbilidad, entre otros fenómenos, lo que les convierte en un colectivo frágil.

El capítulo I incluye la evaluación de un servicio de telemedicina para personas mayores de 65 años con enfermedades crónicas. Para esta tesis doctoral se han seleccionado dos artículos, el primero publicado y el segundo aceptado para su publicación, ambos en *Journal Telemedicine and Telecare*. Los artículos plantean la implementación y evaluación económica de un servicio de telemedicina para pacientes con enfermedad pulmonar obstructiva crónica (EPOC) muy evolucionada y con indicación de oxigenoterapia domiciliaria continua. Ambos artículos son el resultado del proyecto de investigación coordinado *PITeS: Métodos y Herramientas para el Diseño e Implementación de Servicios de Telemedicina y eSalud para la Atención de Pacientes Crónicos*, financiado por el Instituto de Salud Carlos III.

El capítulo II incluye la evaluación de un servicio de seguimiento farmacoterapéutico para personas mayores de 65 años polimedicadas. Para esta tesis doctoral se ha seleccionado un artículo aceptado para publicar, en *Journal of the American Geriatrics Society*, y un informe de evaluación económica en fase de envío a una revista con factor de impacto. El artículo aceptado para publicar está referido a la evaluación económica de un servicio de seguimiento farmacoterapéutico en residencias de ancianos de Andalucía. Este artículo ha sido el resultado del proyecto de investigación "*Evaluación económica del seguimiento farmacoterapéutico en los mayores institucionalizados de Andalucía"*, financiado por la Agencia de Evaluación de Tecnologías Sanitarias de Andalucía. El informe presenta la

evaluación económica de un servicio de seguimiento farmacoterapéutico en farmacias comunitarias de España. Este informe es el resultado del *programa "conSIGUE impacto. Medida del impacto clínico, económico y humanístico del servicio de Seguimiento Farmacoterapéutico en mayores polimedicados en la farmacia comunitaria española"*, promovido por el Consejo General de Colegios Oficiales de Farmacéuticos y el Grupo de Investigación en Atención Farmacéutica de la Universidad de Granada.

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OBJETIVOS

El objetivo principal de esta tesis doctoral es evaluar intervenciones orientadas a la mejora sanitaria de personas mayores de 65 años, en términos de calidad de vida y optimización de los recursos sanitarios, con objeto de demostrar la eficiencia de las mismas.

La telemedicina tiene un gran potencial para proveer un mejor cuidado a los pacientes con EPOC aunque la evidencia de sus beneficios, principalmente en términos de eficiencia, no está clara. En este sentido, el primer artículo del capítulo I tiene como objetivo analizar la efectividad de un servicio de telemedicina aplicado a pacientes con EPOC muy evolucionada y con indicación de oxigenoterapia domiciliaria continua. Se analizó la calidad de vida relacionada con la salud y la adherencia de los pacientes al programa. De igual manera, se evaluó la satisfacción de los pacientes telemonitorizados y de los profesionales sanitarios implicados en su puesta en marcha. El segundo artículo del capítulo I tiene como objetivo estimar la ratio coste-efectividad incremental de dicho servicio de telemedicina comparado con la alternativa de recibir asistencia sanitaria habitual.

El seguimiento farmacoterapéutico es un servicio que tiene como objetivo optimizar la farmacoterapia de los pacientes. Son pocos los estudios que han analizado la eficiencia de este servicio en personas mayores de 65 años. En este sentido, el primer artículo del capítulo II tiene como objetivo evaluar la ratio coste-efectividad incremental de un servicio de seguimiento farmacoterapéutico para personas mayores de 65 años institucionalizadas en residencias de ancianos de Andalucía comparado con la alternativa de recibir asistencia sanitaria habitual. El segundo informe de evaluación económica del capítulo II tiene como objetivo analizar la ratio coste-efectividad de un servicio de seguimiento farmacoterapéutico para personas mayores de 65 años polimedicadas en farmacias comunitarias comparado con la alternativa de recibir dispensación farmacéutica habitual.

DISCUSIÓN CONJUNTA DE LOS RESULTADOS OBTENIDOS EN LOS DISTINTOS TRABAJOS

Esta tesis doctoral está constituida por cuatro estudios recientes, publicados a partir del año 2013 y realizados en los últimos años de mi carrera profesional, que he desarrollado en la Escuela Andaluza de Salud Pública y el Hospital Universitario Virgen del Rocío. A continuación se presenta un pequeño resumen de cada uno de los estudios.

El primer artículo de esta tesis, titulado "*Implementation of a telehealth programme for patients with severe chronic obstructive pulmonary disease treated with long-term oxygen therapy"*, tiene como objetivo analizar la efectividad y los problemas técnicos de la puesta en marcha de un servicio integral de telemonitorización aplicado a pacientes con EPOC muy evolucionada y con indicación de oxigenoterapia domiciliaria. Se realizó un ensayo controlado aleatorizado con 45 pacientes, 24 en el grupo intervención y 21 en el grupo control, durante cuatro meses de seguimiento. Los pacientes del grupo intervención realizaron la medición de los signos vitales a través de un espirómetro, un pulsioxímetro, un medidor de frecuencia cardiaca y un medidor de presión arterial. La respuesta clínica fue el resultado de la comunicación y coordinación de tres agentes: call center clínico, gestor de casos y especialistas en neumología. Los pacientes del grupo control recibieron asistencia sanitaria habitual. La calidad de vida se midió mediante dos cuestionarios: *Saint George Respiratory Questionnaire* y el EuroQol-5D. Los pacientes del grupo intervención redujeron la media de visitas a los servicios de urgencias respecto a los pacientes del grupo control (0,29 ± 0,75 frente a 0,43 ± 0,68; p=0,25), e incrementaron la media de consultas al especialista (0,25 ± 0,61 frente a 0,05 ± 0,22; p=0,20) y la media de ingresos hospitalarios (0,38 ± 0,82 frente a 0,14 ± 0,36; p=0,47). Como consecuencia de la telemonitorización, se registraron un total de 40 alertas. En función del nivel de gravedad, el gestor de casos decidió continuar la monitorización en 32 casos y derivar al especialista en neumología en ocho casos. La calidad de vida fue superior entre los pacientes telemonitorizados (*Saint George Respiratory Questionnaire*: 10,9 ± 21,9 en el grupo intervención frente a 4,5 ± 19,7 en el grupo control (p=0,53); EuroQol-5D: 0,036 ± 0,28 en el grupo intervención frente a 0,003 ± 0,24 en el grupo control (p=0,68)). Tanto los pacientes como los profesionales sanitarios mostraron un alto nivel de satisfacción con el programa de telemonitorización.

El segundo artículo de esta tesis doctoral, titulado "*Cost-utility analysis of a telehealth programme for patients with severe chronic obstructive pulmonary disease treated with long-term oxygen therapy"*, tiene como objetivo realizar un análisis coste-utilidad de un servicio integral de telemonitorización en pacientes con EPOC muy evolucionada y con indicación

de oxigenoterapia domiciliaria comparado con la alternativa de recibir asistencia sanitaria habitual. El análisis tuvo en cuenta si el grado de comorbilidad, definida como la presencia de una o más enfermedades crónicas además de la enfermedad principal, implicó diferencias relevantes en los costes y/o en el año de vida ajustado por calidad (AVAC). Los resultados del análisis de coste-utilidad se expresaron en términos de la relación coste-efectividad incremental (RCEI). El coste medio total fue de 2.440€ para el grupo intervención y 1.206€ para el grupo control, y la ganancia media de AVAC fue 0.0059 para el grupo intervención y 0,0006 para el grupo control (RCEI de 230.688 €/AVAC). Entre los pacientes sin comorbilidad, el coste medio total fue de 889€ para el grupo intervención y 1.516€ para el grupo control, y la ganancia media de AVAC fue 0,0288 para el grupo intervención y 0,0082 para el grupo control (el servicio integral de telemonitorización resultó ser una estrategia dominante). Entre los pacientes con comorbilidad, el coste medio total fue de 2.957€ para el grupo intervención y 1.015€ para grupo control, y la ganancia media de AVAC fue -0,0017 para el grupo intervención y -0.0041 para el grupo control (RCEI de 799.531 €/AVAC). El servicio integral de telemonitorización no resultó una intervención coste-efectiva en comparación a la asistencia sanitaria habitual. Aunque esta estrategia de intervención podría considerarse coste-efectiva para los pacientes sin comorbilidad, existe una considerable incertidumbre en los resultados por lo que se recomienda la realización de más estudios.

El tercer artículo de esta tesis doctoral, titulado "*Cost-utility analysis of a pharmacotherapy follow-up for elderly nursing home residents in Spain"*, tiene como objetivo realizar un análisis coste-utilidad de un servicio de seguimiento farmacoterapéutico en personas mayores de 65 años institucionalizadas frente a la alternativa de recibir atención sanitaria habitual. Se realizó un estudio observacional prospectivo con un grupo de control concurrente durante doce meses de seguimiento. Las principales medidas de resultado fueron los resultados negativos asociados a la medicación, calidad de vida relacionada con la salud y costes (en euros y dólares americanos). Los resultados del análisis de coste-utilidad se expresaron en términos de la RCEI. Se estimaron tres escenarios para la RCEI. Un total de 332 ancianos fueron reclutados: 210 en el grupo intervención y 122 en el grupo control. El médico aceptó el 88,7% (274/309) de las recomendaciones del farmacéutico. Las intervenciones farmacéuticas redujeron la medicación prescrita en 0,47 medicamentos ($p<0,001$), mientras que el grupo control aumentó la medicación prescrita en 0,94 medicamentos ($p<0,001$). Ambos grupos obtuvieron una menor puntuación del EuroQol-5D (-0,0576 en el grupo intervención ($p=0,002$); -0.0999 en el grupo control ($p=0,003$)). Para el primer escenario, el seguimiento farmacoterapéutico fue una intervención dominada por la

atención sanitaria habitual. Los RCEI ajustadas fueron 3.899 €/AVAC (5.002 $/AVAC) para el segundo escenario y 6.574 €/AVAC (8.433 $/AVAC) para el tercer escenario. Para una disposición a pagar de 30.000 €/AVAC (38.487 $/AVAC), las probabilidades de que el seguimiento farmacoterapéutico sea coste-efectivo fueron el 35% para el primer escenario, el 78% para el segundo escenario, y 76% para el tercero escenario. El seguimiento farmacoterapéutico resultó una intervención coste-efectiva frente a la asistencia sanitaria convencional en las personas mayores de 65 años institucionalizadas de Andalucía.

El informe de evaluación económica, titulado "*Cost-utility analysis of a pharmacotherapy follow-up for polypharmacy older people in community pharmacies in Spain"*, tiene como objetivo realizar un análisis coste-utilidad de un servicio de seguimiento farmacoterapéutico en personas mayores de 65 años polimedicadas en el ámbito de farmacias comunitarias frente a la alternativa de recibir una dispensación habitual. Se realizó un ensayo longitudinal controlado aleatorizado por conglomerados durante seis meses de seguimiento. El estudio se realizó en 178 farmacias comunitarias de cuatro provincias españolas: Granada, Guipúzcoa, Tenerife y Las Palmas. La perspectiva del análisis fue la del Sistema Nacional de Salud. Los resultados del análisis de coste-utilidad se expresaron en términos de la RCEI. La RCEI se estimó para cinco escenarios. Un total de 1.403 sujetos fueron reclutadas, 688 en el grupo intervención y 715 en el grupo control. Ambos grupos redujeron la medicación prescrita, en 0,28 medicamentos en el grupo intervención ($p<0,001$) y 0,07 medicamentos en el grupo control ($p=0,063$). El grupo intervención aumentó la utilidad media en 0,0528 ($p<0,001$), mientras que grupo control redujo la utilidad media en 0,0022 ($p=0,815$). Se obtuvo una RCEI de €8,541.63/QALY and €6,777.39/QALY para el primer y segundo escenario respectivamente. Para el resto de escenarios (tercero, cuarto y quinto), el seguimiento farmacoterapéutico resultó una estrategia dominante. Para una disposición a pagar de 30.000 €/AVAC, la probabilidad de que el seguimiento farmacoterapéutico sea coste-efectivo se mueve en un intervalo del 97,5% y el 99,9% en comparación con la dispensación habitual. El seguimiento farmacoterapéutico resultó una intervención coste-efectiva comparado la dispensación habitual para las personas mayores de 65 años polimedicadas en España.

CAPÍTULO I. EVALUACIÓN ECONÓMICA DE UN PROGRAMA DE TELEMEDICINA EN PACIENTES CRÓNICOS

IMPLEMENTATION OF A TELEHEALTH PROGRAMME FOR PATIENTS WITH SEVERE CHRONIC OBSTRUCTIVE PULMONARY DISEASE TREATED WITH LONG-TERM OXYGEN THERAPY

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Summary

We conducted a pilot study of the effectiveness of home telehealth for patients with advanced chronic obstructive pulmonary disease treated with long-term oxygen therapy. Patients were randomized into a telehealth group (n=24) and a control group (n=21) who received usual care. Patients in the telehealth group measured their vital signs on weekdays and performed spirometry on two days per week. The data were transmitted automatically to a clinical call centre. After four months of monitoring the mean number of accident and emergency department visits in the telehealth group was slightly lower than in the control group (0.29 versus 0.43, *P*=0.25). The mean number of hospital admissions was 0.38 in the telehealth group and 0.14 in the control group (*P*=0.47). During the study a total of 40 alerts were detected. The clinical triage process detected eight clinical exacerbations which were escalated by the case manager for a specialist consultation. There were clinically important differences in health-related quality of life in both groups. The mean score on the SGRQ was 10.9 versus 4.5 in the control group (P=0.53). The EuroQol-5D score improved by 0.036 in the telehealth group and by 0.003 in the control group (*P*=0.68). Both patients and healthcare professionals showed a high level of satisfaction with the telehealth programme.

Introduction

Chronic obstructive pulmonary disease (COPD) is a leading cause of morbidity and mortality worldwide, and results in an economic and social burden that is both substantial and increasing. COPD exacerbations account for the greatest proportion of the total COPD burden on the health care system. Estimates for costs related to exacerbations range from 35% to 84% of total direct costs attributable to COPD.[1] Several studies have detected a significant increase in mortality rate after hospitalisation.[2,3] Although it is logical to think that the main determinant of death after hospitalisation is baseline disease severity, recent studies have shown that exacerbations requiring hospital care are an adverse prognostic factor, regardless of baseline disease severity. That is, mortality increases significantly as the frequency and severity of exacerbations increase.[4] Any action to manage exacerbations in these patients at an early stage may help to reduce morbidity and mortality, thereby reducing health resource use and costs.

Various follow-up models to prevent exacerbations and hospitalisations have been proposed. These include self-management, home care and dedicated chronic care models with or without support via information technologies.[5,6,7] The use of telehealth in COPD patients appears to have a possible effect on the quality of life of patients and the number of visits to the accident and emergency (A&E) department and hospital.[8] However, little is known about the efficacy of telehealth in COPD patients with very advanced disease requiring long-term oxygen therapy (LTOT).

The main objective of the present study was to analyse the effectiveness of a telehealth programme in patients with advanced COPD treated with LTOT.

Methods

The study was designed as a randomized controlled trial. For the recruitment, the case manager contacted each of the candidates by telephone to confirm that they complied with the inclusion criteria; he also informed them about the study and its goals, and asked for their consent to participate in the study. Patients were recruited in stages and remained in the study for an average duration of four months. The inclusion criteria were: (1) being an adult patient with a diagnosis of COPD and chronic respiratory failure (CRF) with LTOT indication according to international guidelines;[9] (2) at least one hospitalisation for respiratory illness in the previous year; (3) being clinically stable during the previous three months. The exclusion criteria were: patients who did not follow LTOT at enrolment, had no home telephone line or did not give their informed consent. The study was approved by the appropriate ethics committee.

Between September and December 2010 we identified 88 patients who met the inclusion criteria using the hospital's electronic records system. From this initial selection, 43 patients were excluded (Figure 1): 26 declined to participate, eight died, eight changed their LTOT indication during the recruitment phase and one patient was excluded for another reason.

Telehealth

Patients measured their vital signs from Monday to Friday according to a set schedule. Vital signs were acquired 20 min after taking prescribed inhaled therapy, seated and rested, and while on oxygen therapy. At the beginning of the study, nursing personnel installed the equipment in the patient's home and conducted a training session, showing each patient how to use the equipment and take measurements.

Vital signs were recorded using the following equipment: a spirometer, a pulse oximeter, a heart rate (Spirotel, Medical International Research Inc.) and a blood pressure monitor (model UA-767 BT, A&D Company). Each day, after taking these measurements, the data were sent via a hub (Tele-Modem, Aerotel Medical Systems) connected to the patient's home telephone line. Once measurements had been recorded by each connected instrument, the user pressed a button to activate data transmission.

Follow-up

Patients began participation in the study in a stable situation and the first measurements were taken at home under the supervision of the nursing staff. These measurements were used as reference values (baseline parameters) for each patient and alerts -- to detect possible exacerbations -- were activated by excursions outside the range of these reference values. The information was then received by the clinical call centre (CCC), manned by nurses, who used a triage application. This application provided the following indications:

(1) Green alert: indicates that readings have been taken and are within predefined limits, and no further action is required.

(2) Yellow alert: this is a non compliance or non adherence alert, and means that readings are either overdue or have not been received. In this case, the CCC personnel define the source and type of alert, and a response is given either by the CCC personnel or healthcare professionals according to a protocol.

(3) Red alert: indicates that a reading falls outside the predefined limits. After verification of a red alert by the CCC staff, a clinical response procedure commences according to protocol.

Clinical response

The clinical response is the result of communication between the CCC staff, the case manager and a specialist in respiratory medicine. When a red alert is triggered, and before contacting the case manager, the CCC staff contact the patient to confirm the patient's symptoms, and gain more information about the severity of the exacerbation. If the clinical alert is confirmed, the CCC staff escalate the information to the case manager for an early response to a possible exacerbation. After receiving a red alert, the case manager analyses the vital sign measurements together with the clinical questionnaire responses, accessing the platform via mobile telephony (a smart phone) and initiating the clinical response.

The severity of the exacerbation dictates the subsequent actions:

(1) Mild to moderate: in this case the case manager may choose to monitor vital signs for the following 24 hours, recommend treatment prescribed by the patient's doctor or refer to the primary care doctor.

(2) Severe: referral to specialized care on the same day the alert is triggered.

(3) Very severe: referral to an A&E department.

If the patient is admitted to hospital, the case manager will inform the CCC staff when the patient is discharged and the patient's monitoring process will resume.

Control group

Patients in the control group received conventional medical care. Health-related quality of life (HRQoL) questionnaires were administered at the beginning and at the end of the study during visits to patients' homes by the nursing personnel. Information on the use of healthcare resources during the study was extracted from hospital information system databases.

Outcome measures

Evaluation of the telehealth programme was based on clinical outcome measures, self-perceived outcome measures by the patients and medical staff, and outcome measures from the healthcare system. The vital signs, rate of complications and rate of mortality were analysed. We evaluated the clinical and sociodemographic characteristics of patients at baseline, as well as the Charlson comorbidity index[10] and baseline scores of HRQoL at the start of the study. We followed the recommendations of the American Thoracic Society (ATS)[11,12] and Spanish Society of Pulmonology and Thoracic Surgery (SEPAR)[13] for

spirometry standardization. SEPAR includes additional recommendations for arterial blood gas measurement.[14]

The St George Respiratory Questionnaire (SGRQ)[15] and EuroQol-5D questionnaire[16] were administered at the beginning and end of the trial period. Note that a reduction in the score has the opposite meaning in these questionnaires: in SGRQ a lower score indicates an improvement in quality of life while in the EuroQol-5D it indicates a worsening.

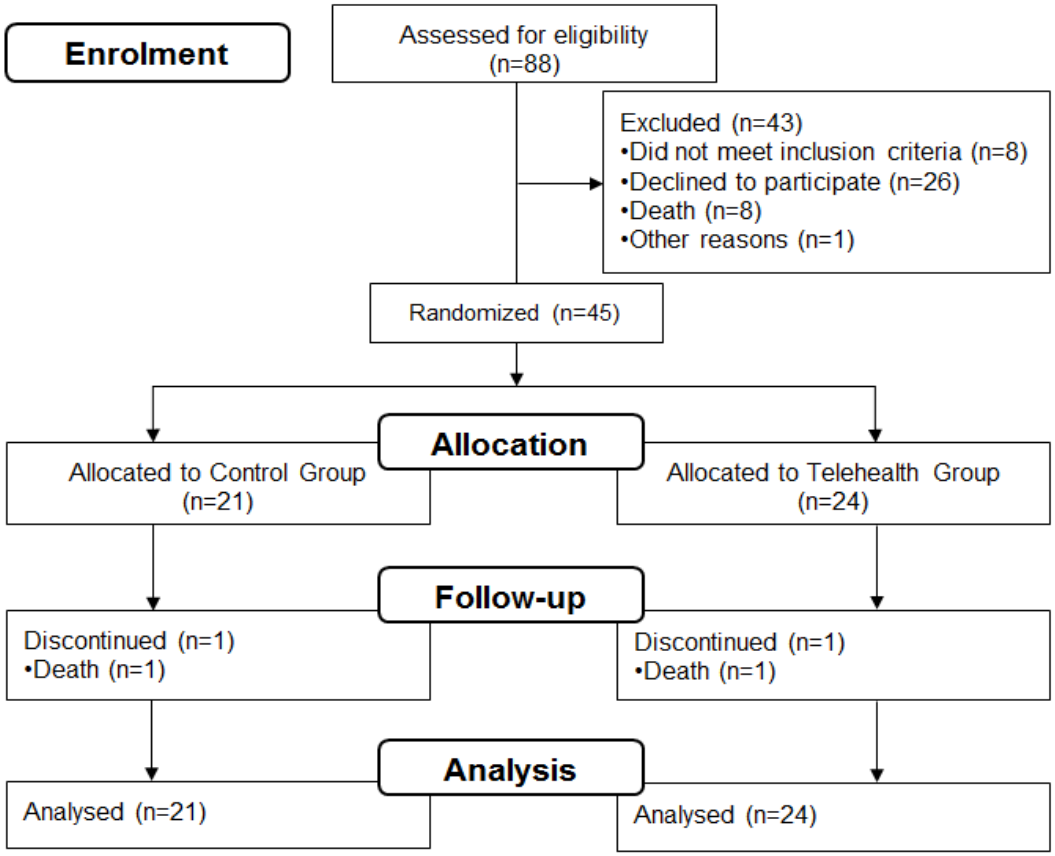

Figure 1 Process of patient enrolment

Exacerbation

Exacerbation was defined as an acute change in the baseline clinical status of the patient beyond the daily variability, which presents with increased dyspnoea, expectoration, purulent sputum, or any combination of these three symptoms[17] and requires a therapeutic change.

Effectiveness

The main outcome measures were exacerbations, A&E department visits and hospital admissions.

Satisfaction

Satisfaction of both patients and clinical professionals with the telehealth programme was assessed by administering a satisfaction questionnaire at the end of the study.

Results

A total of 45 patients were randomized: 21 to the control group and 24 to the telehealth group. Their sociodemographic characteristics, the Charlson comorbidity index and the baseline scores of HRQoL are summarised in Table 1.

Table 1 Baseline characteristics of patients

	Control group	Telehealth group	*P*-value*
No of men	20	23	0.92
No of women	1	1	0.92
Age, years (SD)	71 (10)	74 (8)	0.18
FVC, % pred (SD)	63 (17)	59 (16)	0.69
FEV_1 , % pred (SD)	37 (13)	38 (10)	0.33
RV, % pred (SD)	195 (34)	189 (38)	0.89
TLC, % pred (SD)	142 (15)	138 (15)	0.33
K_{CO} , % pred (SD)	64 (19)	61 (21)	0.96
PaO_2 , mmHg (SD)	53 (5)	52 (5)	0.77
$PaCO_2$, mmHg (SD)	47 (4)	47 (5)	0.86
Charlson index (SD)	2.5 (1.5)	3.7 (2.7)	0.18
Adjusted Charlson index (SD)	5.1 (2.0)	6.6 (2.8)	0.07
SGRQ			
Symptom scores (SD)	44 (23)	63 (23)	0.01
Activity scores (SD)	75 (24)	87 (20)	0.02
Impact scores (SD)	51 (25)	61 (20)	0.18
Total scores (SD)	57 (22)	69 (17)	0.05
Severe problems			
Mobility (%)	0 (0)	3 (14)	0.07
Self-care (%)	3 (14)	7 (33)	0.15
Usual activities (%)	6 (28)	7 (33)	0.74
Pain/discomfort (%)	2 (10)	1 (5)	0.55
Anxiety/depression (%)	2 (10)	2 (10)	0.999
EuroQol-5D (SD)	0.55 (0.33)	0.44 (0.27)	0.24
VAS (SD)	55 (13)	55 (15)	0.89

FVC: forced vital capacity. FEV_1: volume expired in one second. RV: residual volume. TLC: total lung capacity. K_{CO} % pred: carbon monoxide diffusion constant. PaO_2: arterial oxygen partial pressure. $PaCO_2$: arterial carbon dioxide partial pressure

*Mann-Whitney U-test

Patients in the telehealth group took high rates of daily measurements of vital signs: systolic and diastolic blood pressure on 75% of days (average 90 days; SD 0.22), heart rate on 79% of days (average 96 days; SD 0.19), blood oxygen saturation on 71% of days (average 86 days; SD 0.22) and spirometry on 52% of days (average 63 days; SD 0.26). During the study, a total of 14 technical home visits and 408 telephone calls were made by the CCC: an

average of 0.58 visits (SD 0.88) and 17 telephone calls (SD 7.75) per patient. The reasons for the telephone calls by the CCC were as follows: 38% for non- adherence (measurements had not been taken), 34% for non-receipt of data (technical or training problems), 19% clinical alerts (red alerts), 7% for technical reinforcement and 2% for other reasons.

During the study a total of 40 alerts were detected: 19 related to new exacerbation events and 21 following previous exacerbation events. Depending on their severity, the case manager either decided to continue monitoring and follow-up (32 cases) or refer patients to a specialized care consultation (8 cases). Two of these patients did not attend the appointment and ended up being hospitalized.

Two patients, one from each group, died during the study. This represents 5% of control patients and 4% of telehealth patients. The data relating to the use of healthcare resources and the differences in the HRQoL are summarised in Table 2.

Table 2 Use of healthcare resources and the differences in the HRQoL scores

	Control group	**Telehealth group**	***P*-value***
A&E department visits			
Percentage of patients visiting the A&E department at least once	33	17	
Number of visits per patient (SD)	0.43 (0.68)	0.29 (0.75)	0.25
Specialized care consultations			
Percentage of patients who were referred to specialized care unit	4.8	16.7	
Number of visits per patient (SD)	0.05 (0.22)	0.25 (0.61)	0.20
Hospitalisations			
Percentage of patients who were hospitalized at least once	14	21	
Average number of hospitalisations per patient (SD)	0.14 (0.36)	0.38 (0.82)	0.47
Average hospital stay, days (SD)	1.4 (4.0)	4.4 (12.2)	0.50
SGRQ difference			
Symptom score (SD)	-3.7 (19.6)	-12.8 (32.6)	0.31
Activity score (SD)	-4.0 (27.9)	-13.5 (25.4)	0.26
Impact score (SD)	-2.1 (23.2)	-8.7 (24.1)	0.38
Total score (SD)	-4.5 (19.7)	-10.9 (21.9)	0.53
EuroQol-5D difference (SD)	0.0034 (0.24)	0.0359 (0.28)	0.68

*Mann-Whitney U-test

There were no significant improvements in the HRQoL of patients. However, patients were asked at the end of the study if their health had improved over the previous months. Of the control patients, 35% stated that their quality of life had improved, for 12% it had stayed the same, and for 53% it had worsened. In contrast, 46% of the telehealth patients said their

quality of life had improved, 36% that it had stayed the same, and 18% that it had worsened (*P*=0.05).

Satisfaction with the telehealth programme was evaluated by the four clinical professionals involved in the study (two nurses and two respiratory physicians), whose mean age was 44 years (SD 9) and average experience in clinical practice was 17 years (SD 13). The responses to the satisfaction questionnaires of the healthcare professionals and the patients are summarised in Tables 3 and 4, respectively.

The same questionnaire asked healthcare professionals to rate their level of satisfaction with the telehealth programme (from 1=very poor to 10=very good). The mean score was 6.75 (SD 9.96).

Patients were asked to rate from 1 to 10 the following items: programme satisfaction, recommendation of the programme to a relative / friend may it be needed, and whether they would take part in another telehealth programme. The mean scores were 9.30 (SD 1.10), 9.39 (SD 1.95) and 9.61 (SD 0.89) respectively.

Table 3 Satisfaction with the telehealth programme for the healthcare professionals participating in the study. Values shown are numbers of health professionals (%)

	Strongly disagree	Disagree	Agree	Strongly agree	*P*-value*
Compared with conventional care, do you think that this programme has improved patient control and follow-up?	-	-	4 (100)	-	0.13
Compared to conventional care, do you believe this programme has reduced referrals to a lung specialist?	-	1 (25)	3 (75)	-	0.63
Compared to conventional care, do you believe this programme has reduced hospital admissions?	-	-	4 (100)	-	0.13
Do you think the equipment is easy to use for patients?	1 (25)	-	3 (75)	-	0.63
Do you believe that alerts generated by the programme are reliable?	-	3 (75)	1 (25)	-	0.63
Do you believe that the telehealth programme has improved patients' quality of life?	-	1 (25)	3 (75)	-	0.63
Do you think that patients are more satisfied with the telehealth programme compared to conventional care on its own?	-	-	4 (100)	-	0.13

*Binomial test

Table 4 Patient satisfaction with the telehealth programme. Values shown are numbers of patients (%)

	Very dissatisfied	**Dissatisfied**	**Satisfied**	**Very satisfied**	**No answer**	***P*-value***
How satisfied are you with the explanations about the operation and maintenance of equipment, given by staff who installed the equipment in your home?	2 (9)	-	7 (30)	14 (61)	-	0.009
How satisfied are you with the telephone support you received?	1 (4)	-	6 (26)	16 (70)	-	0.042
Are you satisfied with the troubleshooting of clinical and technical problems through the telephone support?	2 (9)	2 (9)	7 (30)	12 (52)	-	<0.001
How would you rate the safe operation of equipment?	2 (9)	5 (22)	10 (44)	5 (22)	1 (4)	0.008
	Strongly disagree	**Disagree**	**Agree**	**Strongly agree**	**No answer**	
The telehealth programme has helped me cope better with my symptoms	1 (4)	6 (26)	6 (26)	9 (39)	1 (4)	0.030
The telehealth programme has helped me understand my illness better	3 (13)	5 (22)	10 (44)	4 (17)	1 (4)	0.030
The telehealth programme has helped me reduce my anxiety levels	1 (4)	3 (13)	5 (22)	13 (57)	1 (4)	0.043
The telehealth programme has allowed me to improve my autonomy and reduced my visits to the health centre or hospital	4 (17)	7 (30)	4 (17)	7 (30)	1 (4)	<0.001
The telehealth programme has had a positive impact on the way I live with my illness	1 (4)	2 (9)	13 (57)	7 (30)	-	0.24
I believe my family have benefited from the telehealth programme by reducing the potential psychological or physical burden related to my disease	2 (9)	1 (4)	11 (48)	6 (26)	3(13)	0.001
	Very difficult	**Difficult**	**Easy**	**Very easy**	**No answer**	
How would you rate the ease of use of equipment?	-	2 (9)	11 (48)	10 (44)	-	0.007

*Chi-squared test

Discussion

The benefit of telehealth programmes in patients with COPD have been described in two systematic reviews.[8,18] However, the present study focused on patients with very advanced COPD and with indications of LTOT. This complicated the already challenging process of recruiting patients into a telehealth study.[19]

Patients showed good compliance with the measurement of vital signs such as blood pressure, heart rate and oxygen saturation measurement, with measurements on 70-80% of days. However, patients performed spirometry measurements on only 52% of days. Hence during the study we decided to change from a daily measurement of spirometry to two measurements per week. The telehealth equipment showed good reliability, recording only 14 incidents related to equipment or failures of the remote connection. There was a large number of calls made by the CCC to patients, mostly due to their non-adherence to their daily measurements (38%) or non-receipt of data (34%). None of these incidents required technical assistance to be provided in the home.

Similar studies have shown a reduction in A&E department visits as well as in hospital admissions in the group of patients using telehealth.[20,21] In the present study, we observed a reduction in the number of A&E department visits but not in hospital admissions. The clinical triage process detected eight clinical exacerbations which were escalated by the case manager for a specialist respiratory consultation. Six of these patients attended the appointment, and were not admitted to hospital for the remainder of the study. Two other patients did not attend the appointment with the respiratory physician and were subsequently admitted to hospital. We also observed that a high percentage (75%) of patients admitted to hospital had previously visited the A&E department. We can therefore conclude that the detected exacerbations did reduce A&E visits and probably subsequent hospital admissions.

One aspect that should be considered in future studies is whether to continue the telehealth programmes during weekends and holidays. Had this been the case in the present study, it would have avoided exacerbations occurring on those days which ended with patients being admitted to hospital (33% of the cases).

Another important aspect of the telehealth programme was the optimization of clinical resources, since the clinical response to the generated alerts did not involve a large number of health professionals. This was mainly due to the excellent communication and coordination established between the CCC, case manager and specialist in respiratory medicine involved in the study. The commitment of the professionals involved in such a programme is crucial for successful telehealth services.[22]

There was no association between the telehealth programme and significant improvements in the HRQoL of patients. There were clinically important differences in both groups, as shown by the improvement of at least 4 units in the SGRQ total score,[23] although patients in the telehealth group improved in all dimensions of the SGRQ, while patients in the control group did so only in the total score. The difference between the groups was 9.1 (SE 8.1) in the Symptoms dimension, 9.5 (SE 8.2) in the Activity dimension, 6.7 (SE 7.2) in the Impact dimension and 6.4 (SE 6.3) in Total dimension. Regarding the EuroQol-5D, patients in the telehealth group obtained an increase in the mean score of 0.03 (SE 0.08) compared to patients in the control group. However, 47% of patients in the control group and 82% of patients in the telehealth group felt that their health status had improved or stayed the same over the months of the study.

Patients showed a high level of satisfaction with the telehealth programme in line with a previous similar study.[24] The question with the poorest response rate was about patients' perception of the programme increasing their autonomy and reducing their visits to the primary care centre or hospital. However, there were high mean scores, above 9 on a scale of 1 to 10, in questions related to the degree of the satisfaction with the programme, with the recommendation of the programme to a relative/friend and the willingness to participate in another telehealth programme. Clinical professionals rated all items positively except for the satisfaction concerning the reliability of the alerts generated by the system. This was due to the high number of false positives, i.e. the alerts generated by non-medical problems, mainly because of patients' failure to adhere to daily measurements. In previous telehealth studies the general approach to triage has been for both technical and clinical triage to be done by the CCC. Other telehealth projects have sought to embed the clinical triage process in the day to day duties of the clinician responsible, often the community nurse who owns the case load. The most efficient programmes are those including both technical and clinical triage processes by the call centre, in our case the CCC, since this is the main route for filtering false positives.

There were two important limitations in the present study: the small sample size and the short study duration.

Conclusions

The telehealth programme for patients with very severe COPD and in need of LTOT was found to be technically feasible. The holistic model consisting of a combination of telemonitoring, the CCC, case manager and a specialist in respiratory medicine was effective in detecting exacerbations and issuing a prompt clinical response. No marked

improvement in the HRQoL and healthcare resource utilization was observed, but there was a significant reduction in A&E department visits, which for this fragile group of patients is usually the threshold for hospital admission. Overall there was a high level of satisfaction for both patients and healthcare professionals with the telehealth programme.

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COST-UTILITY ANALYSIS OF A TELEHEALTH PROGRAMME FOR PATIENTS WITH SEVERE CHRONIC OBSTRUCTIVE PULMONARY DISEASE TREATED WITH LONG-TERM OXYGEN THERAPY

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Abstract

We conducted a pilot study to perform a cost-utility analysis of a telehealth programme for patients with severe chronic obstructive pulmonary disease (COPD) compared with usual care. A randomized controlled trial was carried out over four months with 45 patients treated with long-term oxygen therapy, 24 in the telehealth group (TG) and 21 in the control group (CG). The analysis took into account whether the rank of comorbidity (defined as the presence of additional chronic diseases co-occurring with COPD) entailed relevant differences in costs and/or quality-adjusted life year (QALY). Results of cost-utility analysis were expressed in terms of the incremental cost-effectiveness ratio (ICER). The average total cost was 2,300€ for the TG and 1,103€ for the CG, and the average QALY gain was 0.0059 for the TG and 0.0006 for the CG (resulting an ICER of 223,726€/QALY). For patients without comorbidity, the average total cost was 855€ for the TG and 1,354€ for the CG, and the average QALY gain was 0.0288 for the TG and 0.0082 for the CG (resulting the telehealth programme a dominant strategy). For patients with comorbidity, the average total cost was 2,782€ for the TG and 949€ for the CG, and the average QALY gain was -0.0017 for the TG and -0.0041 for the CG (resulting an ICER of 754,592€/QALY).The telehealth programme may not be cost-effective compared to usual care. Although this intervention strategy could be considered cost-effective for patients without comorbidity, there is considerable uncertainty in these results and further research may be worthwhile.

Introduction

The prevalence of chronic obstructive pulmonary disease (COPD) in Spain has been estimated at 10.2% of the general population aged between 40 and 80 in 2007,[1] and it is the cause of high rates of morbidity, mortality and disability. COPD represented 15.3% of total hospital admissions for respiratory illnesses (7.6% in women and 20.7% in men) in 2011 in Spain. In the over 65 population, this percentage rose to 22.4% (10.1% in women and 31.4% in men).[2] In that same year, 15,869 people (4,075 women and 11,794 men) died from COPD at an average age of 75.[3] In 2008, a total of 69,300 people had disabilities or deficiencies related to the respiratory apparatus (26,000 women and 43,300 men), of these 48,700 were 65 years old or over (18,600 women and 30,100 men).[4]

Evidently, COPD has a significant economic impact on the Spanish National Health Service. The annual cost of COPD in Spain has been estimated at 238.82 million euros (in 1997 euros),[5] 463 million euros (in 1999 euros)[6] and 506.52 million dollars (in 2000 dollars).[7] In two of these studies,[5, 7] the cost of COPD increased significantly in line with the seriousness of the illness, with pharmacological treatment and hospital admissions representing the resources incurring the greatest expense. Thus, hospital admissions represent the main component of the total cost of exacerbations for COPD and they are closely related to severe exacerbations.[8]

Telehealth has the potential to improve patients' lives and provides professionals with new tools with the knock-on benefits for Health Systems.[9] Telehealth applied to COPD has been shown to have a positive effect on the quality of life of patients and reduction in healthcare utilization,[10-13] although few studies have evaluated the cost-effectiveness of their interventions.[14-16]

Previous results of this study showed that the telehealth programme for patients with very severe COPD treated with long-term oxygen therapy was found to be technically feasible. Between September and December 2010 we identified 88 patients who met the inclusion criteria using the hospital's electronic records system. Patients were recruited in stages and remained in the study for an average duration of four months (between February and June approximately). The inclusion criteria were: being an adult patient with a diagnosis of COPD and chronic respiratory failure with long-term oxygen therapy indication according to international guidelines; at least one hospitalisation for respiratory illness in the previous year; and being clinically stable during the previous three months. The exclusion criteria were: patients who did not follow long-term oxygen therapy at enrolment; had no home telephone line or did not give their informed

consent. The holistic model consisting of a combination of telemonitoring (using a spirometer, a pulse oximeter, a heart rate and a blood pressure monitor), a clinical call centre (CCC), a case manager and a specialist in respiratory medicine was effective in detecting exacerbations and issuing a prompt clinical response. No marked improvement in the health-related quality of life and healthcare resource utilization, related with COPD, was observed but there was a significant reduction in accident and emergency (A&E) department visits, which for this fragile group of patients is usually the threshold for hospital admission. Overall there was a high level of satisfaction for both patients and healthcare professionals with the telehealth programme.[17]

The objective of this study was to estimate the incremental cost-effectiveness ratio (ICER) of a telehealth programme for patients with severe COPD against the alternative of receiving usual care.

Methods

Design study

We conducted a pilot study, designed as a randomized controlled trial over four months. A total of 45 patients treated with long-term oxygen therapy were enrolled, 24 in the telehealth group (TG) and 21 in the control group (CG). Full details of study method are given elsewhere.[17] The study was carried out taking into account the recommendations of the proposed guidelines for economic evaluation of health technologies in Spain.[18] The analysis adopted the perspective of the National Health Service. It estimated all identifiable costs to the National Health Service and health outcome in quality-adjusted life year (QALY). The alternatives compared were:

- TG: patients who followed a telehealth programme. Patients measured their vital signs from Monday to Friday using a spirometer, a pulse oximeter, a heart rate and a blood pressure monitor. The data were sent via a hub connected to the patient's home telephone line. The information was then received by the CCC who used a triage application. When an alert was triggered, the CCC contacted the patient to confirm the patient's symptoms, and gain more information about the severity of the exacerbation. After that, the CCC contacted the case manager, who analysed the vital sign measurements together with the clinical questionnaire responses, accessing the platform via mobile telephony and initiating the clinical response. Full details of the telehealth intervention, clinical triage and clinical response are given elsewhere.[17]
- CG: patients who received usual care. Health-related quality of life questionnaires were administered at the beginning and at the end of the study during visits to

patients' homes by the nursing personnel. Information on the use of healthcare resources during the study was extracted from hospital information system databases.

Subgroups analysis

In the previous article,[17] differences were detected in the level of comorbidity amongst patients (Charlson index: 3.7±2.7 in TG vs 2.5±1.5 in CG (p=0.18); adjusted Charlson index: 6.6±2.8 in TG vs 5.1±2.0 in CG, p=0.07) and only COPD specific healthcare utilization was considered. The comorbidity is defined as the presence of additional chronic diseases co-occurring with COPD. This analysis looked at whether the level of comorbidity, measured by Charlson comorbidity index,[19] leads to significant differences in costs and/or the QALYs, discriminating between patients without comorbidity (Charlson index equal to 1) and with comorbidity (Charlson index equal to or higher than 2). For this reason, this economic evaluation has a broader scope of costs in order to highlight potential differences in total healthcare utilization costs between COPD patients with and without comorbidity.

Cost

We measured costs of the healthcare utilization, costs of professionals' intervention and costs of the telehealth system. It presented costs in euros at 2014 prices. Prices from previous years were updated by the Spanish consumer price index.[20] Table 1 shows the unit costs of the resources included in the analysis.

Table 1 Unit cost of resources consumed (updated to 2014 euros)

Variable	Unit cost (€)	Source
A&E department (visit)	177.13	20
Specialized care (first visit)	140.14	20
Specialized care (following visit)	67.02	20
Hospitalisations related with COPD (DRG)	2,875.26	21
Hospitalisations related with others chronic disease (DRG)	2,315.26 to 6,898.89[a]	21
Clinical call center (hour)	23.23	22
Case manager (hour)	23.23	22
Technical staff (hour)	23.08	23
MPM (unit)	9,178.75	23
MPM-Net (unit)	4,877.85	23
Receiving station (unit)	891.65	23
Hosting (month)	1,974.75	23
Blood pressure monitor (unit)	165.74	23
Spirometer, pulse oxymeter and heart rate (unit)	419.60	23
Hub tele-modem (unit)	230.78	23
Mobile phone (unit)	367.15	23

[a]Depending of the causes of hospital admissions. DRG: Diagnosis-related group.

The evaluation of the variables included was performed according to the follow premises:

- A&E department visits, specialized care consultations and hospital admissions were evaluated according to public prices.[21, 22]
- The time employed by the CCC was estimated according to the type of alert generated in the triage application: 25 minutes for clinical alerts, 15 minutes for alerts generated by non-adherence to the system, non-receipt of data and technical reinforcement, and 10 minutes for alerts generated for other reasons. The cost per hour of the CCC, with nursing graduate, was calculated in line with salary rates of Andalusian Health Service.[23]
- The time employed by the case manager was estimated depending on the level of seriousness of the exacerbation: 20 minutes for mild to moderate exacerbations, 25 minutes for severe exacerbations and 30 minutes for very severe exacerbations. The cost per hour of the case manager, with nursing graduate, was calculated in line with salary rates of Andalusian Health Service.[23]
- The time employed by technical staff was estimated at 60 minutes for equipment installation and 30 minutes for technical incidents. This cost includes the journey to the patient's house and was calculated by the company supplying the service.[24]
- The cost of the software and equipment was provided by the service supplying company[24] and was calculated using the equivalent annual cost,[25] a method which takes into account both depreciation and the opportunity cost of the capital. The lifetime of the equipment and software has been set at 5 years and the discount rate at 3%. To calculate the cost of the software we took into account that up to a maximum of 500 patients can be telemonitored with this infrastructure/software and we used this to estimate the cost associated for each patient.

Health outcome

The Spanish version of the EuroQol-5D questionnaire[26] was employed for the quality of life assessment at baseline and at four months of follow-up. This questionnaire describes health status in terms of five dimensions (mobility, self-care, usual activity, pain/discomfort, and anxiety/depression), with each one recording three levels of severity. The scores were used to estimate a utility score, one single index on health-related quality of life ranging between 1 and 0, where 1 is the best possible state of health and 0 is death. However, there were also negative utility scores because some states of health are considered to be worse than death.

Moreover, the St George Respiratory Questionnaire[27] was administered at the beginning and at four months of follow-up.

Statistical methodology

The differences between groups and subgroups in terms of average healthcare utilization, professionals' intervention, costs and QALYs were calculated using non-parametric tests: the Mann-Whitney U test for independent samples and The Wilcoxon signed-rank test for dependent samples.

Cost-utility analysis

The effectiveness of the telehealth programme was estimated as a QALYs gain. For each patient, QALY were calculated by using the area under the curve analysis, with linear interpolation of utility scores between baseline and four months of follow-up.[28] Deceased patients were assigned a EuroQol-5D utility score of zero at four months. For each patient, the raw QALY (not taking into account the differences in the basal utility scores) and QALY gain (taking into account the differences in the basal utility scores) corresponding to the four months of monitoring was calculated.

Cost and QALY were estimated for each patient. Results of cost-utility analysis were expressed in terms of the ICER, calculated as the difference in the average costs between TG and CG divided by the difference in the average QALYs gain between TG and CG. The discounting of costs and QALYs was not necessary because the time horizon of the study, four months, did not extend beyond 12 months.[18]

To analyze uncertainty and verify the robustness of the ICER, we conducted an analysis using a non-parametric bootstrap[29] with 5,000 replications.

The resulting 5,000 ICER replicates were plotted on the cost-effectiveness plane and used to construct an acceptability curve.[30] The cost-effectiveness plane is a graphical way of presenting cost-effectiveness results, with the difference in costs on the vertical axis and the difference in health benefits on the horizontal axis. Since incremental costs and health benefits can both be either positive or negative, there are four possible combinations, which are reflected in the four quadrants of the cost-effectiveness plane:

- Upper-left quadrant: intervention less effective and more costly than comparator.
- Lower-left quadrant: intervention less effective and less costly than comparator.
- Upper-right quadrant: intervention more effective and more costly than comparator.
- Lower-right quadrant: intervention more effective and less costly than comparator.

The acceptability curve represents the proportion of simulations in which the intervention was considered cost-effective over a range of values of the threshold cost-per-QALY.[31] Analyses were carried out in STATA software version 12.

Results

Table 2 shows the baseline characteristics of patients and health-related quality of life by St. George's Respiratory Questionnaire scores. No statistically significant differences between the characteristics of patients were found in both groups at baseline, except for St. George's Respiratory Questionnaire scores: 43.78 in the TG and 62.80 in the CG in the symptom scores (difference of 19.01; p=0.01); 74.92 in the TG and 86.85 in the CG in the activity scores (difference of 11.93; p=0.02); and 57.42 in the TG and 69.13 in the CG in the total scores (difference of 11.71; p=0.05). No statistically significant differences between the characteristics of patients without and with comorbidity.

Table 2 Characteristics of patients at baseline

	Telehealth			Control		
	Without comorbidity (N=6)	With comorbidity (N=18)	Total (N=24)	Without comorbidity (N=8)	With comorbidity (N=13)	Total (N=21)
Males	6 (100.0)	17 (94.4)	23 (95.8)	8 (100.0)	12 (92.3)	20 (95.2)
Age	74.67 ± 10.11	74.33 ± 6.94	74.42 ± 7.61	67.88 ± 8.31	72.54 ± 11.51	70.76 ± 10.44
Adj. Charlson Index	4.00 ± 0.89	7.50 ± 2.66	6.63 ± 2.79	3.50 ± 0.93	6.08 ± 1.80	5.10 ± 1.97
Heart failure	0 (0.0)	13 (72.2)	13 (54.2)	0 (0.0)	11 (84.6)	11 (52.4)
Diabetes	0 (0.0)	6 (33.3)	6 (25.0)	0 (0.0)	3 (23.1)	3 (14.3)
SGRQ						
Symptom scores	60.34 ± 24.34	63.62 ± 21.33	62.80 ± 21.61	46.47 ± 25.94	42.13 ± 22.46	43.78 ± 23.30
Activity scores	92.07 ± 9.03	85.11 ± 20.54	86.85 ± 18.41	71.95 ± 25.85	76.75 ± 23.53	74.92 ± 23.91
Impact scores	63.14 ± 13.03	60.16 ± 20.15	60.90 ± 18.41	49.75 ± 29.55	51.97 ± 23.18	51.12 ± 25.08
Total scores	71.45 ± 5.69	68.36 ± 18.61	69.13 ± 16.27	55.89 ± 26.00	58.36 ± 19.97	57.42 ± 21.85
Severe problems						
Mobility	1 (16.7)	2 (11.1)	3 (12.5)	0 (0.0)	0 (0.0)	0 (0.0)
Self-care	2 (33.3)	5 (27.8)	7 (29.2)	0 (0.0)	3 (23.1)	3 (14.3)
Usual activities	2 (33.3)	5 (27.8)	7 (29.2)	1 (12,5)	5 (38.5)	6 (28.6)
Pain/discomfort	0 (0.0)	1 (5.6)	1 (4.2)	2 (25.0)	0 (0.0)	2 (9.5)
Anxiety/depression	0 (0.0)	2 (11.1)	2 (8.3)	1 (12.5)	1 (7.7)	2 (9.5)

Data are present as n (%) and average ± standard deviation.

SGRQ: St. George's Respiratory Questionnaire.

Table 3 shows the average healthcare utilization (A&E department visits, specialized care consultations and hospital admissions) and the average professionals' intervention (CCC, case manager and technical staff interventions).

Table 3 Average healthcare utilization and professionals' intervention

	Telehealth			Control		
	Without comorbidity	With comorbidity	Total	Without comorbidity	With comorbidity	Total
Healthcare						
A&E department total	0.00 ± 0.00	0.67 ± 1.24	0.50 ± 1.10	1.00 ± 1.07	0.31 ± 0.63	0.57 ± 0.87
A&E department related with COPD	0.00 ± 0.00	0.39 ± 0.85	0.29 ± 0.75	1.00 ± 1.07	0.08 ± 0.28	0.43 ± 0.68
A&E department related with others CD	0.00 ± 0.00	0.28 ± 0.57	0.21 ± 0.51	0.00 ± 0.00	0.23 ± 0.60	0.14 ± 0.36
Specialized care total	0.17 ± 0.41	0.67 ± 1.28	0.54 ± 1.14	0.12 ± 0.35	0.38 ± 0.65	0.29 ± 0.56
Specialized care related with COPD	0.17 ± 0.41	0.28 ± 0.67	0.25 ± 0.61	0.12 ± 0.35	0.00 ± 0.00	0.05 ± 0.22
Specialized care related with others CD	0.00 ± 0.00	0.39 ± 1.19	0.29 ± 1.04	0.00 ± 0.00	0.38 ± 0.65	0.24 ± 0.54
Hospitalisations total	0.17 ± 0.41	0.67 ± 1.03	0.54 ± 0.93	0.25 ± 0.46	0.23 ± 0.44	0.24 ± 0.44
Hospitalisations related with COPD	0.17 ± 0.41	0.44 ± 0.92	0.38 ± 0.82	0.25 ± 0.46	0.08 ± 0.28	0.14 ± 0.36
Hospitalisations related with others CD	0.00 ± 0.00	0.22 ± 0.43	0.17 ± 0.38	0.00 ± 0.00	0.15 ± 0.37	0.10 ± 0.30
Professional interventions						
Clinical call center	18.83 ± 11.72	16.39 ± 6.27	17.00 ± 7.75	-	-	-
Clinical alert	3.50 ± 2.43	3.22 ± 2.02	3.29 ± 2.07	-	-	-
Non- adherence	8.00 ± 9.27	5.83 ± 4.42	6.38 ± 5.84	-	-	-
Non-receipt of data	6.17 ± 5.00	5.67 ± 4.21	5.79 ± 4.31	-	-	-
Technical reinforcement	1.00 ± 1.26	1.33 ± 1.37	1.25 ± 1.33	-	-	-
Other reasons	0.17 ± 0.41	0.33 ± 0.84	0.29 ± 0.75	-	-	-
Case manager	1.33 ± 1.75	1.78 ± 1.93	1.67 ± 1.86	-	-	-
Mild/moderate alert	1.17 ± 1.47	1.39 ± 1.79	1.33 ± 1.68	-	-	-
Severe alert	0.00 ± 0.00	0.28 ± 0.57	0.21 ± 0.51	-	-	-
Very severe alert	0.17 ± 0.41	0.11 ± 0.32	0.13 ± 0.34	-	-	-
Technical staff	1.67 ± 0.82	1.56 ± 0.92	1.58 ± 0.88	-	-	-
Equipments installation[a]	1.00 ± 0.00	1.00 ± 0.00	1.00 ± 0.00	-	-	-
Home visit	0.67 ± 0.82	0.56 ± 0.92	0.58 ± 0.88	-	-	-

[a]Constant. CD: chronic disease. Data are present as average ± standard deviation.

Cost

The average healthcare cost was 2,064€ for the TG and 1,103€ for the CG (difference of 961€; 95% confidence interval (CI): -808.83 to 2,730.55). Among the patients without comorbidity, the average healthcare cost was 609€ in the TG and 1,354€ in the CG (difference of -745€; 95% CI: -3,073.01 to 1,583.80). On the other hand, among the patients with comorbidity, the average healthcare cost was 2,549€ in the TG and 949€ in the CG (difference of 1,600€; 95% CI: -631.75 to 3,831.85).

An average cost of 154€ was estimated for the time of health and technical professionals. Analyzing by subgroups, an average cost of 164€ and 151€ was obtained between patients without and with comorbidity respectively (difference of 13€; 95% CI: -61.19 to 87.41). Finally, the average cost associated to the use of equipment and software was estimated at 82€.

As a final result, the average total cost was 2,300€ for the TG and 1,103€ for the CG, (difference of 1,197€; 95% CI: -579.11 to 2,972.93). Among the patients without comorbidity, the average total cost was 855€ in the TG and 1,354€ in the CG (difference of -499€; 95% CI: -2,823.00 to 1,825.56). On the other hand, among the patients with comorbidity, the average total cost was 2,782€ in the TG and 949€ in the CG (difference of 1,833€; 95% CI: -409.56 to 4,075.21). All this information is included in table 4.

Health outcome: QALY

Two patients, one from each group, died during the study that represented the 4% of the TG and the 5% of the CG. The average increase in the utility score was 0.0359 score for the TG and 0.0034 score for the CG (difference of 0.0324 score; 95% CI: -0.12 to 0.19). Among the patients without comorbidity, the average increase in the utility score was 0.1744 for the TG and 0.0497 for the CG (difference of 0.1247 score; 95% CI: -0.21 to 0.46). On the other hand, the patients with comorbidity reduced their average utility score in 0.0103 scores and 0.0251 for the TG and CG respectively (difference of 0.0147 score; 95% CI: -0.16 to 0.19).

Table 4 shows the average utility scores obtained from the EuroQol-5D questionnaire at baseline and at four months of follow-up, and the raw QALY. The CG obtained a higher average raw QALY than TG, determined by the differences in the basal utility scores.

Table 4 Average costs (€), EuroQol-5D utility scores and raw QALY

	Telehealth			Control		
	Without comorbidity	With comorbidity	Total	Without comorbidity	With comorbidity	Total
Healthcare	609.24 ± 1,492.33	2,548.96 ± 4,066.61	2,064.03 ± 3,666.54	1,353.85 ± 2,518.50	948.91 ± 1,842.63	1,103.17 ± 2,073.11
A&E department	0.00 ± 0.00	118.08 ± 219.05	88.56 ± 195.43	177.13 ± 189.36	54.50 ± 111.66	101.21 ± 154.12
A&E department related COPD	0.00 ± 0.00	68.88 ± 150.53	51.66 ± 132.95	177.13 ± 189.36	13.62 ± 49.13	75.91 ± 143.59
A&E department related other CD	0.00 ± 0.00	49.20 ± 101.76	36.90 ± 90.15	0.00 ± 0.00	40.87 ± 106.12	25.30 ± 84.68
Specialized care	23.36 ± 57.21	69.05 ± 115.19	57.63 ± 104.54	17.52 ± 49.55	48.27 ± 77.21	36.56 ± 68.34
Specialized care related COPD	23.36 ± 57.21	30.80 ± 72.11	28.94 ± 67.57	17.52 ± 49.55	0.00 ± 0.00	6.67 ± 30.58
Specialized care related other CD	0.00 ± 0.00	38.25 ± 102.78	28.69 ± 89.97	0.00 ± 0.00	48.27 ± 77.21	29.88 ± 64.45
Hospitalisations	585.89 ± 1,435.12	2,423.09 ± 3,939.36	1,963.79 ± 3,546.60	1,243.14 ± 2,319.97	883.62 ± 1,713.43	1,020.58 ± 1,917.63
Hospitalisations related COPD	585.89 ± 1,435.12	1,453.73 ± 2,930.11	1,236.77 ± 2,634.56	1,243.14 ± 2,319.97	221.17 ± 797.45	610.49 ± 1,588.70
Hospitalisations related other CD	0.00 ± 0.00	969.36 ± 1,996.77	727.02 ± 1,769.41	0.00 ± 0.00	662.45 ± 1,617.83	410.09 ± 1,295.80
Professional time	164.28 ± 72.12	151.17 ± 50.12	154.45 ± 54.96	-	-	-
Clinical call center	122.63 ± 63.40	107.03 ± 38.51	110.93 ± 44.92	-	-	-
Clinical alert	33.88 ± 23.52	31.20 ± 19.52	31.87 ± 20.08	-	-	-
Non- adherence	46.47 ± 53.87	33.88 ± 25.69	37.03 ± 33.91	-	-	-
Non-receipt of data	35.82 ± 29.02	32.92 ± 24.48	33.64 ± 25.06	-	-	-
Technical reinforcement	5.81 ± 7.35	7.74 ± 7.97	7.26 ± 7.71	-	-	-
Other reasons	0.64 ± 1.58	1.29 ± 3.25	1.13 ± 2.91	-	-	-
Case manager	10.88 ± 14.67	14.65 ± 15.36	13.71 ± 14.96	-	-	-
Mild/moderate alert	8.95 ± 11.29	10.65 ± 13.70	10.22 ± 12.92	-	-	-
Severe alert	0.00 ± 0.00	2.71 ± 5.61	2.03 ± 4.97	-	-	-
Very severe alert	1.94 ± 4.74	1.29 ± 3.76	1.45 ± 3.92	-	-	-
Technical staff	30.77 ± 9.42	29.49 ± 10.64	29.81 ± 10.16	-	-	-
Equipments installation[a]	23.08 ± 0.00	23.08 ± 0.00	23.08 ± 0.00	-	-	-
Home visit	7.69 ± 9.42	6.41 ± 10.64	6.73 ± 10.16	-	-	-
Peripheral devices and software[a]	81.60 ± 0.00	81.60 ± 0.00	81.60 ± 0.00	-	-	-
Peripheral devices[a]	63.39 ± 0.00	63.39 ± 0.00	63.39 ± 0.00	-	-	-
Software[a]	18.21 ± 0.00	18.21 ± 0.00	18.21 ± 0.00	-	-	-
EuroQol-5D utility scores						
Utility scores at baseline	0.4405 ± 0.31	0.4365 ± 0.26	0.4375 ± 0.27	0.5203 ± 0.29	0.5714 ± 0.36	0.5519 ± 0.33
Utility scores at 4 months	0.6150 ± 0.30	0.4262 ± 0.33	0.4734 ± 0.32	0.5701 ± 0.28	0.5463 ± 0.36	0.5554 ± 0.32
Raw QALY	0.1742 ± 0.09	0.1423 ± 0.09	0.1503 ± 0.09	0.1799 ± 0.08	0.1844 ± 0.11	0.1827 ± 0.10

[a]Constant. CD: chronic disease. Data are present as average ± standard deviation.

Cost-utility analysis

Table 5 shows the results from cost-utility analysis based on 5,000 bootstrap replications. The average total cost per patient was 2,300€ for the TG and 1,103€ for the CG, resulting in an incremental cost of 1,197€. The average QALY gain was 0.0059 for the TG and 0.0006 for the CG, resulting in an incremental QALY gain of 0.0053. We obtained an ICER of 223,726€/QALY.

The cost-effectiveness plane shows that 59% of the bootstrap simulations are located in the upper-right quadrant, and the 33% of the bootstrap simulations are located in the upper-left quadrant (figure 1). The acceptability curve shows that for a willingness to pay of 30,000€/QALY, the probability of the telehealth programme being cost-effective is 15% (figure 2).

Table 5 Cost-utility analysis based on 5,000 bootstrap replications.

	Telehealth	Control	Difference (95% Conf. Interval) or ICER
Average cost (€)			
All patients	2,300.08	1,103.17	1,196.91 (-498.97 to 2,892.80)
Without comorbidity	855.13	1,353.85	-498.72 (-2,451.38 to 1,453.94)
With comorbidity	2,781.73	948.91	1,832.83 (-223.00 to 3,888.66)
Average QALY gain			
All patients	0.0059	0.0006	0.0053 (-0.0193 to 0.0300)
Without comorbidity	0.0288	0.0082	0.0206 (-0.0259 to 0.0671)
With comorbidity	-0.0017	-0.0041	0.0024 (-0.0251 to 0.0300)
ICER (€/QALY)			
All patients	-	-	230,688.29
Without comorbidity	-	-	Dominant
With comorbidity	-	-	799,531.48

Bootstrap 95% confidence intervals.

For patients without comorbidity, the average total cost per patient was 855€ for the TG and 1,354€ for the CG, resulting in a reduction cost of 499€. The average QALY gain was 0.0288 for the TG and 0.0082 for the CG, resulting in an incremental QALY gain of 0.0206. For this subgroup, the telehealth programme was a dominant strategy as it was a less costly and more effective intervention than usual care. The cost-effectiveness plane shows that 52% of the bootstrap simulations are located in the lower-right quadrant, and the 27% of the bootstrap simulations are located in the upper-right quadrant (figure 1). The acceptability curve shows that for a willingness to pay of 30,000€/QALY, the probability of the telehealth programme being cost-effective is 78% (figure 2).

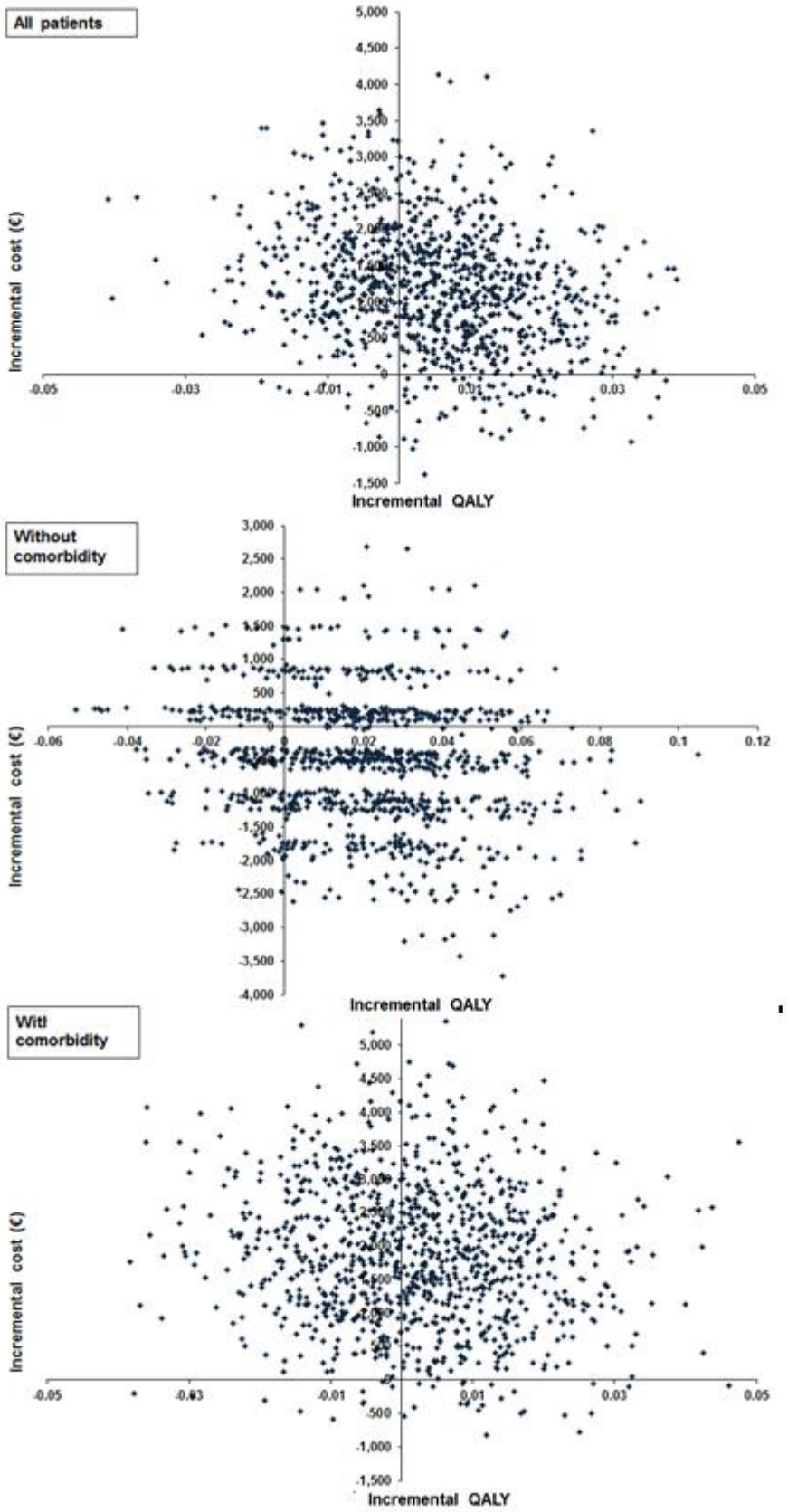

Figure 1 Distribution of bootstrapped ICER in the cost-effectiveness plane

For patients with comorbidity, the average total cost per patient was 2,782€ for the TG and 949€ for the CG, resulting in an incremental cost of 1,833€. The average QALY gain was -0.0017 for the TG and -0.0041 for the CG, resulting an incremental QALY gain of 0.0024. We obtained an ICER of 754,592€/QALY. The cost-effectiveness plane shows that 55% of the bootstrap simulations are located in the upper-right quadrant and the 42% of the bootstrap simulations are located in the upper-left quadrant (figure 1). The acceptability curve shows that for a willingness to pay of 30,000€/QALY, the probability of the telehealth programme being cost-effective is 6% (figure 2).

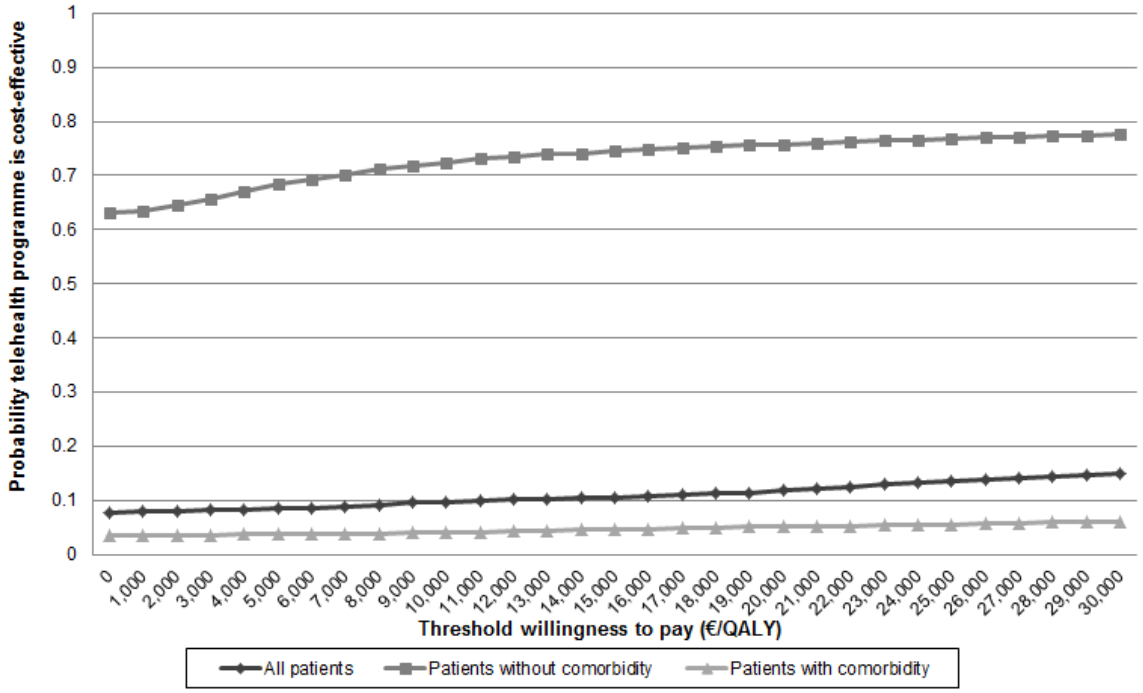

Figure 2 Acceptability curve based on willingness to pay for QALY

Discussion

This study is the first cost-utility analysis of a telehealth programme for patients with severe COPD treated with long-term oxygen therapy to be carried out in Spain. The results highlight that the level of comorbidity of patients brings with it important differences in cost and QALY. One must remember that comorbidities such as heart disease, diabetes mellitus or hypertension often occur in patients with COPD.[32]

With 30,000€/QALY being the threshold for determining whether a health technology is cost-effective in Spain,[33] we can state that the telehealth programme for patients with severe COPD treated with long-term oxygen therapy may not be cost-effective compared to usual

care, and the acceptability curve shows that there is little uncertainty, due to the fact that 15% of the bootstrap simulations are below the threshold of 30,000€/QALY.

The authors took into account if the level of comorbidity leads to significant differences in costs and/or in QALY. Analyzing by subgroups, the telehealth programme could be considered a dominant strategy for patients without comorbidity, and the acceptability curve shows that there is little uncertainty, due to the fact that 78% of the bootstrap simulations are below the threshold of 30,000€/QALY. On the other hand, the telehealth programme for patients with comorbidity may not be cost-effective compared to usual care, and the acceptability curve shows that there is little uncertainty, due to the fact that 6% of the bootstrap simulations are below the threshold of 30,000€/QALY.

Few studies have performed an economic evaluation of telehealth programs in patients with COPD. Paré et al.[34] performed a cost minimization analysis for a telehomecare programme for patients with COPD, assuming equal effectiveness between the telehomecare programme and conventional health care, and they estimated a saving of 355$ per patient over a six month period. Two more recent experiences have estimated the cost-effectiveness of telehealth programs in patients with chronic illnesses over a twelve month period of monitoring. Henderson et al.[35] estimated the cost-effectiveness of a telehealth programme in addition to standard support and treatment, compared to standard support and treatment, in patients with heart failure, COPD or diabetes, and they obtained the incremental cost per QALY of telehealth when added to usual care of £92,000 (£12,000 per QALY in the most optimistic scenario). In Spain, Bayón et al.[36] estimated the cost-effectiveness of a telemonitoring programme (telemonitoring and multi strategy of individualised care), compared to a multi-strategy of individualised care in patients with COPD and heart failure. The telemonitoring programme was less costly and less effective than the conventional procedure, reaching an ICER of 115,569€/QALY.

Although previous studies have shown that the use of telehealth in patients with COPD can reduce the healthcare cost,[34, 37, 38] this telehealth programme did not reduce this cost, and only the A&E department visits cost was lower for patients of TG. Our results also show that hospital admissions due to exacerbation of COPD represent the greatest component of health expenditure, a link detected in other studies.[39] Analyzing by subgroups, differences can be found. The telehealth programme reduced the average healthcare cost among patients without comorbidity, reducing the A&E department visits and hospital admissions cost, but this did not occur with patients with comorbidity. It should be pointed out that in two of the eight exacerbations from the comorbidity subgroup detected by the patients' telehealth system, subjects did not accept the referrals made by the case manager and they were

subsequently admitted to hospital.[17] Furthermore, a high percentage of this group of patients who are admitted to hospital go beforehand to A&E department so that the exacerbations detected by the telehealth system avoided A&E department visits and, probably, subsequent hospital admissions.

Telehealth studies do not often include costs associated to the time employed by professionals and the equipment used.[40] This study included the costs associated to the time employed by professionals, equipment and software, and their represented 10% of the total cost. Analyzing by subgroups, the related costs of the telehealth programme were similar, and their represented 29% and 8% of the total cost for patients without and with comorbidity respectively.

Despite that the patients of TG obtained a higher QALY gain, the raw QALY associated to the four months of follow-up was higher among patients in the CG. This discrepancy was motivated by the difference in the basal utility scores obtain from EuroQol-5D questionnaire. The subgroup of the patients without comorbidity increased their quality of life, although the QALY gain was higher in the TG. On the other hand, the subgroup of the patients with comorbidity reduced their quality of life, although the QALY gain was higher in the TG. In both cases, significant differences were not observed.

This analysis has followed the recommendations of the European Commission for telehealth programmes to produce findings,[9] although this study has two limitations which are frequent in telehealth programs:[15, 16] a small sample size and short duration of the study. The number of patients included in this study was too small to make statistical inferences and to generalize the findings, particularly when subgroup analysis was concerned. It analyzed whether the level of comorbidity led to significant differences in costs and/or in QALY although the results did not allow us to draw a robust conclusion for this population. The authors decided not to estimate the QALY adjusted by the baseline utility values and other variables where there were differences between the patients of both groups, as recommended by Manca et al.,[28] due to the small sample size. Moreover, the follow-up period of four months was too short to capture differences in quality of life and costs. One would not expect improved disease-control due to a telehealth programme to have an impact on quality of life and costs until at least a year after implementation. In addition, seasonal effects can influence the number of exacerbations that a COPD patient can experience within four months depending on when the baseline measurement was taken. Another limitation of the study is that we did not consider carer time in the analysis, although the exclusion of other indirect costs, such as loss of productivity, is justified because of they were retired people.

Despite these limitations, the study is important for several reasons. It adds to the scarce body of international findings on the cost-effectiveness of telehealth programmes for patients with COPD and it is the first study of these characteristics performed in Spain to suggest that this intervention strategy could be cost-effective in COPD patients without comorbidity.

Conclusion

The telehealth programme for patients with severe COPD treated with long-term oxygen therapy may not be cost-effective compared to usual care. Although this intervention strategy could be considered cost-effective for patients without comorbidity, the bootstrap simulations show that there is considerable uncertainty in these results and further research may be worthwhile.

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Conflict of interest

Cristina Gómez-Suárez and Ana Jordán work at Linde Healthcare. The remaining authors have no conflict of interest.

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CAPÍTULO II. EVALUACIÓN ECONÓMICA DE PROGRAMAS DE SEGUIMIENTO FARMACOTERAPÉUTICO EN PACIENTES CRÓNICOS

COST-UTILITY ANALYSIS OF A PHARMACOTHERAPY FOLLOW-UP FOR ELDERLY NURSING HOME RESIDENTS IN SPAIN

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ABSTRACT

Objectives: To compare the cost-effectiveness of a pharmacotherapy follow-up for elderly nursing home (NH) residents with that of usual care.

Design: Prospective observational study with a concurrent control group conducted over 12 months.

Setting: Fifteen NHs in Andalusia assigned to control (n=6) or intervention (n=9).

Participants: Residents aged 65 and older.

Intervention: Pharmacotherapy follow-up.

Measurements: Negative outcomes associated with medication, health-related quality of life, cost, quality-adjusted life-year (QALY), and incremental cost-effectiveness ratio (ICER). ICERs were estimated for three scenarios: unadjusted cost per QALY (first scenario), costs adjusted for baseline prescribed medication and QALYs adjusted for baseline utility score (second scenario), and costs and QALYs adjusted for a fuller set of baseline characteristics (third scenario).

Results: Three hundred thirty-two elderly residents were enrolled: 122 in the control group and 210 in the intervention group. The general practitioner accepted 88.7% (274/309) of pharmacist recommendations. Pharmacist interventions reduced the average number of prescribed medication by 0.47 drugs (p<.001), whereas the average prescribed medication increased by 0.94 drugs in the control group (p<.001). Both groups reported a lower average EuroQol-5D utility score after 12 months (intervention, –0.0576, p=.002; control, –0.0999, p=.003). For the first scenario, pharmacotherapy follow-up was dominated by usual care. Adjusted ICERs were €3,899/QALY ($5,002/QALY) for the second scenario and €6,574/QALY ($8,433/QALY) for the third scenario. For a willingness to pay of €30,000/QALY ($38,487/QALY), the probabilities of the pharmacotherapy follow-up being cost-effective were 35% for the first scenario, 78% for the second, and 76% for the third.

Conclusion: Pharmacotherapy follow-up is considered cost-effective for elderly NH residents in Spain.

Key words: pharmacotherapy follow-up; nursing home; cost-utility analysis; quality-adjusted life-year*;* negative outcomes associated with medication.

In 2011, there were 270,286 Spaniards living in nursing homes (NHs), with an average age of 83.7 and a female:male ratio of 2.18. This number has tripled over the last 10 years (96,338 people in 2001) and represents 3.3% of the total population aged 65 and older.[1] Because elderly NH residents tend to have many health problems and often take multiple medication,[2] inappropriate medication prescription in NHs is often a problem.[3–6]

Drug-related morbidity and mortality are often preventable, and pharmaceutical services can reduce the number of adverse drug reactions, length of hospital stays, and healthcare costs.[7] Moreover, drug-related morbidity and mortality in NHs is an important economic problem.[8]

A recent systematic review of interventions to optimize prescribing for older care homes residents concluded that the interventions led to the identification and resolution of drug-related problems, improvements in appropriateness of medication, and a reduction in drug costs, although there is no evidence of an intervention's effect on adverse drug events, hospital admissions, mortality, or quality of life.[9] Other systematic reviews have concluded that there is little information available about pharmacist interventions in NHs for the optimization of medication use.[10,11]

Few studies of pharmaceutical care programs for elderly adults have undertaken a rigorous economic evaluation, and a more-standardized approach to data collection is required.[12] This study compared the cost-effectiveness of a pharmacotherapy follow-up service for elderly NH residents with that of usual care.

METHODS

The study was designed as a prospective observational study with a concurrent control group conducted over 12 months (2008–09). The target population consisted of elderly NH residents in Andalusia, Spain. Participants were residents aged 65 and older who were cognitively intact and provided informed consent. Nonresident individuals in day care were excluded.

Three hundred sixty institutionalized elderly residents were contacted and asked to participate in the study. Fourteen did not meet inclusion criteria, and 14 declined to participate (Figure 1). Written informed consent was obtained from all participants before inclusion.

Pharmacotherapy follow-up

The Pharmaceutical Care Research Group at the University of Granada, Spain, developed the Dader Method of pharmacotherapy follow-up.[13] This method develops and evaluates a

pharmacotherapeutic state based on correlating health problems and pharmacotherapy used to treat them. A pharmacist evaluates this pharmacotherapeutic state to determine whether the pharmacotherapeutic goals related to each health problem are being met. If not, any potential or real health outcomes not consistent with the pharmacotherapy objectives (negative outcomes associated with medication)[14] are detected before proceeding to the intervention stage for the same pharmacist. The intervention objective is to prevent, detect, and solve the negative outcomes associated with medication. The pharmacist interventions were conducted in collaboration with the resident and the general practitioner. The Dader Method was applied in this study in the following phases.

- Resident history review: Data related to medical problems and current pharmacotherapy were obtained from the participant's history.

- First interview: An interview was conducted to complete information about the participant's history.

- Situation state: From the information obtained in the interview and information contained in the participant's history, the pharmacist drew up the "situation state," a document about the participant's current health status and pharmacotherapy.

- Evaluation phase: This stage assessed whether the desired treatment goals were being achieved by evaluating the pharmacotherapy outcomes. International clinical practice guidelines that the clinical team adapted for the particular case of each participant suggested the therapeutic goals for the treatment of each health problem. For example, in the treatment of arterial hypertension without other health problems, the usual treatment goal is to keep blood pressure values below 140/90.

- Intervention phase: For participants found to have negative outcomes associated with medication, the pharmacist drew up a therapeutic plan including interventions to improve each negative outcome associated with medication. The pharmacist proposed an action plan with the participant and general practitioner.

- Successive interviews were conducted to assess situation states and register health problems or new prescribed medication and evaluate the result of the interventions.

Nursing home

The study was performed in 15 NHs in Andalusia that were assigned to the intervention or control group. Intervention NHs were located in four provinces (one in Córdoba, two in Cádiz, three in Málaga, three in Granada) and control NHs in three provinces (one in Sevilla, one in Cádiz, four in Málaga). Nine NHs were assigned to the intervention group if the

pharmacist was willing to participate, and the pharmacists selected six NHs as an equivalent control group.

There were no significant differences between the NHs used in the study. They were privately owned, with their own nursing and medical staff, and none restricted access of elderly adults because of their degree of disability.

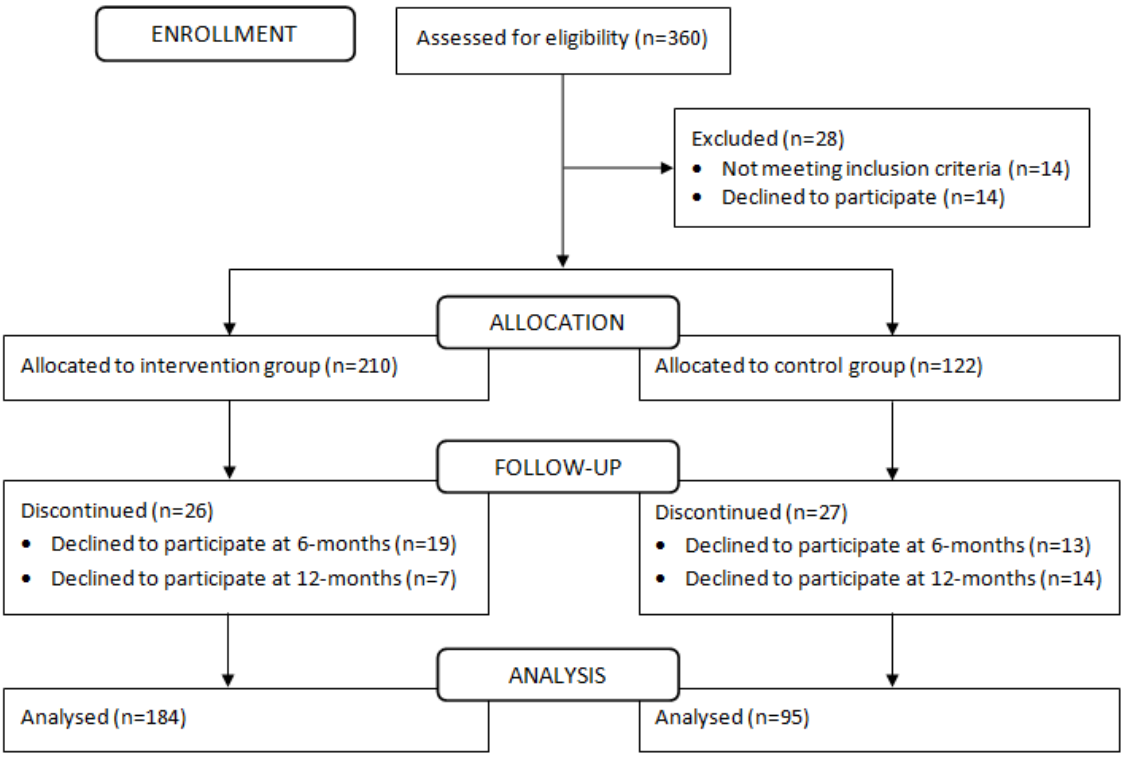


Figure 1: Enrollment, allocation, follow-up, and analysis of institutionalized elderly participants

Control group

The institutionalized elderly control group received usual care without pharmacist intervention. Health-related quality-of-life questionnaires were administered at baseline and 6 and 12 months. Information on prescribed medication was extracted from NH health information systems.

Negative outcomes associated with medication

The main outcome of the pharmacist intervention was the identification and resolution of negative outcomes associated with medication. According to the Third Consensus of Granada,[14] the negative outcomes associated with medication are health-related outcomes

not consistent with pharmacotherapy objectives and are associated with the erroneous use of medicines. Problems related to the medication use process were not recorded in this study (e.g., finding it hard to open a medication bottle).

Pharmacists gave advice about the correct use of medicines to NH residents to prevent or solve negative outcomes associated with medication. There are six kinds of negative outcomes associated (which can be related to necessity, effectiveness, or safety):

- Necessity (untreated health problems): People have a health problem as a consequence of not receiving the medicine they need.

- Necessity (effects from unnecessary medicines): People have a health problem as a consequence of receiving medicine they do not need.

- Effectiveness (nonquantitative ineffectiveness): People have a health problem as a consequence of nonquantitative ineffectiveness of the medication, that is, not depends on the amount of drugs.

- Effectiveness (quantitative ineffectiveness): People have a health problem as a consequence of a quantitative ineffectiveness of the medication, that is, depends on the amount of drugs.

- Safety (nonquantitative safety problems): People have a health problem as a consequence of a nonquantitative safety problem with the medication, that is, not depends on the amount of drugs.

- Safety (quantitative safety problems): people suffer from a health problem as a consequence of a quantitative safety problem with the medication, that is, depends on the amount of drugs.

Health-related quality of life

Health-related quality of life was measured using two questionnaires: the EuroQol-5D[15] and Nottingham Health Profile (NHP).[16,17] Both questionnaires were administered at baseline and 6 and 12 months.

The EuroQol-5D describes health condition using five dimensions (mobility, self-care, usual activities, pain and discomfort, anxiety and depression); each of these is defined using three levels of severity. Scores were used to estimate a utility score—a single index of health-related quality of life ranging from 1 to 0, with 1 being the best possible state of health and 0 being death, although there were also negative utility scores because some states of health are considered to be worse than death. A visual analogue scale was used to measure the

subjects' health status with scores whereby one end of the scale ranks the 'worst' (0) and the other the 'best' (100) health state.

The NHP consists of two parts that assess the individual's health condition. In this study, only 38 questions from the first part of this questionnaire were administered. These questions explore six health dimensions: energy, pain, physical mobility, emotional reactions, sleep, and social isolation. The scores are obtained by considering the percentage of affirmative responses (dividing the total positive responses in one dimension by the total number of items in that dimension and multiplying the figure by 100). In both cases, scores range from 0 to 100, with 0 indicating that the individual responded negatively to all the items in the dimension and does not have any health problems and 100 indicating that the person has all of the health problems.

Costs

The analysis took into account only direct costs, including costs for the pharmacist intervention and prescribed medication. Costs are presented in Euro and U.S. dollars at 2013 prices (exchange rate on July 7, 2013: 1 Euro=US$1.28).

The cost per hour of the pharmacist was obtained from official sources.[18] Each pharmacist recorded time spent conducting each phase, or time was estimated for a group of pharmacists.

- Time for first interview: recorded for each participant.

- Time for situation state and evaluation phase: 45 minutes was estimated per participant.

- Intervention phase: estimate based on the number of negative outcomes associated with medication and pharmacist interventions.

- Successive interviews: estimate based on the number of subsequent interviews in which the pharmacist recorded additional situation states.

The pharmacist recorded prescribed medication for the control group at baseline and 6- and 12-month follow-up. For the intervention group, the pharmacist also recorded prescribed medication after every intervention. Medication cost was obtained from the official drug price.[19]

Statistical methodology

A cost–utility analysis was used to compare pharmacotherapy follow-up with the usual care. This study followed the recommendations of the proposed guidelines for economic evaluation of health technologies in Spain.[20] The effectiveness of the intervention was

estimated as quality-adjusted life-years (QALYs). QALYs were calculated by using an area under the curve analysis, with linear interpolation of utility scores between baseline and 6 and 12 months of follow-up.[21] Deceased residents were assigned a EuroQol-5D utility score of 0 at 6 or 12 months. EuroQol-5D scores were missing for 32 participants at 6 months and for 31 at 12 months. These participants were excluded from the cost–utility analysis.

Cost and QALYs were estimated for each resident. Results of cost–utility analysis were expressed in terms of the incremental cost-effectiveness ratio (ICER), calculated by dividing the difference in total costs between the intervention and control groups by the difference in QALYs between both groups.[22] Participants were not selected randomly. To minimize this limitation, the base case ICERs were estimated for three scenarios.

- First scenario: unadjusted cost per QALY.

- Second scenario: costs adjusted for baseline drug use and QALYs adjusted for baseline utility score.

- Third scenario: costs and QALYs adjusted for a fuller set of baseline characteristics in which significant differences were detected between the groups.

Because the time horizon of the study did not extend beyond 12 months, discounting of costs and QALYs was not necessary.[20]

To analyze the uncertainty of ICER results, a nonparametric bootstrapping was performed with 1,000 replications. The resulting 1,000 ICER replicates were plotted on the cost-effectiveness plane and used to construct a cost-effectiveness acceptability curve.[23] The plane shows the joint distribution of the difference in costs and effects. The acceptability curve represents the proportion of simulations in which the intervention is considered cost-effective over a range of values of the threshold cost per QALY.[24] Analyses were performed in Stata version 12 (Stata Corp., College Station, TX).

RESULTS

Three hundred thirty-two institutionalized elderly adults were enrolled: 122 control, 210 intervention. Table 1 shows the sociodemographic characteristics of the participants and pharmacists. Sixty-six percent of the participants were female (71% intervention, 57% control); the average age of participants was 81.6 (82.2 intervention, 80.5 control), and they had an average consumption of 6.0 drugs (6.7 intervention, 4.9 control) and an average of 4.5 health problems (4.7 intervention, 4.1 control). Fifty-seven percent had a university education or less (54.9% intervention, 63.4% control), 10.7% were self-medicated (11.6% intervention, 9.2% control), 28.9% kept their medication in their rooms (25.9% intervention,

33.9% control), 10.6% were smokers (12% intervention, 8.2% control), 11.5% had drug allergies (13.5% intervention, 8.2% control), and 38.8% took herbal treatments (e.g., mint tea, chamomile) (43.2% intervention, 31.4% control).

Table 1. Baseline Characteristics of Elderly Nursing Home Residents and Pharmacists

Characteristic	Intervention	Control	P-Value[a]
Resident	n=210	n=122	
Age, average ± SD	82.2 ± 6.9	80.5 ± 7.2	.03
Female, n (%)	149 (71.0)	70 (57.4)	.01
Drugs, average ± SD	6.7 ± 3.0	4.9 ± 3.1	<.001
Health problems, average ± SD	4.7 ± 2.1	4.1 ± 2.2	.02
≥primary education[b]	112 (54.9)	71 (63.4)	.14
Self-medication, n (%)[b]	24 (11.6)	11 (9.2)	.51
Drugs in room, n (%)[b]	50 (25.9)	38 (33.9)	.14
Smoking habits, n (%)[b]	25 (12.0)	10 (8.2)	.28
Drug allergy, n (%)[b]	28 (13.5)	10 (8.2)	.15
Taking herbal treatments, n (%)[b,c]	89 (43.2)	38 (31.4)	.03
Diabetes mellitus, n (%)	58 (27.6)	26 (21.3)	.20
Hypertension, n (%)	112 (53.3)	65 (53.3)	.99
Heart failure, n (%)	70 (33.3)	34 (27.9)	.30
Arthrosis, n (%)	58 (27.6)	39 (32.0)	.40
Very severe problems, n (%)			
Mobility	12 (6.0)	10 (8.2)	.45
Self-care	42 (21.0)	17 (13.9)	.11
Usual activities	24 (12.0)	12 (9.8)	.55
Pain and discomfort	27 (13.5)	13 (10.7)	.45
Anxiety and depression	13 (6.5)	12 (9.8)	.28
Visual analogue scale, average ± SD[b]	65.5 ± 22.9	62.7 ± 23.5	.34
Pharmacist	n=10	n=8	
Age, average ± SD	42.0 ± 8.2	37.7 ± 6.5	.37
Female, n (%)	7 (70.0)	8 (100.0)	.09
Years working, average ± SD	13.7 ± 6.3	8.9 ± 6.5	.08

[a]Student t-test or chi-square test.

[b]There are missing values for these variables.

[c]Using lime flower, chamomile, mint tea, for example.

SD=standard deviation.

The most prevalent health problems in the sample were diabetes mellitus (25.3%; 27.6% intervention, 21.3% control), hypertension (53.3% of both groups), heart failure (31.3%; 33.3% intervention, 27.9% control), and arthrosis (29.2%; 27.6% intervention, 32% control). The percentage of participants who perceived very severe problems in different dimensions of their state of health was low: 6.8% in mobility (6% intervention, 8.2% control), 18.3% in self-care (21% intervention, 13.9% control), 11.2% in usual activities (12% intervention, 9.8% control), 12.4% in pain or discomfort (13.5 intervention, 10.7% control), and 7.8% in anxiety or depression (6.5% intervention, 9.8% control).

Negative outcomes associated with medication

The general practitioner accepted 88.7% (274/309) of pharmacist recommendations, and 86.2% (218/253) of pharmacists' interventions were implemented, resolving 1.2 average negative outcomes associated with medication per participant during the 12 months of follow-up.

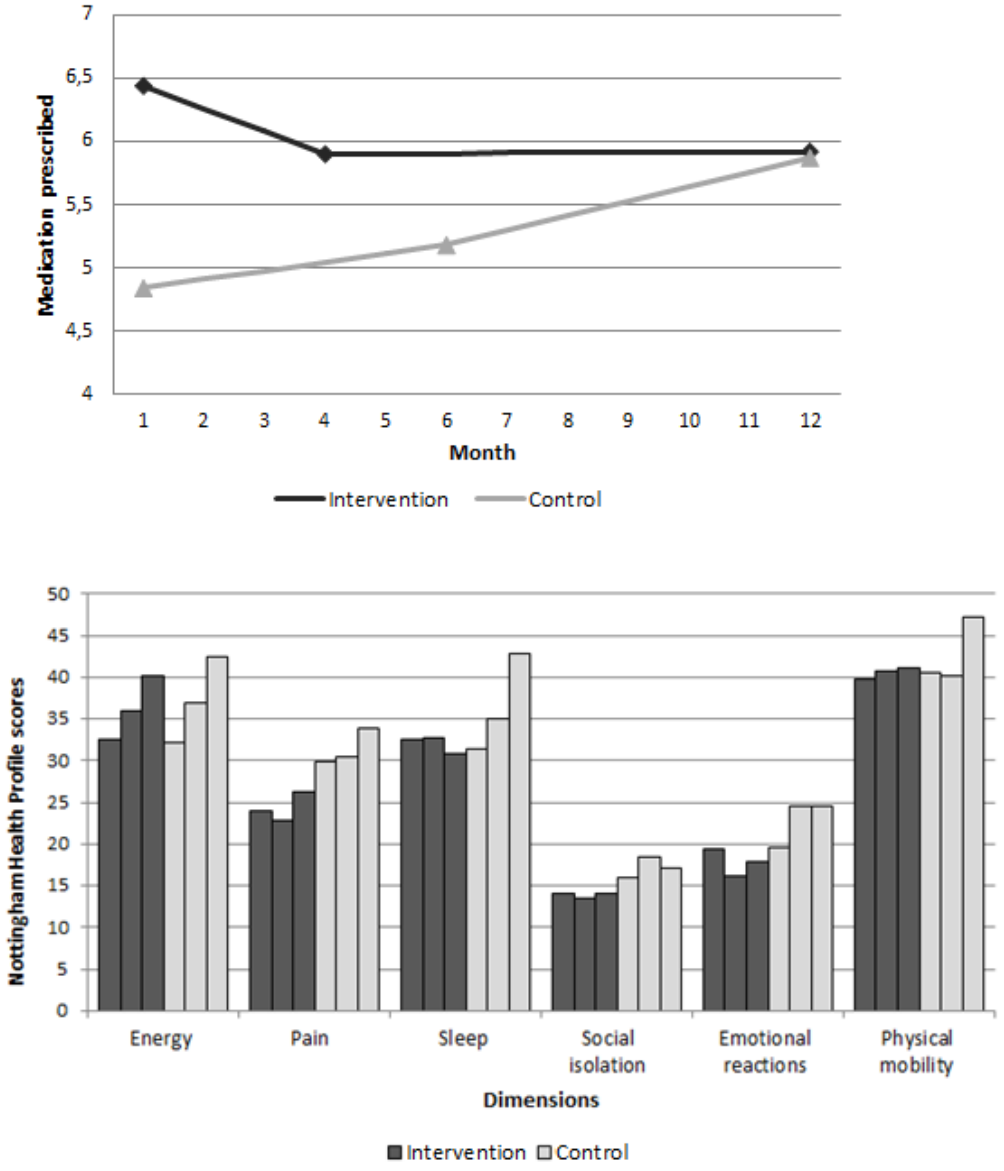


Figure 2. Evolution of average number of prescribed medication of participants who completed 12 months of monitoring (A) and evolution of Nottingham Health Profile scores of six dimensions at baseline (first column), 6 months (second column), and 12 months (third column) for both groups (B).

Pharmacotherapy follow-up: time spent by pharmacists and medication changes

Pharmacists devoted an average of 113.7±26.2 minutes to the stages of pharmacotherapy follow-up: 36.2±9.9 minutes to participant history review and first interview, 45±0 minutes to writing the situation state in the study and evaluation phase (estimated by an expert panel), 20.3±14.2 minutes to the intervention phase, and 12.3±10.8 minutes to the revision phase of intervention results and subsequent interviews.

Pharmacist interventions reduced the average number of prescribed medications by 0.47 drugs (p<.001), whereas the average number of prescribed medications increased by 0.94 drugs in the control group (p<.001). Figure 2 shows the evolution of average prescribed medications in participants who completed the 12 months of monitoring (excluding those who died). The average number of prescribed medications decreased by 0.52 drugs in the intervention group (p<.001), from 6.4±3.1 at baseline to 5.9±2.9 after the first pharmacist intervention (average 125 days) and 5.9±3.0 at 12 months. In the control group, the average number of prescribed medications increased by 1.03 drugs (p<.001), from 4.8±2.9 at baseline, 5.2±2.9 at 6 months and 5.9±3.2 at 12 months.

Health-related quality of life and mortality

Both groups had a lower average EuroQol-5D utility score at 12 months than at baseline. For intervention group participants, the average utility score at the end of the study decreased by 0.058 (p = .002), from 0.595±0.30 at baseline to 0.565±0.33 at 6 months and 0.538±0.33 at 12 months. For control group participants, the average utility score at the end of the study decreased by 0.100 (p =.003), from a score of 0.621±0.29 at baseline to 0.561±0.32 at 6 months and 0.521±0.32 at 12 months. Participants who died were assigned a EuroQol-5D utility score of 0; 27 participants died during the study (17 (8%) intervention, 10 (8%) control).

Both groups had similar scores on the six dimensions of the NHP at baseline, except for the pain dimension (24.7 intervention, 29.7 control; p=.16). The intervention group improved only in the sleep dimension (–1.68 points, p=.43) and the emotional reactions dimension (–1.59 points, p=.37), whereas control group scores did not improve on any dimension at 12 months. Figure 2 shows the evolution of NHP scores from baseline to 6 and 12 months for both groups.

Costs

The average cost related to time that pharmacists spent in stages of pharmacotherapy follow-up was €74 ($95). The average cost related to prescribed medication for the 12 months of follow-up was €1,151 ($1,476) for the intervention group and €826 ($1,059) for the

control group. The average cost in the interventions group fell €0.18/d ($0.23/d) per resident, whereas the average cost in the control group increased by €0.58/d ($0.75/d) per resident (difference in daily average prescribed medication cost between baseline and 12 months).

Cost-utility analysis

The average total cost per resident was €1,225 ($1,571) for the intervention and €826 ($1,059) for the control group—an incremental cost of €399 ($512; p=.002), largely due to the difference in drug prescriptions at baseline. Average QALY scores were 0.565 for the intervention group and 0.566 for the control group—an incremental QALY score of –0.001 (p=.98), largely due to the difference in utility scores at baseline.

Table 2 shows the results for three scenarios of base case ICERs. For the raw ICER (first scenario), usual care dominated pharmacotherapy follow-up because the intervention was more expensive and less effective than usual care. The adjusted ICERs were €3,899/QALY ($5,002/QALY) for the second scenario and €6,574/QALY ($8,433/QALY) for the third scenario. Nonparametric bootstrapping was used to analyze the uncertainty of these results.

For the first scenario, most of the plotted points are located in the upper-left quadrant of the cost-effectiveness plane, characterized by higher-cost, less-effective interventions, and the upper-right quadrant, characterized by higher-cost, more-effective interventions. The acceptability curve shows that, if willingness to pay is €30,000/QALY ($38,487/QALY), the probability of the pharmacotherapy follow-up being more cost-effective than usual care, is 35%.

For the second scenario, most of the plotted points are located in the upper-right quadrant the cost-effectiveness plane. The acceptability curve shows that, if the willingness to pay is €30,000/QALY ($38,487/QALY), the probability of the pharmacotherapy follow-up being more cost-effective than usual care is 78%.

For the third scenario, the cost-effectiveness plane shows that most of the plotted points are located in the upper-right quadrant. The acceptability curve shows that, if the willingness to pay is €30,000/QALY ($38,487/QALY), the probability of the pharmacotherapy follow-up being cost-effective, compared to usual care, is 76%.

The distributions of the 1,000 replicates of the ICER, expressed in Euro and US dollars, on the cost-effectiveness plane are similar (higher proportional cost, same effectiveness). For this reason, Figure 3 shows the results expressed only in Euro.

Table 2. Cost, Quality-Adjusted Life Years (QALYs), and Incremental Cost-Effectiveness Ratio (ICER) (€/QALY and $/QALY) for Three Base Case Scenarios

	Intervention	Control	Group Difference (95% Conf. Interval) or ICER
Cost			
Raw, €	1,224.98 (1,062.34–1,387.62)	825.82 (641.32–1,010.32)	399.16 (150.01–648.31)
Raw, $	1,571.53 (1,362.88–1.780.18)	1,059.45 (822.75–1,296.14)	512.08 (192.45–831.71)
Average difference, €[b]	—	—	79.72 (–147.80–307.24)
Average difference, $[b]	—	—	102.27 (–189.61–394.16)
Average difference, €[c]	—	—	141.29 (–91.30–373.89)
Average difference, $[c]	—	—	181.27 (–117.13–479.66)
QALYs			
Raw	0.5655 (0.5212–0.6098)	0.5662 (0.5099–0.6225)	–0.0007 (–0.0697–0.0684)
Average difference[d]	—	—	0.0204 (–0.0247–0.0655)
Average difference[c]	—	—	0.0215 (–0.0234–0.0664)
ICER			
1st scenario, €/QALY[e]	—	—	Dominated
1st scenario, $/QALY[e]	—	—	Dominated
2nd scenario, €/QALY[f]	—	—	3,898.69
2nd scenario, $/QALY[f]	—	—	5,001.63
3rd scenario, €/QALY[g]	—	—	6,573.56
3rd scenario, $/QALY[g]	—	—	8,433.22

Exchange rate: 1 Euro=1.28 U.S. dollars.

[b]Adjusted for baseline prescribed medication.

[c]Adjusted for age, sex, drugs, health problems, taking herbs, and utility score.

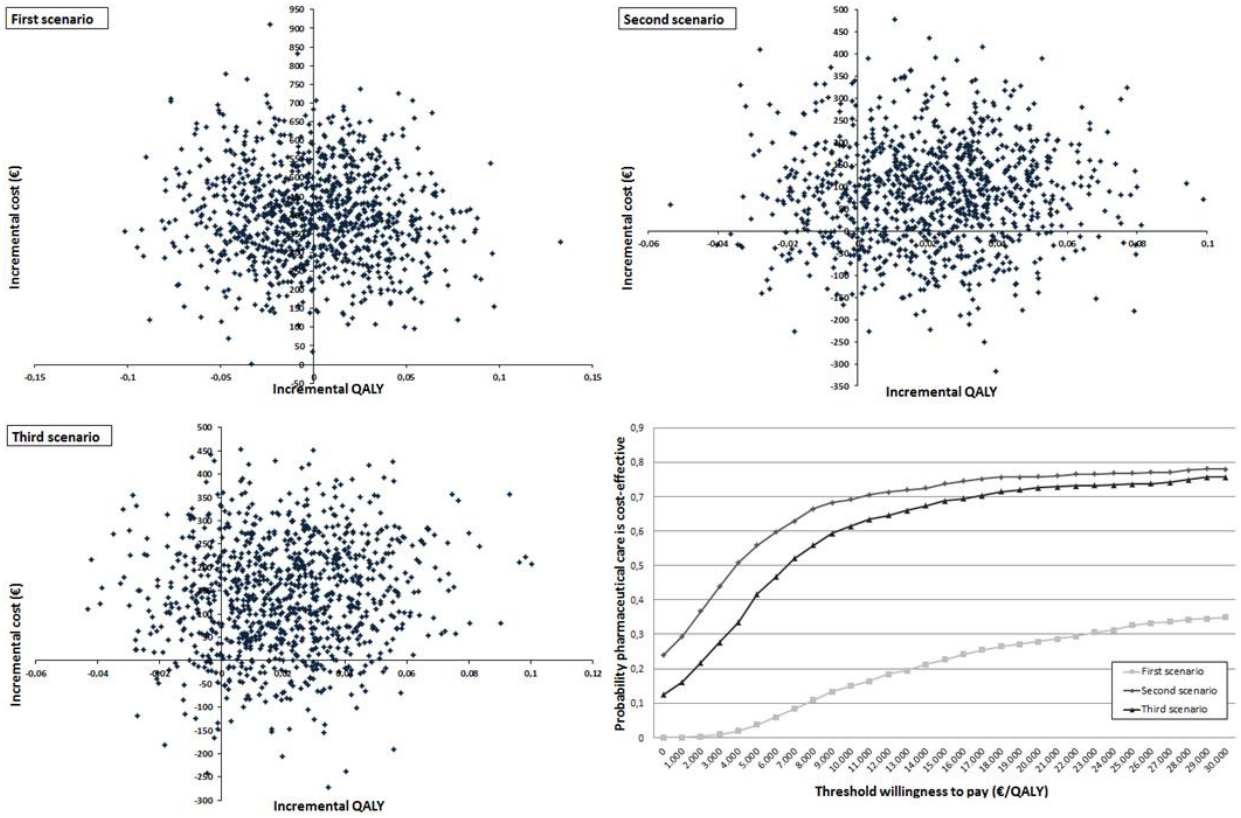
[d]Adjusted for utility score.

[e]Calculated by dividing difference in total costs by difference in QALYs between both groups.

[f]Calculated by dividing difference in total costs adjusted for drugs between intervention and control group by difference in QALYs adjusted for utility score between both groups.

[g]Calculated by dividing difference in total costs adjusted for age, sex, drugs, health problems, taking herbs, and utility score between intervention and control group by the difference in QALYs adjusted for age, sex, drugs, health problems, taking herbs, and utility score between both groups.

Figure 3. Distribution of bootstrapped incremental cost-effectiveness ratio (n = 1,000) in the cost-effectiveness plane and acceptability curve based on willingness to pay for quality-adjusted life-year QALY for the three scenarios.



DISCUSSION

Elderly NH residents have many health problems and take many medications, which often involves the use of inappropriate drugs[25] and drug-related adverse events.[26] The expected increase in size of this population in Spain,[27] as in other developed countries, makes it important that interventions to improve the quality of life of elderly adults, such as pharmaceutical care services, which aim to optimize the prescription of drugs and avoid negative outcomes associated with medication, be developed.

In this study, general practitioners accepted 88.7% of pharmacist recommendations, and 86.2% of pharmacist interventions were implemented. These results show a higher percentage than pharmacist recommendations accepted by general practitioners (75.6% (565/747)) and accepted recommendations implemented (76.6% (433/565)) in a randomized controlled trial of clinical medication review by a pharmacist for elderly care homes residents in the United Kingdom over 6 months.[28]

Pharmacist interventions resolved an average of 1.2 negative outcomes associated with medication per participant during 12 months of follow-up. The Dader Method is effective for identifying negative outcomes associated with medication (known as drug-related problems in other studies) in NHs, as was shown in a hospital emergency department,[29–32] in a hospital,[33] and in the community.[34]

Pharmacists spent an average of 114 minutes in the pharmacotherapy follow-up, which resulted in a cost of €74 ($95) for the 12 months of the study, less than the $138 obtained in a similar study (2005 prices).[35]

The average number of prescribed medication increased in the control group by 0.94 drugs, increasing the average cost by €0.58/d ($0.75/d) per resident, whereas the average number of prescribed medication decreased in the intervention group by 0.47 drugs, saving an average of €0.18/d ($0.23/d) per resident. Similar pharmacist interventions have obtained higher savings. A previous study estimated an average saving of £0.70 per participant over 28 days of follow-up,[28] and another study estimated an average saving of $30.33 per participant per month.[36]

In a recent review, no intervention was found to optimize prescription for elderly care homes residents that measured quality of life.[9] In this study, pharmacotherapy follow-up was associated with less impairment in quality of life, although neither group of residents saw an improvement in their quality of life, measured using the EuroQol-5D. QALYs are a valid measure of health outcomes because they take into account morbidity and mortality in one figure that measures health in terms of years of life in good health. A high percentage of participants had several chronic diseases, which may explain the reduction in quality of life (using the EQ5D) in both groups. Using the NHP questionnaire, the intervention group had an improvement in quality of life in two of the six dimensions on the questionnaire, whereas the control group had no improvement in any dimension. These improvements in the dimensions of sleep and emotional reactions may be related to pharmaceutical interventions in anxiolytic medication (a type of medication that is common in elderly adults taking many medications).

With €30,000/QALY being the threshold for determining whether a health technology is cost-effective in Spain,[37] pharmaceutical care for elderly residents in NHs is more cost-effective than usual care. Three base case ICERs were estimated. In the first scenario (raw ICER), pharmaceutical care was a dominated intervention (higher cost and less effective than usual care), and the acceptability curve showed that there was much uncertainty because 35% of the bootstrap simulations were less than €30,000/QALY

($38,487/QALY). In the second scenario, the ICER was €3,899/QALY ($5,002/QALY), and the acceptability curve showed that there was little uncertainty because 78% of the bootstrap simulations were less than €30,000/QALY ($38,487/QALY). In the third scenario, the ICER was €6,574/QALY ($8,433/QALY), and the acceptability curve showed that there was little uncertainty because 76% of the bootstrap simulations were less than €30,000/QALY ($38,487/QALY). A previous study evaluated the cost-effectiveness of a pharmaceutical care intervention to reduce the number of prescriptions of inappropriate psychoactive medication in elderly NH residents in Northern Ireland, and the incremental cost-effectiveness ratio was –130.39/0.309 ($130.39 lower cost per resident and a difference in the proportion of residents receiving one or more inappropriate psychoactive drugs of 30.9 percentage points).[35]

This study has two limitations: nonrandom selection of the sample of elderly adults and noninclusion of certain costs related to the use of health resources, such as emergency visits or hospital admissions. The first limitation has been addressed by adjusting the results for the variables with significant differences. The second limitation concerns not adopting the perspective of the National Health System, recommended by the guidelines,[20,22] but considering a more restrictive perspective focusing on the variation in direct costs of medication and pharmacist time.

Despite these limitations, the study is important for several reasons. It strengthens the limited international evidence of the cost-effectiveness of pharmacotherapy follow-up (or pharmaceutical care, in general) for detecting negative outcomes associated with medication in NHs, and it is the first study of its kind conducted in Spain to suggest that this intervention strategy can be efficient for institutionalized elderly adults.

CONCLUSION

The results of this study suggest that pharmacotherapy follow-up is cost-effective for elderly residents in Andalusian NHs, although there is considerable uncertainty in these results. Pharmacotherapy follow-up is an effective intervention for optimizing prescribed medications and detecting negative outcomes associated with medication but not for improving the quality of life of institutionalized elderly adults, although it reduces spoilage.

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COST-UTILITY ANALYSIS OF A PHARMACOTHERAPY FOLLOW-UP FOR OLDER PEOPLE WITH POLYPHARMACY IN COMMUNITY PHARMACIES IN SPAIN

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ABSTRACT

The objective of this study was to estimate the incremental cost-effectiveness ratio (ICER) of a pharmacotherapy follow-up service for older people with polypharmacy in community pharmacies against the alternative of receiving usual pharmaceutical dispensation.

The study was designed as a longitudinal cluster randomized trial carried out over six months of follow-up. The target population consisted of older people with polypharmacy and the study was conducted in 178 community pharmacies in Spain. The analysis adopted the perspective of the National Health Service (NHS). It estimated all identifiable costs to the NHS and health outcome in quality-adjusted life years (QALYs). The ICERs were estimated for different scenarios, depending on the costs included in each (for the first four scenarios) or the adjust for baseline variables (for the fifth scenario). In order to analyze the uncertainty of ICER results, we performed a nonparametric bootstrapping with 5,000 replications. A total of 1,403 older people were enrolled, 688 in the intervention group (IG) and 715 in the control group (CG).

The average time employed by the pharmacist in the stages of the pharmacotherapy follow-up service was 443 minutes. Both groups reduced the average number of prescribed medications, although this reduction was greater in the IG (0.28 drugs; $p<0.001$) than in the CG (0.07 drugs; $p=0.063$).

As for the impact of pharmacotherapy follow-up on the consumption of health resources, in the IG there was a reduction in the percentage of patients who visited the accident and emergency (A&E) department and in hospital admissions compared to the months before the study. Amongst the elderly patients in the CG there was also a reduction in the number who visited the A&E department, although this was less pronounced than in the IG, while the percentage of older people who were admitted at least once to hospital was the same before and during the study. The elderly in the IG saw an improvement in their quality of life by 0.0528 in the utility score ($p<0.001$). In turn, the elderly in the CG saw a slight reduction in their quality of life by 0.0022 in the utility score ($p=0.815$). We obtained an ICER of €8,541.63/QALY and €6,777.39/QALY for the first and second scenario respectively, and a pharmacotherapy follow-up service as dominant strategy for the third, fourth and fifth scenario. For a willingness to pay of €30,000/QALY, the probability of the pharmacotherapy follow-up being cost-effective, compared to usual pharmaceutical dispensation, moves in a range between 97.5% and 99.9% for the five scenarios.

Pharmacotherapy follow-up is an effective intervention for optimizing prescribed medication and improving the quality of life of older people with polypharmacy in community pharmacies. The results from the cost-utility analysis suggest that pharmacotherapy follow-up is cost-effective.

INTRODUCTION

In 2013, 18% of the Spanish population were elderly,[1] conventionally defined as aged 65 or over. This percentage was higher in the female population, at 20% compared to 16% among the male population. As a result of population ageing, this percentage will represent 22% of the Spanish population over the next 10 years (20% for males and 24% for females).[2] Older people usually have many health problems and take a lot of medication and this often leads to the use of inappropriate drugs[3] and drug-related adverse events.[4]

Polypharmacy is a common phenomenon that increases with age, as well as the associated morbidity. Although there is a wide range of definitions and different situations associated with this phenomenon,[5] the most widespread approach is a comorbidity patient with more than five drugs.[6] Inappropriate polypharmacy is a particular concern in older people and is associated with negative health outcomes.

Medication is the most widely used healthcare technology for dealing with health problems. In Spain, public expenditure through official prescriptions in the National Health Service (NHS) totaled 9,183 million Euros in 2013.[7] Although this figure represents a 6% drop compared to the previous years' expenditure, such a high level of expenditure requires methods to ensure a rational use of medication, optimizing the results obtained from their use and guaranteeing the control of the health problems dealt with. Failures in effectiveness and safety have a cost for patients' health and a cost in terms of hospital admissions and accident and emergency (A&E) department visits, appointments with the general practitioner and pharmacological treatments.

Under the practice of pharmaceutical care,[8] different pharmaceutical professional services have been developed orientated towards patients in an attempt to optimize their pharmacotherapy.[9] This concept includes services with substantially different methodologies. One of these is pharmacotherapy follow-up, a service in which the pharmacist evaluates patients' pharmacotherapy and intervenes in collaboration with the general practitioner and the patients themselves, to ensure that therapeutic goals are achieved. One of the main points of the pharmacotherapy follow-up service is that it attempts to optimize pharmacotherapy, not just by focusing on the process of use of medication, but also by improving the clinical results produced by the medication in patients.

A review of interventions to improve the appropriate use of polypharmacy for older people concluded that interventions, such as pharmaceutical care, appear beneficial in terms of reducing inappropriate prescribing although it is unclear if these interventions

resulted in a clinically significant improvement.[10] According to this review, it is clear that when pharmacists play a proactive role in performing medication reviews and in the active education of other healthcare professionals, pharmacotherapy for older patients is improved. However, the evidence of the impact of pharmacists' interventions on health outcomes, quality of life or cost-effectiveness of care is mixed.[11] Few studies of pharmaceutical care programs for the elderly have undertaken a rigorous economic evaluation and a more standardized approach to data collection is required.[12]

The objective of this study was to estimate the incremental cost-effectiveness ratio (ICER) of a pharmacotherapy follow-up service for older people with polypharmacy in community pharmacies against the alternative of receiving usual pharmaceutical dispensation.

METHODS

Design study

The study was designed as a longitudinal cluster randomized trial carried out over six months of follow-up. It was conducted in community pharmacies in Spain from November 2011 to January 2013. The target population consisted of elderly people, aged 65 or over, with polypharmacy, who took five or more drugs.

We contacted 1,474 older people to ask them to participate in the study and 71 of these were excluded because they did not meet inclusion criteria: 28 patients were not old enough, 36 patients did not take five or more drugs and 7 patients had both conditions simultaneously (figure 1). Written informed consents were obtained from all patients before inclusion.

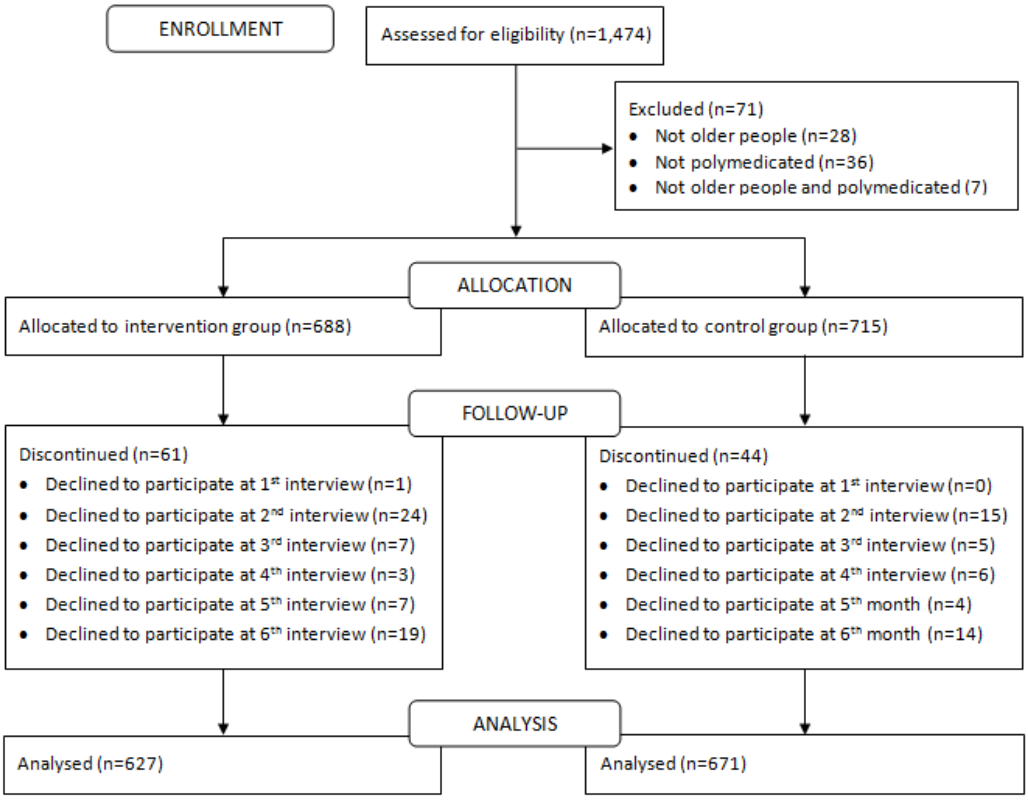

Figure 1 Process of older people enrolment, allocation, follow-up and analysis

The study was carried out taking into account the recommendations of the proposed guidelines for economic evaluation of health technologies in Spain.[13] The analysis adopted the perspective of the NHS. It estimated all identifiable costs to the NHS and health outcome in quality-adjusted life years (QALYs). The alternatives compared were:

- Intervention group (IG): older people who followed a pharmacotherapy follow-up service in community pharmacies

- Control group (CG): older people who received usual dispensation in community pharmacies.

Pharmacotherapy follow-up service

The Dader Method of pharmacotherapy follow-up was developed by the Pharmaceutical Care Research Group at the University of Granada, Spain.[14]

The aim of the pharmacotherapy follow-up service is to detect medication related problems, for the prevention and resolution of negative outcomes associated with medication.[15] In the context of this service it is important to differentiate conceptually

between the terms medication related problem and negative outcomes associated with medication.[16] A negative outcomes associated with medication is a result obtained in the patient's health which is not adequate for the aim of the pharmacotherapy, and which is associated or may be associated to the use of medications. In other words, it is a health problem which is not under control due to a failure in the pharmacotherapy.

The patients in the IG received the pharmacotherapy follow-up service following the methodology agreed upon by a group of pharmaceutical care experts.[17]

Table 1 Phases of the pharmacotherapy follow-up service

Stage	Description
First interview	Patients took all the medication they were taking to the pharmacy and the pharmacist asked them a series of questions to obtain information about their health problems, clinical information about the control of health problems, drugs used by patients at the time of the interview, guidelines prescribed for the prescribed medication by the general practitioner and guidelines followed for all drugs.
Elaboration of the situation state	The pharmacist processed the information obtained from patients during the interviews and corresponding to the patients' situation at the date on which the interview was conducted.
Study phase	The pharmacist searched for information in the knowledge database of the General Council of Pharmaceutical Associations of Spain (Bot PLUS),[18] and in other sources of information (clinical practice guides, books, therapy manuals etc.) to enable them to identify the medication related problems and negative outcomes associated with medication.
Evaluation Phase	The pharmacist described the medication related problems and negative outcomes associated with medication identified in the patient.
Definition of the action plan	The pharmacist agreed with patients on certain therapeutic objectives to be reached with the pharmacotherapy and proposed interventions with patients and/or the general practitioner to prevent, resolve or improve the identified medication related problems and negative outcomes associated with medication.
Intervention phase	The pharmacist went through with the action plan interventions.
Follow-up to ascertain the level of acceptance of the interventions and evaluate their results.	The pharmacist obtained information about the acceptance or non-acceptance of the proposed interventions by those affected (general practitioners and/or patients). After this, the pharmacist obtained clinical information about patients' health problems (negative outcomes associated with medication) and about the elements of the process of use of the drugs (medication related problems) and repeated the process described for the pharmacotherapy follow-up service.
Additional contacts	Additional contacts with the patient related to the provision of pharmacotherapy follow-up service

Community pharmacies

The study was performed in 178 community pharmacies in four Spanish provinces: 64 in Guipúzcoa (34 in IG vs 30 in CG), 42 in Granada (24 in IG vs 18 in CG), 39 in Santa

Cruz de Tenerife (16 in IG vs 23 in CG) and 33 in Las Palmas de Gran Canarias (14 in IG vs 19 in CG).

The number of patients assigned in each province was: 525 in Guipúzcoa (278 in IG vs 247 in CG), 324 in Granada (194 in IG vs 130 in CG), 307 in Santa Cruz de Tenerife (115 in IG vs 192 in CG) and 247 in Las Palmas de Gran Canarias (101 in IG vs 146 in CG).

Control group

The older people in the CG received usual pharmaceutical dispensation in the community pharmacies. Health-related quality of life questionnaires were administered in six interviews between the beginning and the end of the study. Medication prescribed was extracted from community pharmacy databases. Information on the use of healthcare resources during the study was extracted from hospital information system databases for each province.[19-21]

Health-related quality of life

Health-related quality of life was measured by the Spanish version of the EuroQol-5D-3L questionnaire.[22] The EuroQol-5D describes health status in terms of five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), each of these is defined with three levels of severity. The scores were used to estimate a utility score, one single index on health-related quality of life ranging between 1 and 0, where 1 is the best possible state of health and 0 is death. However, there were also negative utility scores because some states of health are considered to be worse than death. A visual analogue scale was used to measure the subjects' health status with scores whereby one end of the scale ranks the 'worst' (0) and the other the 'best' (100) health state.

Costs

We measured costs of the prescribed medication, the time employed by the pharmacist, the A&E department visits, the hospital admissions and the investment in the pharmacy. It presented costs in Euros at 2014 prices. Prices from previous years were updated by the Spanish consumer price index.[23] The following variables were included in the analysis:

- Medication cost, excluding additional medication associated with hospitalizations, was obtained from the official drug price.[24]

- Time employed by the pharmacist in each stage of the pharmaceutical follow-up programme. To measure labour costs we took into account both aspects of the

pharmacist (professional category and years of experience)[25] and of the pharmacy (province and annual turnover), which have a significant influence on the value of this variable, thereby improving the reliability of this figure. This cost was estimated by a pharmaceutical care expert group.[26]

- A&E department visit costs were calculated according to public prices.[27]

- Hospital admission costs were calculated according to public prices of the diagnosis-related groups (DRGs).[28] In order to analyse the impact of the pharmacotherapy follow-up intervention, three experts in the field evaluated the causes of hospital admissions independently. They had to identify hospital admissions related to negative outcomes associated with medication that could have been avoided with pharmacotherapy follow-up.

- The investment required to launch the pharmacotherapy follow-up in community pharmacies and its subsequent maintenance over time was estimated by a pharmaceutical care expert group.[26] To calculate the cost, we assumed: a mean of 2,500 customers per pharmacy; 16% of customers may be older people with polypharmacy; 60% of older people with polypharmacy would accept the pharmacotherapy follow-up service.

Statistical methodology

The differences between groups and subgroups in terms of average healthcare utilization, professionals' intervention, costs and QALYs were calculated using parametric tests.

Cost-utility analysis

A cost-utility analysis compared pharmacotherapy follow-up with the alternative of usual pharmaceutical dispensation. The effectiveness of the intervention was estimated as QALYs. The QALYs were calculated by using an area under the curve analysis, with linear interpolation of utility scores between baseline and six months of follow-up.[29]

Cost and QALYs were estimated for each older person. Results of cost-utility analysis were expressed in terms of the ICER, calculated by dividing the difference in total costs between the intervention and CG by the difference in QALYs between both groups.[30] The ICERs were estimated for different scenarios depending on the costs included in each:

- First scenario: including costs for the prescribed medication, pharmacist intervention and required investment in the pharmacy.

- Second scenario: including costs for the prescribed medication, pharmacist intervention, required investment in the pharmacy and A&E department visits.

- Third scenario: including costs for the prescribed medication, pharmacist intervention, required investment in the pharmacy, A&E department visits and hospital admissions.

- Fourth scenario: including costs for the prescribed medication, pharmacist intervention, required investment in the pharmacy, A&E department visits and hospital admissions related with negative outcomes associated with medication.

- Fifth scenario: taking into account the differences in the drug prescriptions and the basal utility scores, we used the costs adjusted for baseline drug use and QALYs adjusted for baseline utility score.

Because the time horizon of the study did not extend beyond 12 months, discounting of costs and QALYs was not necessary. In order to analyze the uncertainty of ICER results, we performed a nonparametric bootstrapping with 5,000 replications.[31] The resulting 5,000 ICER replicates were plotted on the cost-effectiveness plane and used to construct a cost-effectiveness acceptability curve.

The cost-effectiveness plane is a graphical way of presenting cost-effectiveness results, with the difference in costs on the vertical axis and the difference in health benefits on the horizontal axis.[32] Since incremental costs and health benefits can both be either positive or negative, there are four possible combinations, which are reflected in the four quadrants of the cost-effectiveness plane:

- Upper-left quadrant: intervention less effective and more costly than comparator.
- Lower-left quadrant: intervention less effective and less costly than comparator.
- Upper-right quadrant: intervention more effective and more costly than comparator.
- Lower-right quadrant: intervention more effective and less costly than comparator.

The acceptability curve represents the proportion of simulations in which the intervention is considered cost-effective over a range of values of the threshold cost-per-QALY.[33] Analyses were carried out in STATA software version 12.

RESULTS

A total of 1,403 older people were enrolled, 688 in the IG and 715 in the CG. Table 2 shows the sociodemographic characteristics of the participants.

Table 2 The socio-demographic characteristics of the older people

	Intervention	Control	P value
Age	75.36 ± 6.48	74.91 ± 6.58	0.195
Female	409 (60.1)	441 (61.7)	0.535
Living with couple	355 (59.8)	384 (59.3)	0.856
Not education	149 (27.0)	116 (18.6)	0.001
Drugs	7.74 ± 2.50	7.39 ± 2.37	0.009
A&E department visits	193 (28.1)	211 (29.5)	0.547
Hospital admissions	44 (6.4)	31 (4.3)	0.086
Mobility problems	1 (0.1)	12 (1.7)	0.003
Self-care problems	11 (1.6)	13 (1.8)	0.754
Usual activities problems	24 (3.5)	25 (3.5)	0.998
Pain/discomfort problems	99 (14.4)	122 (17.1)	0.173
Anxiety/depression problems	36 (5.2)	51 (7.1)	0.142
Visual analogue scale	64.98 ± 18.55	62.95 ± 19.64	0.049

Data are present as average ± SD or n (%).

Both groups of older people had similar characteristics except in the level of education (27% in the IG and 18.6% in the CG had not completed compulsory education; p=0.001) and the average consumption of drugs (7.74 drugs in the IG and 7.39 drugs in the CG; p=0.009).

The percentage of older people who perceived very severe problems in different dimensions of their health state was low, with the exception of the pain/discomfort dimension: 0.9% in mobility (0.1% in the IG and 1.7% in the CG; p=0.003), 1.7% in self-care (1.6% in the IG and 1.8% in the CG), 3.5% in usual activities (3.5% in the IG and 3.5% in the CG), 15.8% in pain/discomfort (14.4 in the IG and 17.1% in the CG) and 6.2% in anxiety/depression (5.2% in the IG and 7.1% in the CG). However, significant differences were detected in their health status, measured by the VAS (64.98 in the IG and 62.95 in the CG; 0.049).

EuroQol-5D scores and prescribed medication were missing for 105 older people during the study. These participants were excluded from the following results.

Pharmacotherapy follow-up intervention time

The average time employed by the pharmacist in the stages of the pharmacotherapy follow-up service was 442.74 ± 652.24 minutes: 44.57 ± 29.77 minutes in the first interview; 40.26 ± 34.24 minutes for writing the situation state; 75.44 ± 87.26 minutes in the study phase; 39.05 ± 40.60 minutes in the evaluation phase; 29.93 ± 36.76 minutes in the therapeutic plan; 17.83 ± 21.67 minutes in the intervention phase; 162.47 ± 496.03 minutes for follow up; and 33.19 ± 36.34 minutes for additional contacts.

Prescribed medication

Both groups reduced the average number of prescribed medications (Table 3), although this reduction was greater in the IG (0.28 drugs; p<0.001) than in the CG (0.07 drugs; p=0.063). The difference in the observed reduction between the two groups was 0.21 drugs (p=0.001).

Table 3 Evolution of average prescribed medication

	Intervention	Control	P value
1st interview	7.76 ± 2.51	7.32 ± 2.32	0.001
2nd interview	7.68 ± 2.45	7.27 ± 2.41	0.002
3rd interview	7.62 ± 2.45	7.26 ± 2.34	0.007
4th interview	7.54 ± 2.45	7.24 ± 2.36	0.025
5th interview	7.50 ± 2.40	7.26 ± 2.36	0.065
6th interview	7.48 ± 2.39	7.25 ± 2.40	0.096
Difference 1st to 6th	-0.28 ± 1.25	-0.07 ± 0.95	0.001

Data are present as average ± SD.

Healthcare resources

Both groups experienced a reduction in the percentage of patients with at least one visit to the A&E department during the six months before and the six months of the study, although this reduction was greater in the IG (27.9% in pre-study vs 14.2% in study; difference 13.7%; p<0.001) compared to the CG (29.1% in pre-study vs 24.9% in study; difference 4.2%; p=0.044).

Following the same trend, the mean number of visits to the A&E department during the six months before and the six months of the study dropped in both groups, although this reduction was greater amongst elderly patients who received pharmacotherapy follow-up services (0.43 ± 0.83 visit in pre-study vs 0.19 ± 0.51 visit in study; difference 0.24; p<0.001) compared to the elderly patients in the CG (0.55 ± 1.55 visits during pre-study vs 0.42 ± 1.21 visits during study; difference 0.13; p<0.001).

As for hospital admissions, the percentage of older people with at least one hospital admission during the six months before and the six months of the study dropped among the patients of the IG (6.9% in pre-study vs 4.1% in study; difference 2.8%; p<0.001), while this percentage increased among the elderly in the CG (4.3% in pre-study vs 5.1% in study; difference 0.8%; p=0.044).

Continuing with this tendency, the mean number of hospital admissions during the six months before and the six months of the study dropped among the elderly who received the pharmacotherapy follow-up services (0.09 ± 0.35 visits in pre-study vs 0.05 ± 0.23 visits in study; difference 0.04; p=0.007) and increased amongst the elderly

in the CG (0.05 ± 0.25 hospitalization during pre-study vs 0.07 ± 0.36 hospitalization during study; difference 0.02; p=0.106).

After the group of experts had reviewed the cause of each hospital admission, the percentage of older people with at least one hospital admission dropped to 3.2% in the IG and 4.3% in the CG (p=0.285), with a mean of hospital admissions during the six months of the study of 0.03 ± 0.19 in the IG and 0.06 ± 0.31 in the CG.

Health-related quality of life

Table 4 shows the average utility scores and VAS scores obtained from the EuroQol-5D questionnaire at the six interviews.

The elderly in the IG saw an improvement in their quality of life between the start and finish of the study by 0.0528 in the utility score (p<0.001) and 4.97 in VAS score (p<0.001). In turn, the elderly in the CG saw a slight reduction in their quality of life between the start and finish of the study by 0.0022 in the utility score (p=0.815) and 0.90 in VAS score (p=0.127). The difference observed between both groups was 0.0550 in the utility score (p<0.001) and 5.87 in the VAS score (p<0.001).

Table 4 Evolution of average utility score and VAS scores

	Intervention	Control	P value
1st utility score	0.7148 ± 0.28	0.6953 ± 0.31	0.238
2nd utility score	0.7327 ± 0.28	0.7109 ± 0.31	0.184
3rd utility score	0.7425 ± 0.27	0.6969 ± 0.32	0.006
4th utility score	0.7490 ± 0.28	0.7031 ± 0.32	0.006
5th utility score	0.7563 ± 0.27	0.6871 ± 0.34	<0.001
6th utility score	0.7677 ± 0.27	0.6931 ± 0.32	<0.001
Difference 1st to 6th	0.0528 ± 0.20	-0.0022 ± 0.24	<0.001
1st Visual analogue scale	65.44 ± 18.07	63.22 ± 19.42	0.034
2nd Visual analogue scale	66.05 ± 17.85	63.25 ± 18.55	0.006
3rd Visual analogue scale	67.11 ± 17.22	62.72 ± 18.75	<0.001
4th Visual analogue scale	67.19 ± 17.34	63.07 ± 18.55	<0.001
5th Visual analogue scale	68.20 ± 17.32	61.86 ± 19.52	<0.001
6th Visual analogue scale	70.46 ± 17.06	62.29 ± 19.20	<0.001
Difference 1st to 6th	4.97 ± 15.29	-0.90 ± 15.19	<0.001

Data are present as average ± SD.

On the basis of this data, we calculated the QALY corresponding to the six months of study. The average QALY scores were 0.3721 ± 0.12 and 0.3488 ± 0.15 for the IG and CG respectively, resulting in an incremental QALY score of 0.0233 (p=0.002) largely due to the difference in utility scores at baseline.

Costs

The total cost included the estimation of the prescribed medication, the time employed by the pharmacist, the healthcare utilization and the investment in the pharmacy.

An average cost of €184.50 ± 271.82 was estimated for the time taken in the pharmacists' interventions. The average cost related to prescribed medication for the 6 months of follow-up was €655.91 ± 818.53 for the IG and €657.67 ± 600.09 for the CG. The IG saw a reduction in the mean daily cost of prescribed medication between the start and finish of the study, while the CG experienced a slight increase in the mean cost of prescribed medication (Table 5). Pharmacists' interventions saved an average medication cost of €0.17/day (p=0.057) while in the CG there was an increase in the average cost by €0.02/day (p=0.774). The difference in the reduction observed between both groups was of €0.20/day (p=0.079).

Table 5 Evolution of average prescribed medication cost.

	Intervention	Control	P value
1st interview	3.72 ± 4.96	3.62 ± 3.29	0.654
2nd interview	3.61 ± 4.52	3.61 ± 3.38	0.996
3rd interview	3.62 ± 4.58	3.63 ± 3.41	0.968
4th interview	3.57 ± 4.52	3.64 ± 3.44	0.752
5th interview	3.61 ± 4.53	3.68 ± 3.47	0.745
6th interview	3.55 ± 4.50	3.64 ± 3.46	0.705
Difference 1st to 6th	-0.18 ± 2.38	0.02 ± 1.68	0.079

Data are present as average ± SD.

The patients in the CG presented a greater consumption of health resources, both in terms of visits to the A&E department and hospital admissions.

The average A&E department visit cost was €33.05 ± 90.98 for the TG and €74.18 ± 213.93 for the CG (difference of €41.12; p<0.001), and the average hospitalization cost was €215.52 ± 1,263.93 for the TG and €496.79 ± 3,720.07 for the CG (difference of €281.27; p=0.065). After excluding admissions for causes not related to negative outcomes associated with medication, the average hospitalization cost was €173.99 ± 1,184.95 for the TG and €441.60 ± 3,573.71 for the CG (difference of €267.61; p=0.067). The average healthcare cost was €248.58 ± 1,285.76 for the TG and €570.97 ± 3,765.75 for the CG (difference of €322.40; p=0.037), and after excluding admissions for causes not related to negative outcomes associated with medication €207.04 ± 1,207.20 for the TG and €515.77 ± 3,621.15 for the CG (difference of €308.73; p=0.037).

Finally, the average cost estimated as the required investment was €4,688.47 for a period of 5 years and an average annual maintenance cost of €2,967.02, resulting an average cost €16.27 per older people.

Cost-utility analysis

Table 6 shows the results from cost-utility analysis based on 5,000 bootstrap replications for each scenario. We obtained an ICER of €8,541.63/QALY and €6,777.39/QALY for the first and second scenario respectively, and a pharmacotherapy follow-up service as dominant strategy for the third, fourth and fifth scenario.

For the first and second scenario, 99.9% of the bootstrap simulations are located in the upper-right quadrant of the cost-effectiveness plane. For the third, fourth and fifth scenarios, most of the bootstrap simulations are located in the lower-right quadrant (75.1%, 72.6% and 77.3% respectively) and in the upper-right quadrant (24.8%, 27.3% and 22.7%) of the cost-effectiveness plane (Table 6).

Table 6 Cost-utility analysis based on 5,000 bootstrap replications

Scenarios	Cost (€)			QALY			ICER (€/QALY)	Cost-effectiveness plane[a]			
	Intervention	Control	Difference (95% CI)	Intervention	Control	Difference (95% CI)		U-L	L-L	U-R	L-R
1st scenario	856.69	657.67	199.02 (133. 80 to 301.78)	0.3721	0.3488	0.0233 (0.009 to 0.038)	8,541.63	0.1	0	99.9	0
2nd scenario	889.73	731.85	157.89 (87.40 to 260.79)	0.3721	0.3488	0.0233 (0.009 to 0.038)	6,777.39	0.1	0	99.9	0
3rd scenario	1,105.26	1,228.64	-123.38 (-440.46 to 204.57)	0.3721	0.3488	0.0233 (0.009 to 0.038)	Dominant	0	0.1	24.8	75.1
4th scenario	1,063.73	1,173.44	-109.71 (-413.51 to 206.00)	0.3721	0.3488	0.0233 (0.009 to 0.038)	Dominant	0	0.1	27.3	72.6
5th scenario	-	-	-126.34 (-419.71 to 177.91)	-	-	0.0156 (0.008 to 0.023)	Dominant	0	0	22.7	77.3

[a] Represented the percentage of the bootstrap simulations that are located in the different quadrants of the cost-effectiveness plane.

U-L: Upper-left quadrant; L-L: Lower-left quadrant; U-R: Upper-right quadrant; L-R: Lower-right quadrant.

The acceptability curve shows that if the willingness to pay is €30,000/QALY, the probability of the pharmacotherapy follow-up being cost-effective, compared to usual pharmaceutical dispensation, is 97.5% for the first scenario, 98.2% for the second scenario, 99.8% for the third scenario, 99.8% for the fourth scenario and 99.9% for the fifth scenario (Figure 2).

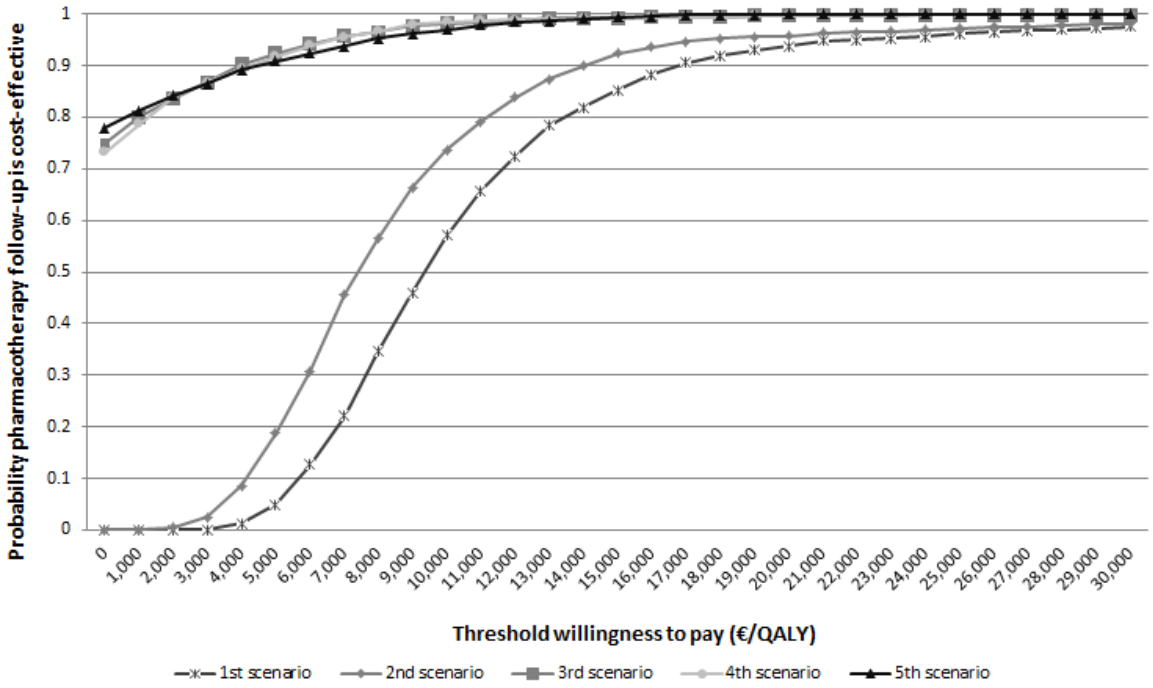

Figure 2 The acceptability curve based on willingness to pay for QALY for the five scenarios

DISCUSSION

The morbidity and mortality related to medication represents an important health problem which is particularly significant among the elderly. This study suggests that pharmacotherapy follow-up performed in pharmacies by pharmacists is an efficient technology for tackling a health problem which is gaining prevalence in increasingly ageing societies.

Pharmacists spent an average of 443 minutes in the pharmacotherapy follow-up which resulted in a cost of €184 for the six months of the study. If the pharmacotherapy follow-up were extended to one year, only the follow-up and additional contacts phases would have to be extrapolated to annual values. Pharmacists dedicated a mean of 199 minutes in the initial phases of the service: interview, situation state, study phase and evaluation phase. These periods of time indicate that the phases of the pharmacotherapy follow-up service were conducted with attention and rigour. In turn, the time employed in the implementation of the

interventions was less than that registered in the previous phases, which seems to point to adequate interaction with other health professionals.

Pharmaceutical care appears beneficial in terms of reducing inappropriate prescribing.[34] However, the aim of the pharmacotherapy follow-up is not to reduce the consumption of medication used by the patient, but to improve the clinical results associated to the use of these drugs. To achieve this objective, the pharmacist who performs the pharmacotherapy follow-up proposes the interventions s/he considers most appropriate for each patient, which does not necessarily mean adding or withdrawing drugs. It is logical, therefore, that the number of drugs is only reduced in a few cases.

The effectiveness of services which are similar to pharmacotherapy follow-up show contradictory results in relation to their effect on the number of drugs.[35] In this study, we saw a drop in the number of drugs in both groups, although this tendency was greater among the patients from the IG (0.28 drugs; $p<0.001$) than in the CG (0.07 drugs; $p=0.063$). In a recent study of a pharmacotherapy follow-up for elderly nursing home residents in Spain,[36] pharmacist interventions reduced the average number of prescribed medications by 0.47 drugs ($p<0.001$), whereas the average number of prescribed medications increased by 0.94 drugs in the CG ($p<0.001$). Participants were residents aged 65 but their health state was worse than in this study, and this may explain why that intervention was more effective in optimizing prescribed medication.

As for the impact of pharmacotherapy follow-up on the consumption of health resources, in the IG there was a reduction in the percentage of patients who visited A&E departments and in hospital admissions compared to the months before the study. Amongst the elderly patients in the CG there was also a reduction in the number who visited the A&E departments, although this was less pronounced than in the IG, while there was an increase in the percentage of patients who were admitted at least once to hospital. However, after reviewing the causes of the hospital admissions and ruling out those that could not have been avoided with this intervention, the percentage of older people who were admitted at least once to hospital was the same before and during the study.

The results of this study point to a positive effect of pharmacotherapy follow-up on health-related quality of life. Patients who received the pharmacotherapy follow-up service benefitted from a significant increase in their quality of life, measured using the EuroQol-5D-3L questionnaire. One possible explanation for this could be related to the high level of contact between the patient and pharmacist during the implementation of the pharmacotherapy follow-up service; this was higher than usual contact with other services and could have had a greater impact on the quality of life perceived by the patient.

Furthermore, it is logical that better control of health problems is going to be reflected in an improvement in quality of life. In contrast, this improvement was not mirrored in the elderly patients in the CG where there was a decrease in their health-related quality of life.

With €30,000/QALY being the threshold for determining whether a health technology is cost-effective in Spain,[37] we can state that pharmacotherapy follow-up for older people with polypharmacy in community pharmacies is cost-effective compared to usual pharmaceutical dispensation. We estimated five scenarios for ICERs. For the first and second scenario, the ICER was €8,542/QALY and €6,777/QALY and the acceptability curve showed that there was little uncertainty, due to the fact that 97.5% and 98.2% of the bootstrap simulations were below €30,000/QALY respectively. For the third, fourth and fifth scenario, pharmaceutical care was a dominant intervention (less costly and more effective than usual pharmaceutical dispensation) and the acceptability curve showed that there was little uncertainty, due to the fact that 99.8%, 99.8% and 99.9% of the bootstrap simulations were below €30,000/QALY respectively.

Jódar-Sánchez et al.[36] evaluated the cost-effectiveness of a pharmacotherapy follow-up service for elderly residents in nursing homes in Spain, obtaining an adjusted ICER of €6,574/QALY (in the more realist scenario). The worse result obtained in this study may be because, rather than adopting the perspective of the NHS, it considered a more restrictive perspective focusing on the variation in direct costs of medication and pharmacists' time.

The main limitation of this study was the non-random selection of the sample of elderly patients. The randomization of the pharmacies instead of patients (design by cluster) was intended to ensure that the same pharmacist did not have patients from both the IG and the CG which could have led to problems of selection bias, ethical conflicts and potential problems of contamination between groups in some pharmacies.

Despite this limitation, the study is important for several reasons. It strengthens the limited international evidence on the cost-effectiveness of pharmacotherapy follow-up service (or pharmaceutical care, in general) for improving the appropriate use of polypharmacy and detecting negative outcomes associated with medication for older people in community pharmacies.

In Spain this type of service is not offered by the NHS or any regional health service of the autonomous regions. And yet the results of the study suggest high social benefits, particularly in relation to the number of potentially avoided hospital admissions. The incorporation of this health technology into the portfolio of services offered by the Spanish NHS or other health services committed to a universal system open to all citizens,

constitutes an option which political decision-makers should value highly due to its potential to improve the efficiency of the treatment of older people with polypharmacy. This is a health problem which will inevitably grow in importance as population ageing becomes more of a problem in most developed countries.

CONCLUSION

Pharmacotherapy follow-up is an effective intervention for optimizing prescribed medication and improving the quality of life of older people with polypharmacy in community pharmacies. The results from the cost-utility analysis suggest that pharmacotherapy follow-up is cost-effective.

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CONFLICT OF INTEREST

The authors have no financial or any other kind of personal conflicts with this paper.

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CONCLUSIONES

- La puesta en marcha del servicio integral de telemonitorización aplicado a pacientes mayores de 65 años con EPOC muy evolucionada y con indicación de oxigenoterapia domiciliaria continua ha sido técnicamente factible. El modelo híbrido constituido por la plataforma de telemonitorización, el gestor de casos y el especialista en neumología es efectivo para detectar exacerbaciones y emitir una respuesta clínica de manera urgente. No se ha observado mejoras significativas en calidad de vida ni en el consumo de recursos sanitarios, si bien se aprecia una reducción en las visitas a urgencias, que para este colectivo es la antesala del ingreso hospitalario. Se ha obtenido un elevado nivel de satisfacción en los pacientes telemonitorizados y los profesionales clínicos.
- El servicio integral de telemonitorización aplicado a pacientes mayores de 65 años con EPOC muy evolucionada y con indicación de oxigenoterapia domiciliaria continua no es una intervención coste-efectiva comparada con la alternativa de recibir atención sanitaria habitual. Aunque este servicio integral de telemonitorización puede considerarse una intervención coste-efectiva para los pacientes sin comorbilidad, existe una considerable incertidumbre en los resultados por lo que se recomienda la realización de más estudios.
- El servicio de seguimiento farmacoterapéutico es una intervención efectiva para optimizar la medicación prescrita y detectar resultados negativos asociados a la medicación en personas mayores de 65 años institucionalizadas, aunque no se observa mejoras de la calidad de vida. Aunque el servicio de seguimiento farmacoterapéutico es una intervención coste-efectiva comparada con la alternativa de recibir asistencia sanitaria habitual, existe una considerable incertidumbre en los resultados por lo que se recomienda la realización de más estudios.
- El servicio de seguimiento farmacoterapéutico es una intervención efectiva para optimizar la medicación prescrita y mejorar la calidad de vida de las personas mayores de 65 años polimedicadas en el ámbito de las farmacias comunitarias. El servicio de seguimiento farmacoterapéutico es una intervención coste-efectiva comparada con la alternativa de recibir dispensación farmacéutica habitual.