Universitat Autònoma de Barcelona

ANÁLISIS DE LOS SISTEMAS DE AYUDA EN LA TOMA DE DECISIONES FARMACOTERAPÉUTICAS DE LA ESTACIÓN CLÍNICA DE ATENCIÓN PRIMARIA DE CATALUÑA DURANTE LOS AÑOS 2016, 2017 Y 2018: MEJORA DE LA SEGURIDAD EN EL USO DE MEDICAMENTOS

M.Àngels Pons Mesquida

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ANÁLISIS DE LOS SISTEMAS DE AYUDA EN LA TOMA DE DECISIONES FARMACOTERAPÉUTICAS DE LA ESTACIÓN CLÍNICA DE ATENCIÓN PRIMARIA DE CATALUÑA DURANTE LOS AÑOS 2016, 2017 Y 2018: MEJORA DE LA SEGURIDAD EN EL USO DE MEDICAMENTOS.

Memoria presentada por M.Àngels Pons Mesquida,
para la obtención del título de Doctora en Farmacologia Clínica por la Universitat Autònoma de Barcelona.

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Barcelona, 2022

Departament de Farmacologia, de Terapèutica i de Toxicologia

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El Dr. Eduard Diogène Fadini, professor titular del Departament de Farmacologia, de Terapèutica i de Toxicologia de la Universitat Autònoma de Barcelona,

CERTIFICA: Que la present tesi doctoral, presentada per M.Àngels Pons Mesquida, amb títol "Análisis de los sistemas de ayuda en la toma de decisiones farmacoterapéuticas de la estación clínica de atención primaria de Cataluña durante los años 2016, 2017 y 2018: mejora de la seguridad en el uso de medicamentos", ha estat realitzada sota la seva direcció.

I, per a què consti als efectes oportuns, signa el present certificat a Barcelona, 12 de maig de 2022.

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CERTIFICA: Que la present tesi doctoral, presentada per M.Àngels Pons Mesquida, amb títol "*Análisis de los sistemas de ayuda en la toma de decisiones farmacoterapéuticas de la estación clínica de atención primaria de Cataluña durante los años 2016, 2017 y 2018: mejora de la seguridad en el uso de medicamentos*", ha estat realitzada sota la seva co-direcció.

I, per a què consti als efectes oportuns, signa el present certificat a Barcelona, 11 de maig de 2022.

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Memòria presentada per M. Àngels Pons Mesquida per optar al grau de Doctora en Medicina i Cirurgia per la Universitat Autònoma de Barcelona.

El treball "Análisis de los sistemas de ayuda en la toma de decisiones farmacoterapéuticas de la estación clínica de atención primaria de Cataluña durante los años 2016, 2017 y 2018: mejora de la seguridad en el uso de medicamentos" ha estat realitzat al Departament de Farmacologia, de Terapèutica i de Toxicologia, sota la Direcció del Dr. Eduard Diogène Fadini i el Dr. Albert Jesús Figueras Suñé

Barcelona, 12 de maig de 2022

Doctorand

M. Àngels Pons Mesquida

AGRADECIMIENTOS

Llegar a poder presentar la tesis doctoral ha sido un camino largo y laborioso, que ha sido posible gracias a distintas personas que me han ido acompañado en el trayecto. A todos ellos, gracias.

A mi director de tesis desde los inicios, el Dr. Eduard Diogène, a quien aprecio enormemente, quiero expresarle mi especial agradecimiento por su confianza, por su templanza, por su ilusión, por su apoyo en todo momento y por hacerme ver que era posible llegar a presentar la tesis doctoral a partir de mi trabajo profesional diario.

A mi co-director de tesis, el Dr. Albert Figueras, a quien deseo expresarle mi gratitud por su estímulo continuo durante la elaboración de la tesis, por su positivismo en los momentos de dificultades, por sus siempre acertadas aportaciones, por ayudarme a que esta tesis finalice con éxito.

A Míriam Oms, actual responsable de la Unidad de Coordinación y Estrategia del Medicamento del ICS, quiero agradecerle su apoyo y confianza continua, siempre animándome, facilitándome el camino y realizando enriquecedoras aportaciones en los artículos publicados.

Y, indudablemente, a mi familia, por hacerme feliz. A Eduardo, mi marido, por estar siempre a mi lado en las risas y en los llantos, por apoyarme día a día, por hacerme la vida más fácil y por formar un gran equipo conmigo. A mi hijo Hugo y a mi futuro hijo Tiago, que son y serán los responsables de incrementar nuestra felicidad. A mi padre, que aun no estando presente, siempre me da fuerzas para superar las dificultades que se presentan en la vida, y a mi madre y a mi hermano, por estar siempre cerca dispuestos a ayudar.

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LISTADOA ABREVIATURAS

AE:	Atención Especializada
AEMPS:	Agencia Española de Medicamentos y Productos Sanitarios
AINE:	Antiinflamatorio No esteroideo
AP:	Atención Primaria
ATC:	Clasificación Anatómica Terapéutica
CIE-10:	Clasificación Internacional Enfermedades
DPO:	Dirección Por Objetivos
EAM:	Efecto Adverso a Medicamento
EAP:	Equipo de Atención Primaria
ECAP:	Estación Clínica Atención Primaria
HCE:	historia Clínica Electrónica
IA:	Inteligencia Artificial
ICS:	Institut Català de la Salut
ISRA:	Inhibidores Sistema Renina Angiotensina
MHDA:	Medicamentos Hospitalarios de Dispensación Ambulatoria
PLN:	Procesamiento de Lenguaje Natural
PRM:	Problema Relacionado con Medicación
SADC:	Sistema de Ayuda a la Toma de Decisiones
SNOMED CT:	Systematized Nomenclature of Medicine- Clinica Terms
TIC:	Tecnología de la Información y la Comunicación

RESUMEN

Antecedentes

En el 2008 el Institut Català de la Salut (ICS) implementó en su Estación Clínica de trabajo ECAP unos Sistemas de Ayuda a la Toma de Decisiones Clínicas (SADC) a nivel de prescripción con el objetivo de mejorar la seguridad clínica en el uso de medicamentos, el PREFASEG y el Self Audit.

El PREFASEG genera automáticamente avisos *on-line* al facultativo cuando detecta algún posible Problema Relacionado con la Medicación (PRM). En el momento del alta de un nuevo tratamiento valora la idoneidad del tratamiento, de manera individualizada para el paciente, en función de: los medicamentos activos, las características demográficas (edad y sexo), y sus condiciones clínicas (patologías, variables bioquímicas), a la vez que proporciona una recomendación terapéutica.

El Self Audit facilita a los médicos la posibilidad de revisar sistemáticamente algunos PRM de sus pacientes, en el momento que lo consideren oportuno. Facilita la búsqueda de pacientes con algún problema farmacológico relacionado con los medicamentos que tiene prescritos, facilitando la gestión del cambio y / o suspensión de la medicación desde la herramienta. De esta manera se sistematizan algunos aspectos de la revisión de la medicación de los pacientes, a partir de un ejercicio de evaluación profesional.

El objetivo del presente estudio fue analizar y presentar los principales resultados derivados del uso del PREFASEG y del Self Audit en la atención primaria (AP) de Cataluña. En el caso del Self Audit, también se analiza el efecto de un indicador de seguridad incentivado sobre los resultados obtenidos.

Método:

Estudio descriptivo transversal que analiza los avisos relacionados con los PRM detectados por PREFASEG y Self Audit durante los años 2016, 2017 y 2018 en la AP de Cataluña.

Se analizaron el número de los distintos avisos de PRM generados por PREFASEG y Self Audit, los fármacos implicados y la aceptación o rechazo de la recomendación dada desde la herramienta. En el caso de PREFASEG un aviso se consideró “aceptado” cuando no se prescribió

el medicamento que generó el aviso *on-line*. En el caso de Self Audit, un aviso se consideró "resuelto" cuando se dio de baja el medicamento que generaba el PRM o bien cuando se resolvió la condición clínica que lo generaba.

Los principales avisos de PRM estudiados fueron: duplicidades terapéuticas, alertas de seguridad de la Agencia Española del Medicamento, fármacos desaconsejados en geriatría y pacientes polimedicados con PRM de elevada relevancia clínica.

Se analizaron las prescripciones de 6.411 médicos de AP del ICS que utilizan el ECAP y presentan sus servicios a 5.8 millones de catalanes a través de 288 equipos de AP.

Resultados:

A nivel de PREFASEG, en los 3 años estudiados, se analizaron 67.2 millones de nuevas prescripciones, de las cuales el PREFASEG generó 4.379.866 avisos (1 por cada 15 altas de tratamiento). La aceptación fue de 1.222.159 avisos (28%); se aceptaron 1 de cada 4 avisos. Las interacciones farmacológicas y las duplicidades terapéuticas fueron los avisos con mayor detección, representando el 40% (1.691.886) y el 30% (1.436.721) del total de avisos, respectivamente. Los principales grupos farmacológicos implicados en los avisos de seguridad fueron los antiinflamatorios no esteroideos (AINE) y los Inhibidores Sistema Renina Angiotensina (ISRA).

A nivel de Self Audit, el análisis global mostró una resolución de los PRM inferior al 10%. Estudiando los 3 tipos de PRM de alta relevancia clínica vinculados al indicador de seguridad incentivado (duplicidades, alertas de seguridad de la AEMPS y de polimedicados con PRM de alta relevancia clínica) se observó en conjunto una resolución del 41% en 2016 (17.358), del 21% en 2017 (11.304) y del 20% (8.135) en 2018.

Conclusión:

PREFASEG es una herramienta que parece contribuir a evitar la generación de potenciales PRM de seguridad y el Self Audit ayuda a reducir PRM de seguridad existentes en la HC de manera sistemática, obteniendo mejores resultados en los PRM vinculados a un indicador de seguridad incluido en los incentivos de los médicos de AP. No obstante, es importante mejorar estos SADC para lograr incrementar el grado seguimiento de los avisos y, con ello, mejorar la seguridad de los pacientes.

INTRODUCCIÓN

INTRODUCCIÓN

Uso de medicamentos en las últimas décadas

En las últimas décadas, el consumo de fármacos ha ido aumentando en todo el mundo, especialmente en los países altamente desarrollados, lo que ha generado que los pacientes estén más expuestos a los fármacos y a sus posibles efectos adversos. Además, el uso simultaneo de varios medicamentos, la polifarmacia[1](Bushardt RL et al 2008), se ha convertido en una práctica habitual debido al envejecimiento de la población[2 3 4] y la multimorbilidad[5]. Los médicos, a menudo, tratan cada enfermedad de sus pacientes de manera individual sin tener en cuenta la multimorbilidad[6,7]. Aunque la polifarmacia puede ser necesaria y adecuada en algunos casos[8], aumenta el riesgo de errores de medicación y efectos adversos[9 10 11 12]. Las revisiones periódicas de la medicación son especialmente provechosas en los pacientes con polifarmacia[8].

La Comisión Europea en uno de sus informes indicaba que entre el 3 y el 10% de las causas de ingresos hospitalarios entre 2012 y 2014 eran los efectos adversos a medicamentos (EAM) (2.5-8.4 millones anuales), y que entre el 2.1 y el 6.5% de los pacientes hospitalizados experimentaron algún EAM (1.8- 5.5 millones anuales)[13]. Ante esta realidad, desde los últimos años de la década de 1990, la seguridad clínica del paciente se ha convertido en una prioridad de los sistemas sanitarios[14 15]. Varias iniciativas han situado la necesidad de una nueva cultura de la seguridad en el entorno sanitario y político[16 17 18]. Para ello ha resultado esencial definir actuaciones para evitar, prevenir y mejorar los efectos adversos o lesiones derivadas de los procesos de atención sanitaria que sean prevenibles (puesto que algunas reacciones adversas son inherentes al tratamiento, y no pueden ni evitarse ni minimizarse).

No hay que perder de vista que el 50% de los acontecimientos adversos relacionados con errores de medicación son evitables. En España, el estudio ENEAS realizado en la Atención Especializada (AE) demostró que el 42.8% de los eventos adversos eran evitables y que más de un tercio de estos eventos adversos estaban relacionados con la medicación [19]. Posteriormente en el estudio APEAS [20], realizado en la Atención Primaria (AP) se observó una prevalencia del 10% de eventos adversos, de los que el 48% estaban relacionados con la medicación. De ellos, poco más de la mitad correspondía a errores en la prescripción de medicación y el resto a reacciones adversas a los medicamentos.

Otro de los factores que favorece la aparición de problemas relacionados con los medicamentos está relacionado con la fragmentación del sistema sanitario. El paciente va moviéndose dentro del sistema y es atendido por diferentes niveles asistenciales: atención primaria, atención especializada, atención a las urgencias, centros socio-sanitarios y residencias geriátricas. Además, nuestro sistema de salud se orienta a la atención de las enfermedades, como condiciones individuales, lo que redunda en dificultades para ofrecer una atención más integral a los pacientes con multimorbilidad[6 21 22]. Son diversos los autores que defienden que estos pacientes reciben una atención fragmentada, incompleta, ineficiente e ineficaz[23 6].

Contexto de los inicios de los Sistemas de Ayuda a la toma de decisiones clínicas (SADC)

Afortunadamente, en paralelo a este incremento del consumo de fármacos poblacional y a sus implicaciones, se ha producido un importante avance en el desarrollo de tecnologías aplicadas al ámbito sanitario. Han sido diversas las organizaciones internacionales (Institute of Medicine, Joint Commission on Accreditations of Healtcare Organizations, National Quality Forum…) que han impulsado que las nuevas tecnologías de la información y la comunicación (TIC) se orienten a mejorar la calidad asistencial, la seguridad y el coste-efectividad en el cuidado del paciente.

En 1999 el informe técnico 'To err is human' del *Institute of Medicine (US)* [14] puso de manifiesto la necesidad de desarrollar las nuevas tecnologías de la información (TIC) para reducir los errores médicos. Así distintos informes posteriores, afirmaban que el registro electrónico de la actividad asistencial propio de la historia clínica electrónica (HCE), junto con la integración en dicha HCE de sistemas de ayuda en la toma de decisiones clínicas (SADC), contribuirían a mejorar la calidad para el sistema sanitario[24 25 26 27 28].

En esta línea, los SADC empezaron a implantarse a finales de la década de los 90, siendo Estados Unidos el máximo exponente de ese desarrollo[29] (Ozdas A y Miller RA 2007). Se esperaba una implantación rápida al contar con el apoyo de las autoridades estadounidenses, sin embargo la complejidadades y las dificultades en los desarrollos tecnológicos enlentecieron la implantación[30 31].

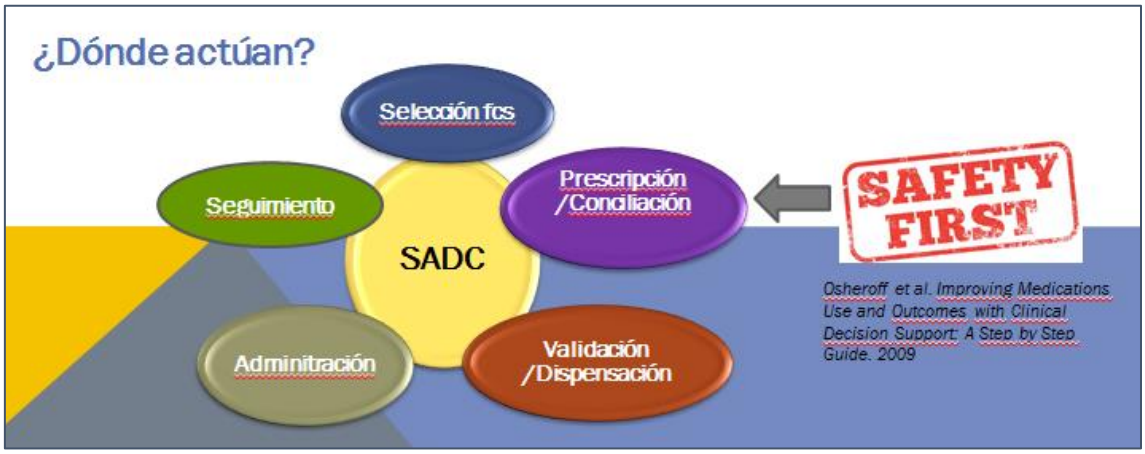
En España, la implantación de los SADC llegó más tarde y se produjo de forma lenta y muy heterogénea en los diferentes territorios del estado y en los distintos niveles asistenciales. Actualmente existe amplia variabilidad en los SADC implantados en los diferentes hospitales del estado español y en los distintos centros de atención primaria.

Definición y características generales de los SADC

En la literatura científica encontramos diversas definiciones de SADC a lo largo de los años [32] [33]. Según *Kawamoto et al 2005*[34]*,* un SADC seria cualquier sistema electrónico diseñado para ayudar a la toma de decisiones clínicas, que tiene en cuenta las características del paciente para generar una evaluación específica de éste y así poder proporcionar una recomendación para ser valorada por los clínicos. Otros autores, definen los SADC como aplicaciones informáticas que integran información sobre medicamentos y datos relacionados con los procesos clínicos de los pacientes para generar un aviso o alerta de manejo clínico[35] [30]. Estos sistemas combinan de manera inteligente el conocimiento clínico y la información de los pacientes presentando recomendaciones al profesional adecuado, en el momento apropiado y proporcionando recomendaciones específicas acorde con las características del paciente [36] [37].

Estos sistemas pueden incorporarse en cualquiera de las etapas del proceso de atención sanitaria, como el diagnóstico, el tratamiento o prevención, así como pueden dirigirse a cualquier profesional del equipo asistencial (médicos, enfermeros, farmacéuticos…). No obstante, cabe destacar el avance de los SADC en el área del medicamento, pudiendo actuar en la selección de fármacos, en la prescripción y conciliación de la medicación, en la validación sanitaria y dispensación, en la administración del medicamento y en el seguimiento terapéutico del paciente[37] (ver figura1). Algunos autores defienden que los SADC dirigidos a la fase inicial de prescripción pueden ser los que mayor impacto tienen en la mejora de la seguridad de los pacientes[38]. Además, la integración de los SADC en la historia clínica electrónica (HCE), ha permitido dotar las historias de señales interactivas que alertan a los profesionales ante situaciones de riesgo para el paciente[26], favoreciendo la mejora del proceso de prescripción y la seguridad clínica de los pacientes[39] [38] [40] [41].

Figura 1. Aplicación de los SADC en el área del medicamento



La literatura científica evidencia que los beneficios de los SADC son múltiples[42 43 44], así diferentes estudios defienden que contribuyen a mejorar la dosificación y la selección de fármacos, la realización de actividades preventivas, la indicación de pruebas, la disminución de la morbilidad. Algunos autores apuntan que también ayudan a mejorar los resultados de calidad asistencial[45].

En términos generales, los principales beneficios esperados de los SADC integrados en la HCE se podrían resumir en los siguientes puntos:

- Disminuir los errores derivados de la práctica asistencial
- Mejorar la seguridad en la prescripción farmacológica
- Aumentar el tiempo dedicado a la atención al paciente en la consulta
- Mejorar la adherencia a las guías de práctica clínica
- Mejorar el registro clínico
- Disminuir el tiempo de aplicación de las nuevas evidencias científicas (que se estima que es de 5 años)
- Facilitar la conciliación entre niveles asistenciales
- Reducir los costes sanitarios y las hospitalizaciones

Según Osheroff [37], para que los SADC sean útiles y eficientes es indispensable garantizar que se cumplan los “5 rights” o “5 verdades”:

- Información correcta.
- Persona/profesional correcto.
- Formato de la intervención correcto.
- Vía de comunicación correcta.
- Momento correcto en el flujo de trabajo.

En contraposición, el principal riesgo asociado a los SADC se define como 'fatiga mental experimentada por los facultativos que se enfrentan a numerosos alertas i avisos'. Con la carga de trabajo actual del personal sanitario, es imprescindible controlar el número de avisos que se pueden generar, proporcionar información útil, precisa y con una recomendación clara de la actuación a realizar. La emisión excesiva de alertas en situaciones clínicas irrelevantes puede llevar a una "alert fatigue" o "saturación de alertas", ya que la interrupción continua del flujo de trabajo del prescriptor conduce a una mayor omisión global de las alertas, omitiendo incluso aquellas consideradas más importantes[46 47 48 49]. Para disminuir el riego de fatiga de alertas es necesario aumentar la especificidad de los avisos, no interrumpir innecesariamente el flujo de trabajo y dar la información de forma clara.

Los SADC enfocados a nivel de prescripción se pueden clasificar en base a diferentes criterios. Si atendemos al momento de aparición del aviso o alerta en el proceso asistencial, según la clasificación de Chaffee[50], encontramos SADC de tipo pasivo o activo. Los pasivos requieren de activación voluntaria por parte del profesional y el usuario tiene la opción de acceder o no a la información, en cambio los activos generan avisos de forma automática frente a unas determinadas condiciones. Por otra parte, los avisos o alertas pueden tener carácter informativo o promover la interrupción de una acción, como puede ser evitar la prescripción de un medicamento[51]. Kupperman GJ et al [52], definieron dos tipos de SADC: los básicos y los avanzados. Los SADC básicos generan avisos relacionados únicamente con la medicación que toma el paciente como, por ejemplo: alergias, interacciones entre fármacos, dosis máximas o mínimas, duplicidades farmacológicas. Los SADC avanzados generan avisos teniendo en cuenta las características clínicas (variables clínicas, diagnósticos) y demográficas (edad, sexo) de los pacientes. Como SADC avanzados también nos encontramos protocolos y guías de práctica clínica informatizadas[53 54 55]que permiten selección y dosificación de fármacos según comorbilidades. Según algunos autores[56], los SADC avanzados proporcionan una mayor proporción de alertas clínicamente relevantes que los sistemas básicos.

Definición y características de los SADC de Cataluña: PREFASEG y SELF AUDIT

Ante la necesidad de mejorar la seguridad en el uso de medicamentos, el *Institut Català de la Salut* (ICS), entidad pública que presta servicios de salud en AP al 85 % de la población catalana, en el 2008 empezó a diseñar y desarrollar un conjunto de SADC con el objetivo de facilitar a los profesionales la toma de decisiones en el ámbito de la prescripción y mejorar la seguridad en el uso de medicamentos.

Los SADC desarrollados desde el ICS para la atención primaria de salud comparten las siguientes características:

- dan soporte a la totalidad de médicos de medicina de familia (n= 6.400) y equipos de AP (n = 288) del ICS. El ICS da cobertura en AP al 85% de la población catalana (5.8 millones de habitantes).
- están integrados en la estación clínica de trabajo de AP, llamada ECAP, que utilizan el 100% de los facultativos de AP del ICS
- interaccionan con el conjunto de la información clínica y asistencial presente en la historia clínica informatizada de los pacientes facilitando la individualización de les recomendaciones generadas.
- actúan en la fase de la prescripción farmacológica.
- detectan varios tipos de Problemas Relacionados con la Medicación (PRM) de diferentes grupos farmacológicos.
- se han diseñado e implementado con la colaboración de un grupo multidisciplinar de profesionales y teniendo en cuenta las necesidades de los clínicos usuarios.
- las recomendaciones terapéuticas facilitadas se basan en la evidencia científica disponible y en el consenso clínico.
- los contenidos clínicos que generan las alertas o avisos se actualizan periódicamente por un grupo de expertos en base a las nuevas evidencias científicas disponibles en cada momento.
- tienen trazabilidad interna que permite evaluar su utilización mediante indicadores específicos, explotables y fáciles de interpretar.
- se han adaptado a los requisitos del Sistema de Recepta Electrónica de Cataluña.

- se realizan actividades formativas continuas para los médicos, por parte de los farmacéuticos y farmacólogos de AP, para trasladar las novedades relacionadas con las herramientas y fomentar la resolución de problemas relacionados con la medicación a través de éstas.

Características generales de PREFASEG:

El PREFASEG, siglas de PREscripción FArmacéutica SEGura, es una herramienta informática que actúa de forma interactiva alertando a los clínicos de problemas relacionados con la seguridad en el uso de los medicamentos en el mismo momento que el profesional está dando de alta un tratamiento. Se trata de una herramienta que genera avisos de forma automática frente a unas determinadas condiciones, por lo que se clasifica de SADC de tipo activo. Así cuando desde la estación clínica ECAP el médico da de alta un nuevo medicamento, se verifica on-time y de manera individualizada la idoneidad del tratamiento en función del historial clínico y terapéutico del paciente [57].

El módulo escanea el nuevo medicamento con las otras prescripciones activas, con las características del paciente (edad, sexo) y con las condiciones clínicas (problemas de salud registrados y valores de variables bioquímicas) informadas en la historia clínica del paciente. El PREFASEG interactúa con el profesional a través de una pantalla emergente, agrupando los avisos de seguridad y proporcionando información sobre los riesgos para la salud y dando las orientaciones terapéuticas pertinentes en cada caso. Las recomendaciones que se dan promueven evitar generar esa prescripción, por lo tanto, se pueden definir como SADC interruptivos. De esta forma, la herramienta ayuda a evitar la generación de nuevos PRM. Este funcionamiento por avisos automáticos se ha demostrado tener mayor impacto en la reducción de PRM [52].

El PREFASEG está integrado en el ECAP y también funciona en las consultas externas de los hospitales que utilizan el módulo de prescripción .NET (30% de los hospitales de Cataluña).

Para explicar el funcionamiento de PREFASEG vamos a suponer que el médico prescribe un nuevo fármaco para el paciente. En ese instante se activa PREFASEG que realiza una valoración on-time de la prescripción, comprueba que es segura para el paciente y que no le supone un

potencial riesgo para su salud. Esta evaluación se realizará considerando los diferentes PRM que detecta la herramienta:

(1) Interacciones farmacológicas
(2) Duplicidades terapéuticas
(3) Fármacos desaconsejados en geriatría
(4) Contraindicaciones con una alerta de seguridad publicada por la Agencia Española del Medicamentos y Productos Sanitarios (AEMPS)
(5) Contraindicaciones por problemas de salud y/o variables clínicas
(6) Teratógenos en embarazadas
(7) Combinaciones de fármacos anticolinérgicos
(8) Antecedentes de hipersensibilidades o alergias (sospechas, no confirmadas)
(9) Reacciones adversas a medicamentos

Para llevar a cabo esta comprobación se tienen en cuenta los siguientes datos:

- La prescripción activa que este paciente ya tiene en su historial.
- Los diagnósticos o problemas de salud activos del paciente.
- Algunas variables clínicas con valores alterados.
- La edad y/o sexo del paciente.

En caso de producirse algún aviso de seguridad asociado al alta de medicamento, se muestra al médico los avisos correspondientes (incluyendo el riesgo para el paciente y la alternativa terapéutica) para que decida:

- Continuar con el alta de producto
- Cambio de producto

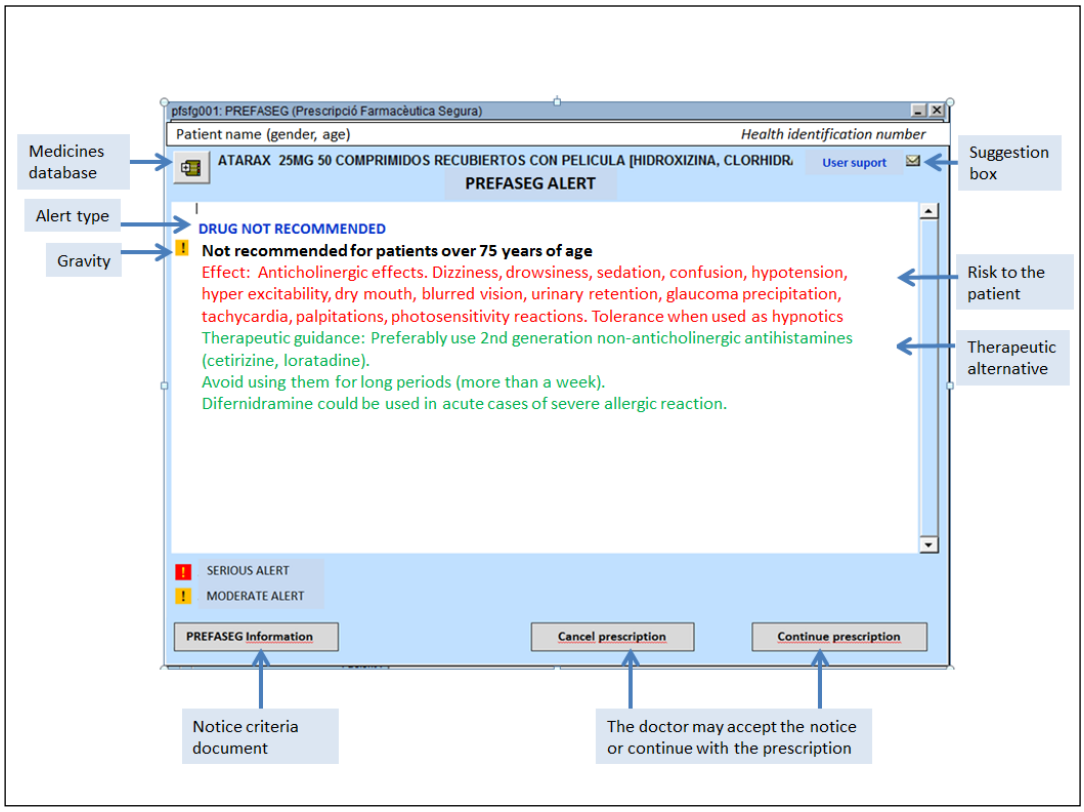
Los avisos de seguridad sobre los potenciales PRM se muestran al médico de forma simple y amigable en una única pantalla para una rápida comprensión.

De cada aviso se muestra la siguiente información en pantalla (ver figura 2):

- Icono de gravedad (dos grados, alerta moderada y alerta grave)
- Medicamento y principio activo origen o causante del aviso (que se está dando de alta)
- [Medicamento y principio activo en conflicto] o [Edad] o [Problema de salud] ...
- Riesgo para el paciente
- Alternativa terapéutica

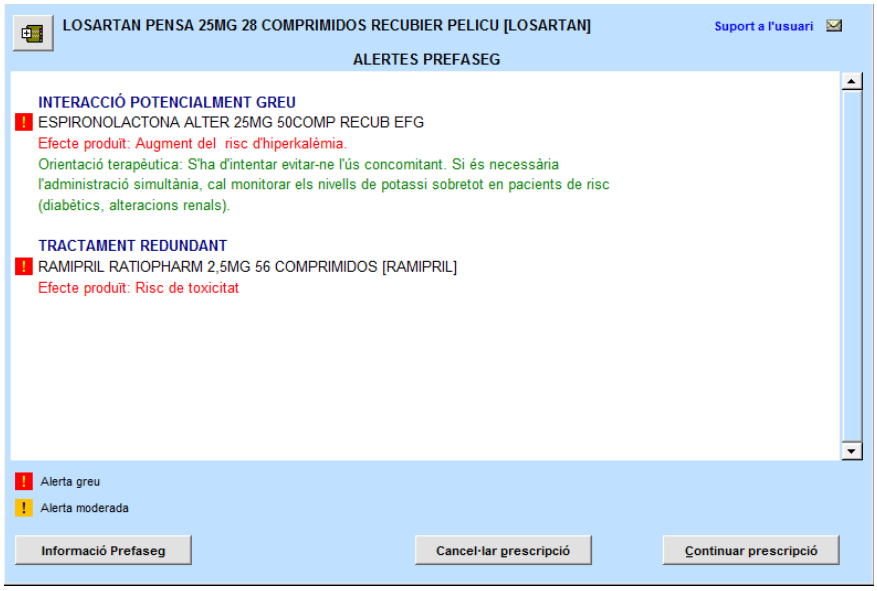
En la figura 2 se muestra un ejemplo de pantalla ante la casuística del alta de un producto desaconsejado para pacientes mayores de 75 años.

Figura 2. Pantalla de PREFASEG con los elementos informativos



Es posible que haya más de una alerta: puede pasar que un producto genere dos o más potenciales problemas de seguridad diferentes en el momento de darlo de alta, de forma que se informa al médico de todos los avisos que se produzcan (ver figura 3).

Figura 3. Pantalla ejemplo de PREFASEG con varios avisos de seguridad y su recomendación terapéutica



Cada aviso detectado en PREFASEG queda registrado como "datos de auditoría", con la información ("atributo") de si ha sido aceptada o si se ha continuado con la prescripción del producto.

La explotación de estos datos permite conocer si hay avisos más aceptados que otros y así ir mejorando la definición de contenidos para adaptarla a la realidad asistencial.

El PREFASEG está compuesto de un núcleo de cálculo en PL/SQL Oracle en el que se han optimizado los cálculos que acceden a tablas de contenidos clínicos, con una mínima interface visual para la comunicación de avisos de seguridad desarrollada en Developer Forms, la misma tecnología que la estación clínica de trabajo. De esta forma el look&feel de las pantallas de avisos es la misma que ECAP y se consigue una integración máxima.

Los contenidos clínicos de los avisos de PRM fueron definidos y consensuados, tal y como indican algunos autores [31 33 58], por un grupo multidisciplinar de profesionales expertos del ICS (médicos de atención primaria, farmacéuticos y farmacólogos clínicos). Periódicamente se revisan y actualizan los contenidos acordes con la evidencia científica disponible y más actualizada en cada momento, como ejemplo se incluyen para fármacos desaconsejados en geriatría las referencias a criterios más actuales Stopp/Start y Beers. Los contenidos son editables en cualquier momento y se actualiza desde una plataforma específica de mantenimiento llamada

'Know How'. Cada aviso de PRM se clasifica en relevancia clínica alta (icono de color rojo) o media-baja (icono de color naranja), siguiendo las recomendaciones de algunos autores [59]. (Paterno MD, et al. 2009)

Características generales de SELF AUDIT:

El Self Audit es un sistema informático integrado en la HCE que facilita a los médicos la posibilidad de revisar sistemáticamente algunos PRM de sus pacientes, en el momento que lo consideren oportuno. La herramienta facilita la búsqueda de pacientes con algún problema farmacológico relacionado con los medicamentos que tiene prescritos, facilitando la gestión del cambio y / o suspensión de la medicación. De esta manera se sistematizan algunos aspectos de la revisión de la medicación de los pacientes, a partir de un ejercicio de evaluación profesional[60].

Se trata de un SADC de tipo pasivo ya que requiere de activación voluntaria y el médico debe acceder para visualizar la información que proporciona. Por lo tanto, no altera el flujo de trabajo en la consulta[61 62] y es el profesional que decide el momento más adecuado para revisar los pacientes con PRM. El Self Audit está disponible únicamente para la atención primaria de salud.

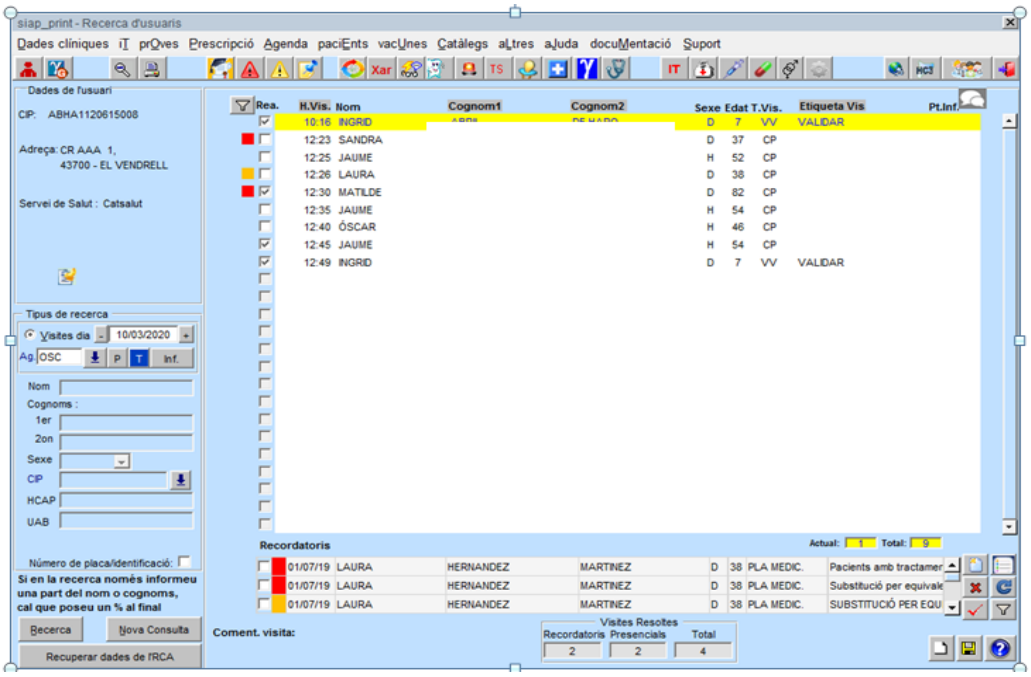
Los PRM son definidos por un grupo de profesionales expertos del ICS. Cada año se revisa el contenido de los PRM de acuerdo con la información científica disponible y, por este motivo, un mismo tipo de PRM puede variar de un año a otro. Cada PRM se clasifica en relevancia clínica alta (marcados con icono color rojo) o baja (marcados con icono color amarillo).

Ligado al Self Audit de prescripción, en 2008 se diseñó un indicador de seguridad -que seleccionaba algunos PRM clínicamente más relevantes- y que se incentivó para los médicos de AP del ICS y se incluyó en el programa de pago por objetivos. Con este indicador se pretendía fomentar la cultura de la seguridad en el uso de medicamentos y potenciar la utilización del Self Audit.

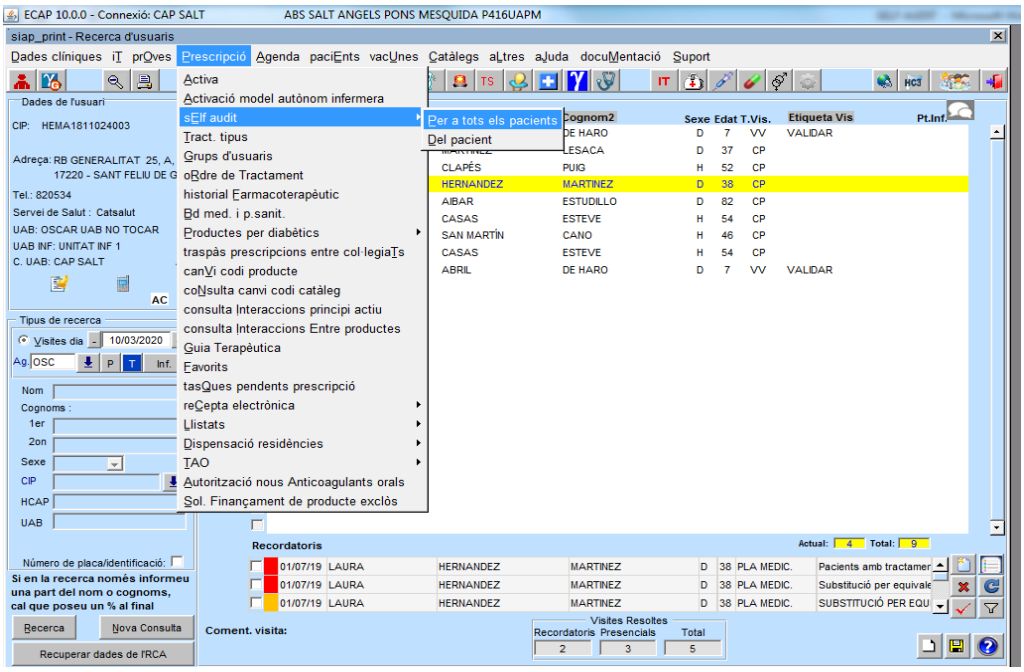
Para explicar el funcionamiento de la herramienta hay que tener en cuenta que hay diversas maneras de acceder al Self Audit. Una de ellas es desde la agenda de visitas del día, donde junto al nombre de los pacientes aparece un icono de color que marca aquellos que tienen algún problema relacionado con los medicamentos prescritos en la HCE, por si el médico desea aprovechar la visita para revisar la medicación (ver pantalla 1). La otra forma de acceder es desde

un menú principal del ECAP, donde se accede al listado de todos los pacientes de su población asignada que están afectados por algún tipo de PRM (ver pantalla 2).

Pantalla 1

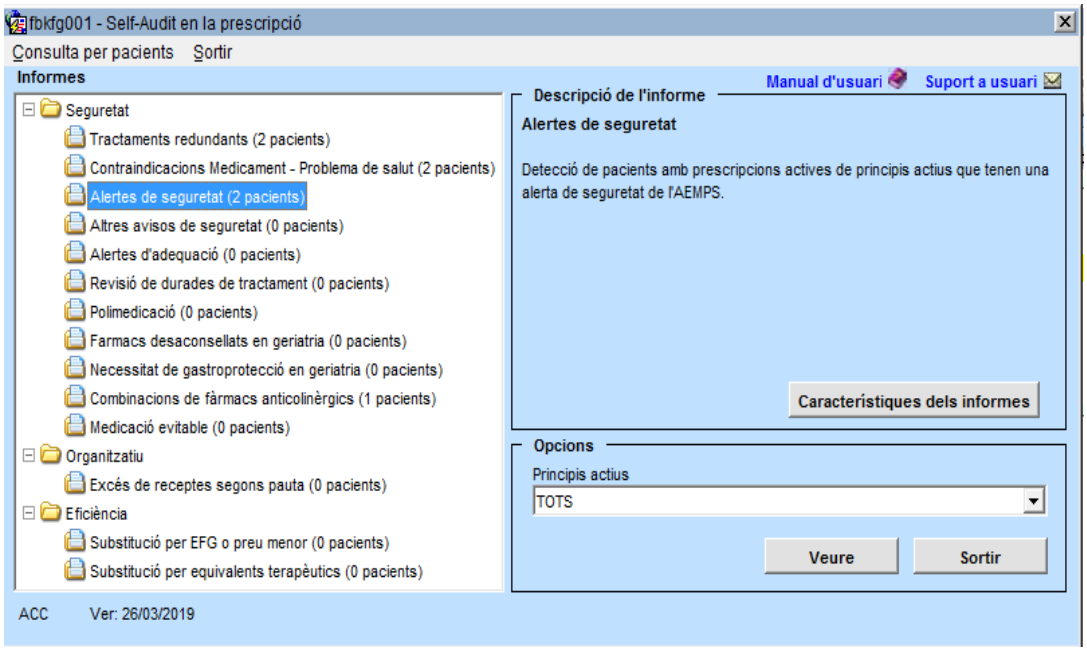


Pantalla 2



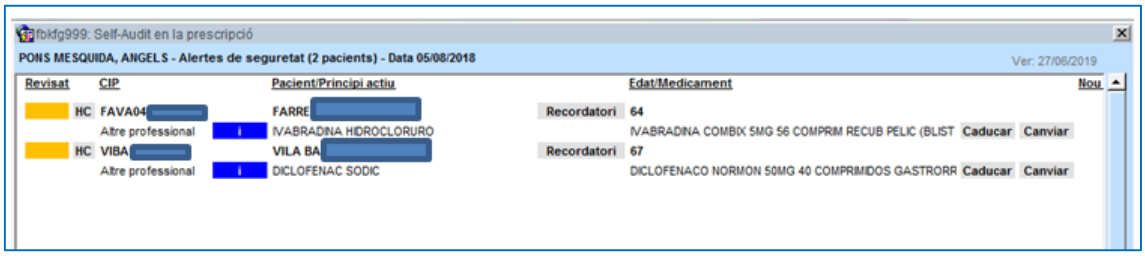
Una vez se ha accedido al Self Audit el programa muestra la pantalla principal (pantalla 3), en la cual se visualiza un esquema con los diferentes tipos de PRM que se identifican. En cada tipo de PRM, entre paréntesis, se especifica el número de pacientes afectados. Al clicar encima de un PRM, en la parte derecha de la pantalla se visualiza una breve descripción del contenido. El botón "Características del informe", da acceso a un documento donde se especifican detalladamente los criterios predeterminados para la detección de esos pacientes. Una vez el médico ha seleccionado un informe concreto, pulsando el botón "Ver" tendrá acceso a la relación de incidencias de sus pacientes, tal y como se muestra en la pantalla 4.

Pantalla 3

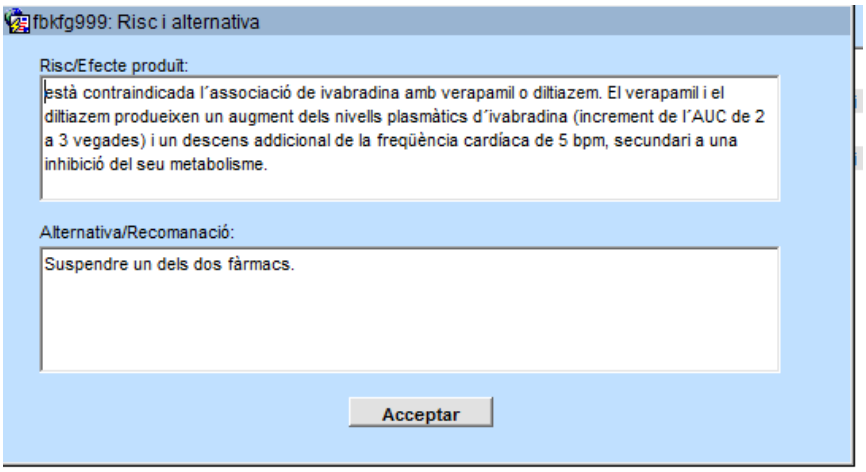


En la pantalla 4 se visualiza la relación de pacientes (CIP) con algún PRM y el detalle. Clicando sobre el símbolo de HC, el médico accede a la Historia Clínica Compartida de Cataluña donde podrá consultar toda la información clínica del paciente. Desde esa misma pantalla el médico tiene la opción de 'caducar' el medicamento o 'cambiar' por otro. Clicando sobre la 'i' informativa el programa proporciona el detalle del riesgo y la recomendación terapéutica a seguir (pantalla 5).

Pantalla 4

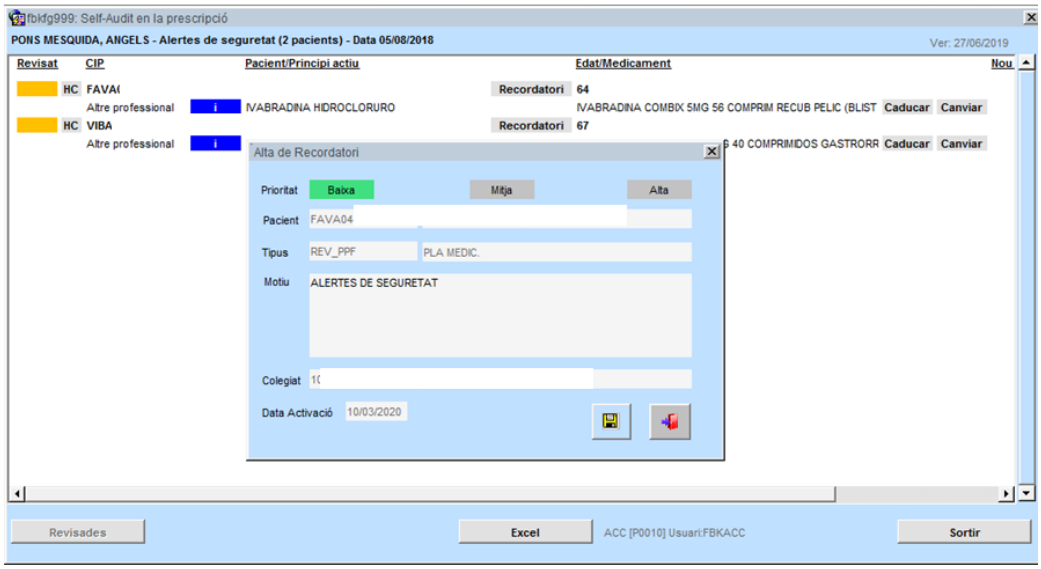


Pantalla 5



Además, hay la posibilidad de generar un 'recordatorio' para reservarse un espacio en la agenda en el mismo día o en algún día próximo para revisarse con tiempo ese paciente con PRM (pantalla 6).

Pantalla 6



Cuando el médico haya revisado el paciente y considere que su tratamiento es el correcto, haya o no cambiado algún medicamento de su prescripción, deberá marcar la casilla naranja y la incidencia quedará sombreada en verde y registrada la acción en la HC.

Las acciones realizadas en Self Audit sobre la prescripción quedan registradas y son explotables para su seguimiento.

Contenidos clínicos de PREFASEG Y SELF AUDIT

En términos generales, para dotar de contenido clínico y farmacológico el PREFASEG y Self Audit se siguió la siguiente metodología:

Fase 1. Búsqueda bibliográfica. De los diferentes PRM abordados en PREFASEG y Self Audit se procedió a realizar una búsqueda bibliográfica a través de la base de datos Pubmed, revisando los artículos nacionales e internacionales que se consideraron más relevantes y que mejor se adaptaban a nuestro entorno sanitario. Se consideraron las advertencias de seguridad incluidas en las Guías de Práctica Clínica del ICS (http://ics.gencat.cat/ca/assistencia/coneixement-assistencial/guies-de-practica-clinica/).

Fase 2. Consenso con el grupo de expertos. Se realizó una revisión de la bibliografía, se seleccionaron los grupos farmacológicos a intervenir y se definieron los mensajes que acompañaban los avisos dirigidos al médico prescriptor. Cada aviso de PRM se clasificaba en relevancia clínica alta (icono de color rojo) o media-baja (icono de color naranja), siguiendo las recomendaciones de algunos autores [59] (Paterno MD, et al. 2009). Los avisos rojos reflejaban situaciones de contraindicaciones absolutas recogidas así en sus fichas técnicas o en la literatura consultada. Los avisos de color amarillo eran considerados precauciones en las fichas técnicas.

Fase 3. Adaptar el contenido clínico a los formatos de tablas necesarios para cargar en el programa informático de PREFASEG y Self Audit, es decir, traducción a un lenguaje legible informáticamente. El contenido clínico se traspasó a los programas desde unas tablas de configuración en Excel, y para ello fue necesario la codificación de los principios activos según la clasificación ATC (Sistema de Clasificación Química Anatomicoterapéutica) y la codificación de

los problemas de salud según el CIE-10 (Clasificación Internacional de Enfermedades). Para trabajar los contenidos, se construyeron agrupaciones de ATC o agrupaciones de problemas de salud. Para definir y configurar cada tipo de aviso se podían utilizar agrupaciones de ATC y en algunos casos era posible la combinación de varios atributos, tal y como se refleja en la tabla 1.

Tabla 1. Atributos combinables en la configuración de cada aviso de PREFASEG

Tipo de PRM	**Atributos combinables en la configuración de cada PRM**
Interacciones	▪ Agrupaciones de principios activos por ATC
Duplicidades terapéuticas	▪ Agrupaciones de principios activos por ATC
Alertas de seguridad de la AEMPS	▪ Edad ▪ Agrupaciones de principios activos por ATC ▪ Agrupaciones de problemas de salud ▪ Dosis del principio activo ATC que genera el aviso
Desaconsejados en geriatría	▪ Edad ▪ Agrupaciones de ATC ▪ Agrupaciones problemas de salud ▪ Etiquetas de variables clínicas (Filtrado Glomerular y potasio)
Contraindicaciones por problemas de salud	
Contraindicaciones por variables clínicas	
Teratógenos en embarazadas	
Combinaciones de fármacos anticolinérgicos.	▪ Agrupaciones de ATC
Antecedentes de alergias o hipersensibilidades (sospechas, no confirmadas)	▪ Agrupaciones de ATC
Reacciones adversas a medicamentos	▪ Agrupaciones de ATC

PREFASEG y Self Audit comparten la mayoría de PRM de seguridad que generan avisos. En la tabla 2 se describen los principales PRM de seguridad detectados por ambas herramientas.

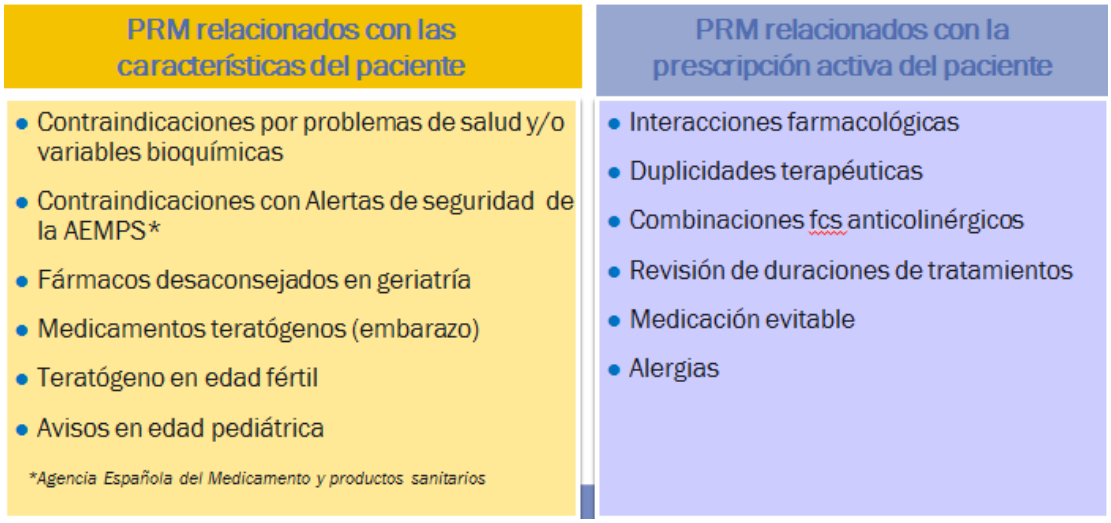
Tabla 2. Descripción de los PRM de seguridad que detectan PREFASEG y Self Audit

Tipo de PRM seguridad	Breve descripción
Contraindicaciones con alerta de seguridad AEMPS	Avisos en pacientes que tienen alguna contraindicación con algún medicamento que tenga una alerta relevante de seguridad de la Agencia Española del Medicamento y Productos Sanitarios (AEMPS). Dependiendo de la alerta se consideran parámetros de edad del paciente, problemas de salud activos, dosis del fármaco y/o otros medicamentos prescritos.
Contraindicaciones por problemas de salud	Avisos en pacientes que tienen alguna contraindicación de medicamento por algún problema de salud de patología crónica.
Fármacos desaconsejados por edad	Avisos en pacientes mayores de 75 años que tienen medicación inapropiada, con un perfil beneficio-riesgo más desfavorable por su edad [63 64 65].
Duplicidades terapéuticas	Avisos en pacientes que llevan la prescripción no beneficiosa de dos o más medicamentos con el mismo principio activo (sólo o en combinación) o con la misma acción farmacológica de manera simultánea en el tratamientos de un paciente.
Interacciones (sólo en PREFASEG)	Avisos en pacientes en que uno de los medicamentos que toma simultáneamente con otro/s puede modificar la intensidad (aumento o disminución) del efecto habitual o genera la aparición de efectos diferentes al esperado (subterapéuticos, terapéuticos o toxicológicos).
Duraciones inadecuadas de algunos tratamientos	Avisos en pacientes con tratamientos que superan la duración recomendada en ficha técnica y para la cual no hay evidencia científica que el beneficio de su utilización sea superior a los riesgos.
Combinaciones de elevada carga anticolinérgica.	Avisos en pacientes con tratamientos concurrentes de un antiespasmódico urinario y algún otro fármaco con actividad anticolinérgica significativa[66 67].

Algunos tipos de PRM diferentes entre los dos SADC son las alergias y las interacciones, que generan avisos en PREFASEG pero no se hacen búsquedas de pacientes con estos PRM en Self Audit. Respecto el PRM de alergias se consideró que tenía sentido clínico avisar en el momento que se generaba un nuevo tratamiento. El PRM de interacciones está pendiente de desarrollo tecnológico en Self Audit. Otros contenidos, como los PRM relacionados con duraciones inadecuadas de tratamientos, son diferentes en ambas herramientas, Self Audit identifica duraciones inadecuadas de tratamientos de larga duración, como doble antiagregación con duraciones superiores a 12 meses y PREFASEG, desde febrero 2019, genera algunos avisos de duraciones inadecuados de tratamientos agudos.

En base a la clasificación de Kupperman GJ et al [52], algunos avisos de Self Audit y PREFASEG se considerarían avisos de tipo básicos, que detectan PRM relacionados con los medicamentos, y otros como las contraindicaciones o los medicamentos con alertas de seguridad de la AEMPS se podrían considerar avisos de tipo avanzado, ya que tienen en cuenta características del paciente como problemas de salud activos y/o algunas variables clínicas como el potasio y el filtrado glomerular. En la figura 4 se diferencian los PRM detectados por las herramientas en base a si son de tipo básico o avanzado.

Figura 4. Clasificación de los PRM en básicos o avanzados



Diseño e implementación de PREFASEG y Self audit

Tal como se describe en Bonada N et al[68] , en el diseño e implementación de los SADC deben considerarse 3 etapas: constitución de un equipo de trabajo multidisciplinar, definición de las características funcionales y, monitorización y seguimiento del funcionamiento de los SADC.

Etapa 1. Constitución de un equipo de trabajo multidisciplinar

Tal como apuntan diversas publicaciones[31 33 58], para el diseño, implantación, mantenimiento y seguimiento de los SADC es imprescindible la creación de un equipo de trabajo multidisciplinar. Con estas premisas la unidad de farmacia del ICS que ha liderado y coordinado desde el inicio los proyectos de PREFASEG y de Self Audit, creó en el 2007 dos grupos de trabajo pluridisciplinares formados por médicos de AP, farmacéuticos de AP y profesionales informáticos. Un grupo definía las necesidades a desarrollar en el PREFASEG y el otro grupo se encargó del diseño y definición del Self Audit. Después de unos años desde la implantación de los SADC en la HC, estos grupos se unificaron y se han responsabilizado de actualizar y consensuar la información y los avisos que se muestran en PREFASEG y Self Audit.

Etapa 2. Definición de las características funcionales

En su artículo Bonada N et al destaca que para poder diseñar e implantar un SADC es necesario disponer de los siguientes requisitos:

- Prescripción Electrónica Asistida.
- Historia Clínica informatizada.
- Sistema informático capaz de reconocer/interpretar los datos clínicos necesarios para crear los criterios de decisión.

Con esas premisas, el diseño de los SADC debe contemplar fundamentalmente 4 parámetros: los datos fuente, los "triggers" o parámetros de alerta, las intervenciones y las alternativas a ofrecer[70 71]. A modo de ejemplo, cogiendo el tipo de PRM de contraindicaciones, los parámetros a tener en cuenta serian:

- Datos fuentes: medicamentos contraindicados en alguna patología
- Trigger: los problemas de salud que generan provocan el aviso (diagnósticos)
- Intervención: aviso on-line o por listado para evitar la prescripción o darla de baja
- Alternativa: mensaje de aviso que se proporciona desde el SADC pudiendo dar tratamiento opcional concreto.

En el diseño del *Sofware* de PREFASEF y de Self Audit se tuvieron en cuenta que fueran sistemas intuitivos, fáciles de usar, útiles para los usuarios, que estuvieran integrados en el flujo de trabajo y que no importunarán sin motivo a los profesionales [72] [73].

Etapa 3. Monitorización y seguimiento del funcionamiento

Los avisos generados por el PREFASEG y Self Audit quedan identificados internamente en la HCE del paciente. Las acciones realizadas en los SADC sobre la prescripción quedan registradas y son explotables para su seguimiento.

A nivel de PREFASEG, cada mes se acumulan las alertas generadas y aceptadas a través de la herramienta en un repositorio informático. Anualmente se analiza el conjunto de datos a través de las extracciones informáticas de las bases de datos del ECAP. Para poder evaluar el impacto clínico y la eficiencia de la herramienta es imprescindible la monitorización de todos los aspectos relacionados con la generación de las alertas. También es fundamental para la mejora de los contenidos clínicos que la alimentan.

El Self Audit también tiene un sistema interno de trazabilidad de las actuaciones realizadas. Las búsquedas de pacientes predefinidas desde la herramienta generan unas estadísticas semanales que permiten monitorizar el número de PRM de cada tipo en un momento dado en todos los pacientes del ICS.

McCoy AB et al[26] exponen que para evaluar el correcto funcionamiento de los SADC se requiere monitorizar la idoneidad de la alerta en el contexto clínico del paciente, la aceptación de las alternativas propuestas por el sistema o tiempo de respuesta hasta la consecución del cambio promovido.

Ligado al seguimiento y la monitorización de los avisos generados por Self Audit, y con la finalidad de fomentar la cultura de la seguridad del paciente, desde la Unidad de farmacia de AP del ICS, se diseñó un indicador de seguridad que se explica más adelante.

Del análisis de la monitorización y el seguimiento del funcionamiento se obtiene información para mejorar los SADC. Será esencial monitorear aspectos como los siguientes:

- Idoneidad avisos (momento aparición, información aporta, alternativas).
- Aceptación avisos (omisión, relevancia clínica omisión, recomendaciones aceptadas).
- Tiempo de respuesta (tiempo hasta conseguir cambio promovido).

Para un adecuado seguimiento del funcionamiento y aceptación de los SADC es importante que se diseñen indicadores específicos, se evalúen y se devuelva un feedback a los profesionales usuarios de estas herramientas. En esta línea, relacionado con el seguimiento y la monitorización de los avisos generados por Self Audit, desde la Unidad de farmacia de AP del ICS, se diseñó un indicador de seguridad.

Indicador de seguridad incentivado ligado a avisos de seguridad de Self Audit

Ligado al SelfAudit de prescripción, en 2008 se diseñó un indicador de seguridad -que seleccionaba algunos PRM clínicamente más relevantes- y que se incentivó para los médicos de Atención Primaria del ICS y se incluyó en el programa de pago por objetivos. Con este indicador se pretendía fomentar la cultura de la seguridad en el uso de medicamentos y potenciar la utilización del Self Audit.

El indicador de seguridad en el uso de medicamentos, se incluyó por primera vez en la Dirección por Objetivos (DPO) de los médicos de Atención Primaria del ICS en el año 2008. Con este indicador incentivado económicamente se pretendía fomentar la cultura de la seguridad en el uso de medicamentos y a la vez potenciar la utilización de la nueva herramienta de soporte a la prescripción que se había implementado en la estación clínica ECAP en ese mismo año, el Self Audit de prescripción.

El indicador del año 2008 media una dimensión de seguridad incluida en el Self Audit: duplicidades terapéuticas. Se consideró duplicidad terapéutica la prescripción no beneficiosa de dos o más medicamentos de administración sistémica con el mismo principio activo y/o la

misma acción farmacológica en el tratamiento de un mismo paciente. Era un indicador que se media a nivel de Equipo de Atención Primaria (EAP) y no a nivel individual de cada médico. El objetivo solicitado para obtener una calificación positiva del indicador era reducir el número de pacientes con duplicidades terapéuticas en un determinado porcentaje. El porcentaje de reducción solicitado se determina a partir del % de duplicidades de partida del EAP, pudiéndose solicitar una reducción del 40%, 30%, 20% o ninguna en función de los casos basales. Los datos para la medición del objetivo se miraban de prescripción activa del ECAP. El primer año se fijó un basal al iniciar el año, a partir del cual se determinó la meta y se midió la consecución del objetivo a finales del año.

En los años siguientes, el indicador de seguridad fue cambiando y evolucionando. En 2016, 2017 y 2018, periodo estudiado, la composición del indicador se sofisticó, tanto en contenido como en la manera de medirlo. Se fueron haciendo varios cortes de evaluación durante el año. El objetivo solicitado para obtener una calificación positiva del indicador se establecido en base a un sistema de percentiles partiendo de los datos de todos los EAP del ICS, no siendo especialmente estrictos en la meta solicitada.

Los contenidos clínicos que nutren el Self Audit se actualizan anualmente, incluyendo nuevos contenidos y/o modificando los existentes, esto supone que las incidencias o casos detectados en las diferentes dimensiones de seguridad pueden ser diferentes de un año a otro, lo cual hace que no siempre se puedan comparar los resultados entre años.

Tabla 3. Resumen definición indicador anual

Indicador de seguridad		**PRM incluidos en el indicador**		
Año	**Nº Cortes evaluación**	**Duplicidades**	**Alertas**	**Polimedicados**
2016	2: setiembre y diciembre	53 grupos	13 alertas	Incidencias en paciente de ≥ 65 años con ≥ **10** medicamentos de tipo: • Duplicidades relevantes • Alertas de seguridad AEMPS • Medicación evitable • Doble antiagregación >12 meses • Calcitonina/ Parathormona > 24m • *Bifosfonatos >5 anys*
2017	3: Junio, setiembre y diciembre	56 grupos	13 alertas	Incidencias en paciente de ≥ 65 años con ≥ **8** medicamentos de tipo: • Duplicidades relevantes • Alertas de seguridad AEMPS • Medicación evitable • Doble antiagregación >12 meses • Calcitonina/ Parathormona > 24 m • *Combinaciones anticolinérgicos*
2018	3: junio, setiembre y diciembre	56 grupos	13 alertas (se elimina Ranelato estroncio y se incluye Canaglifozin)	Incidencias en paciente de ≥ 65 años con ≥ **8** medicamentos de tipo: • Duplicidades relevantes • Alertas de seguridad • Medicación evitable • Doble antiagregación >12 meses • Calcitonina/ Parathormona > 24 m • *Nitrofurantoina > 7 días* • *Dexketoprofen/tramadol > 5 días* • *Combinaciones anticolinérgicos*

- En duplicidades terapéuticas cada año se incluyen en cada tipo de duplicidad los nuevos medicamentos que han surgido en el mercado (nuevos ATC). También se pueden crear nuevos grupos de duplicidades o se pueden modificar - por criterios clínicos- algunos grupos ya existentes.

- En la dimensión de alertas de seguridad de la AEMPS se han ido monitoreando las contraindicaciones de los fármacos: Aliskireno, Citalopram, Escitalopram, Cilostazol, Trimetazidina, Raloxifè/ Bacedoxifè, Ranelat d'Estronci, COXIBS, Diclofenac, Aceclofenac, Ivabradina, Agomelatina, Canaglifozina y triple whammy.

  Los principales cambios de contenido fueron durante el 2018, donde se eliminó la alerta del ranelato de estroncio, se añadió un aviso con canaglifozina y se modificó la definición de la alerta de citalopram y escitalopram. La finalidad de estos cambios de contenido tiene como objetivo intentar ser más específicos en los casos a detectar y poder definir una intervención concreta.

- En la dimensión de polimedicados el principal cambio se produjo, en 2017, cuando la población diana (pacientes polimedicados de 65 años o más) pasó de tener 10 fármacos a 8, representando un aumento importante del número de casos de la población diana.

  Otros cambios también relevantes en esta dimensión fueron que en 2017 ya no se incluyó el PRM relacionado con la duración de bifosfonatos > 5 años y se empezó a monitorear la combinación de fármacos anticolinérgicos. En 2018, se añadió la duración de tratamientos con Nitrofurantoina > 7 días y Dexketoprofen/tramadol > 5 días.

Dificultades asociadas a la implantación y desarrollo de PREFASEG y al Self Audit

En el diseño, implantación y desarrollo de los SADC pueden aparecer multitud de barreras y dificultades que pueden acabar suponiendo ciertas limitaciones:

- Integración entre sistemas de información. La falta de integración e intercambio de información clínica entre programas informáticos y niveles asistenciales, dificulta la obtención de algunos datos clínicos que se utilizan para generar avisos a través de los SADC. La integración de diferentes sistemas implica que estos trabajen conjuntamente compartiendo los datos clínicos. En el caso de PREFASEG y Self Audit no hay intercambio de información con los datos registrados en los hospitales, ya que los sistemas informáticos son completamente independientes y no sincronizan información entre ellos.

- Dificultad de gestionar la información clínica. La información clínica relacionada con un paciente puede provenir de diferentes bases de datos que gestionan grandes volúmenes de información: datos de prescripción de medicamentos, datos de laboratorio, datos de diagnósticos… Los programas informáticos deben tener la capacidad de gestionar grandes cantidades de información de manera ágil y dar rápida respuesta a los usuarios. La utilización de estándares universales como la codificación ATC para medicamentos o la codificación CIE-10 para patología, facilitan la gestión de la información.

- Actualización continua de los contenidos clínicos. La evidencia científica va cambiando permanentemente y genera la necesidad de actualizar los contenidos clínicos que nutren los SADC para que sean útiles a los médicos y transmitan confianza. Eso implica dedicar recursos profesionales a revisar contenidos de manera rutinaria y disponer de alguna plataforma de mantenimiento para ser agiles y autónomos en esa actualización. En el caso de PREFASEG y Self Audit existe un grupo de trabajo que se reúne cada dos-tres meses para revisar, mejorar e ampliar los contenidos clínicos que generan los avisos. También se dispone de una plataforma de mantenimiento de contenidos.

- Coste económico de mantener y evolucionar los programas. Para que los SADC resulten útiles a los clínicos y no queden obsoletos, es esencial disponer de personal que mantenga actualizados los contenidos clínicos, que detecte y defina áreas de mejora de los SADC y que evolucione los programas informáticos adaptándose a las necesidades de los usuarios. Todo ello representa un coste económico que la entidad debe estar dispuesta a asumir.

- Falsa seguridad en el uso de medicamentos. Los SADC como PREFASEG y Self Audit están pensados para ayudar a los profesionales a la toma de decisiones clínicas a nivel de prescripción, para mejorar la seguridad clínica en el uso de medicamentos. Sin embargo, las herramientas no pueden avisar de todo, ya sea por limitaciones técnicas o por falta de

información registrada. En ocasiones los profesionales pueden confiarse en exceso en la cobertura de seguridad que pueden otorgar los SADC generando situaciones de falsa seguridad en la prescripción de medicamentos. Por ejemplo, en el caso de PREFASEG y Self Audit no se disponen de avisos de seguridad relacionados con la Medicación Hospitalaria de Dispensación Ambulatoria (MHDA) y por lo tanto no se generan avisos relacionados con esta medicación.

- Omisión de los avisos clínicos. La baja aceptación de los avisos es uno de los efectos no deseados de los SADC. Las principales razones, recogidas en la bibliografía, por las que hay una baja respuesta por parte de los clínicos a los avisos están relacionadas son la gran cantidad de avisos y la baja relevancia clínica de estos. Los clínicos tienden a obviar los avisos por falta de especificidad, por falta de contextualización del aviso con las características del paciente o por falta de claridad de la recomendación dada.

Mejoras futuras en el PREFASEG y en el Self Audit

En el futuro, los esfuerzos deben orientarse a salvar las dificultades asociadas a la implantación y desarrollo de los SADC. En el caso de PREFASEG y Self Audit los principales requisitos de mejora detectados se exponen a continuación:

- Para mejoras en la interoperabilidad e integración entre sistemas es necesario:

    - Potenciar el intercambio de información clínica entre programas informáticos diferentes y entre niveles asistenciales. En Cataluña existe diversidad de proveedores de salud y es frecuente que cada uno tenga su sistema informático específico y que no siempre sea fácil la sincronización de información entre sistemas.

    - Normalizar y estandarizar la información clínica y asistencial, utilizando una terminología médica común en todos los sistemas. La utilización, por ejemplo, de la codificación SNOMED CT (Systematized Nomenclature of Medicine- Clinical Terms) [74] permitiría enviar, recibir e integrar información médica entre diferentes sistemas [75] [76].

- Para mejoras relacionadas con el mantenimiento y actualización de los contenidos se requiere:

    - Aumentar el grado de especificidad de los avisos, para evitar la fatiga de alertas a los clínicos e incrementar el grado de aceptación de las recomendaciones.

    - Ampliar el contenido clínico, incluyendo avisos relacionados con la medicación MHDA y la medicación no financiada.

    - Disponer de plataformas de mantenimiento de contenidos más agiles y flexibles, que permitan ser autónomos en las actualizaciones sin requerir de intervención técnica.

- Para mejoras a nivel de desarrollos informático es esencial:

    - Incorporar sistemas inteligentes para la gestión de la información clínica para optimizar los avisos generados por los SADC. Un ejemplo sería incluir herramientas de Procesamiento de Lenguaje Natural (PLN) que permitiría obtener información incluida en la historia clínica en formato texto y la estructuraría de forma codificada y entendible para los sistemas informáticos [77] [78].

    - Definir algoritmos ágiles para interpretar la información y establecer ramas de decisión según cada caso.

    - Agilizar los tiempos de respuestas, rendimiento, permitiendo gestionar un gran volumen de datos sin que suponga lentitud de respuesta.

    - Utilizar un lenguaje informáticos más novedoso, evolucionado y más flexible.

    - Evolucionar el Look & Feel de PREFASEG y Self Audit para hacer las herramientas más amigables e intuitivas, prestando especial atención en los aspectos visuales y de usabilidad.

- Facilitar sistemas automáticos para la extracción de la información de trazabilidad y el seguimiento de la aceptación de los avisos generados por PREFASEG y Self Audit.

- Para mejoras relacionadas con la difusión del conocimiento se precisa:

  - Publicar los datos disponibles de la utilización del PREFASEG y Self Audit para compartir el conocimiento, establecer estrategias de sinergia con otros territorios o países [79].

  - Definir nuevos estudios sobre: impacto de los SADC sobre resultados en salud, satisfacción del paciente y del usuario respecto los SADC.

HIPOTESIS Y OBJETIVOS

Hipótesis del trabajo:

Los SADC incorporados a la HCE del ICS ayudan a evitar la generación de PRM y reducen los existentes según la información recogida en las HCE de los pacientes.

Objetivo principal:

Describir las características de los SADC incorporados en la HCE de la atención primaria de Cataluña en el ámbito farmacoterapéutico, así como analizar su contribución para evitar nuevos PRM en el momento de la prescripción y analizar la capacidad de ayudar a reducir el número de pacientes con PRM, contribuyendo a mejorar la seguridad clínica en el uso de medicamentos

Objetivos específicos:

1. Describir las características funcionales del Self Audit y del PREFASEG, así como detallar las diferentes dimensiones de seguridad que disponen estos SADC.
2. Analizar, en ambas herramientas, los tipos de PRM relacionados con duplicidades terapéuticas, tratamientos con alguna alerta de seguridad de la AEMPS, contraindicaciones por problemas de salud, fármacos desaconsejados por edad del paciente, duraciones inadecuadas de algunos tratamientos, combinaciones de elevada carga anticolinérgica.
3. Medir la aceptación en AP de los avisos de seguridad que aparecen en la HCE a través del módulo de seguridad PREFASEG en el momento de realizar una prescripción.
4. Comparar el uso de PREASEG entre el ámbito de atención primaria y el ámbito hospitalario.
5. Medir la reducción en el número de PRM que se detectan a través de la herramienta de Self Audit en la AP.
6. Realizar un análisis descriptivo del uso del PREFASEG y del Self Audit en AP en los diferentes territorios de Cataluña.

7. Identificar el perfil de medicamentos más frecuentemente implicados en cada PRM.
8. Analizar el efecto de un indicador asistencial incentivado en la reducción de los PRM a nivel de la AP.
9. Realizar un análisis temporal de la resolución de los PRM detectados a nivel de AP

MATERIAL Y MÉTODOS

Métodos:

Se diseñó un estudio descriptivo, transversal, que se inició en enero 2016 y continuó hasta diciembre 2018.

Se desarrolló en el ámbito de la AP del ICS, principal entidad proveedora de servicios sanitarios de Cataluña, región del nordeste de España, que da cobertura a una población de 5.8 millones de habitantes de los diferentes territorios catalanes, a los que atiende mediante una red de 288 equipos de AP y 8 hospitales. El ICS es una empresa de carácter público que cuenta con un total de 42.374 profesionales que prestan servicios al 80% de la población de Cataluña.

Muestra de estudio:

La muestra estudiada la constituyeron todas las prescripciones de los 6.411 médicos de AP del ICS (es decir el 100% de la plantilla médica) que utilizaron la HCE durante el período de estudio.

Dado que todos los médicos de AP del ICS empleaban el Self Audit y el PREFASEG en su práctica habitual, no se dispuso de un grupo control para establecer una comparación. Por ello, analizamos la evolución de los resultados del uso de las herramientas a lo largo del tiempo.

Variables e indicadores relacionados con PREFASEG

La variable principal del estudio fue el número de avisos de PRM generados por PREFASEG. Otra de las variables estudiadas fue el número de avisos aceptados. Un aviso se consideró “aceptado” cuando: el medicamento que generó el aviso de seguridad no se prescribió, por lo que no se dio de alta ese medicamento en la HC del paciente.

Algunos avisos de PREFASEG van asociados a recomendaciones de seguimiento clínico o de reducción de dosis. Por tanto, seguir estas recomendaciones no comporta la retirada del medicamento que ha generado el aviso. En consecuencia, estos avisos no se han considerado como avisos aceptados.

En PREFASEG se definieron los siguientes PRM:

(1) Interacciones farmacológicas
(2) Duplicidades terapéuticas
(3) Fármacos desaconsejados en geriatría
(4) Contraindicaciones con una alerta de seguridad publicada por la AEMPS
(5) Contraindicaciones por problemas de salud y/o variables clínicas
(6) Teratógenos en embarazadas
(7) Combinaciones de fármacos anticolinérgicos
(8) Antecedentes de hipersensibilidades o alergias (sospechas, no confirmadas)
(9) Reacciones adversas a medicamentos

Se analizó el global de avisos de PRM generados y aceptados por PREFASEG. De forma más detallada se estudiaron los PRM de seguridad relacionados con duplicidades terapéuticas, fármacos desaconsejados en geriatría y alertas de seguridad de la AEMPS (agencia reguladora de medicamentos en España).

Los avisos de PRM de "duplicidades terapéuticas" detectaban pacientes con alguna prescripción no beneficiosa de dos o más medicamentos con el mismo principio activo (solo o en combinación) y/o con la misma acción farmacológica. Se abordaron duplicidades de más de 50 grupos farmacológicos distintos de uso habitual en la AP. De cada grupo se diferenciaban "duplicidades relevantes clínicamente" y "duplicidades de ajustes de dosis" (combinaciones buscadas con un objetivo terapéutico). Dependiendo de la relevancia se generaban avisos marcados con diferentes colores: rojo (alta relevancia) y naranja (media relevancia).

Durante el período de estudio, los avisos de PRM de "alertas de seguridad de la AEMPS" notificaban contraindicaciones de: "triple whammy", coxibs, diclofenaco, aceclofenaco, cilostazol, Ivabradina, agomelatina, escitalopram, citalopram, trimetazidina, raloxifeno/bazedoxinfeno, ranelato de estroncio, aliskireno y canaglifozina (detalle tabla 4). Estos avisos se consideraron avisos de alta relevancia porque eran contraindicaciones absolutas, además de tener una alerta de seguridad específica de la AEMPS y por eso salían con una marca en color rojo.

Los avisos de PRM de "fármacos desaconsejados en geriatría" detectaban pacientes mayores de 75 años que tenían medicación inapropiada, con un perfil de beneficio-riesgo más desfavorable por su edad. La selección de medicamentos considerados inapropiado para los ancianos mayores de 75 años se basó con los criterios Beers 2015[4], STOP/START[64], Priscus[80] y EU-PIM[81] . Estos avisos se mostraban en pantalla como avisos de relevancia media-baja, ya que la literatura los cataloga como que se deben administrar con precaución.

Recogida y análisis de datos relacionados con PREFASEG:

Los datos analizados proceden de la estación clínica ECAP que alberga la prescripción activa de los pacientes, sin embargo, no se han analizado datos de pacientes concretos. El estudio se restringió a los medicamentos prescritos y financiados por el Sistema Nacional de Salud, y de uso en la AP.

En enero del 2016 se empezó a extraer información sobre los distintos tipos de avisos de PRM generados por PREFASEG, los cuales quedaban identificados internamente en la HCE del paciente. Así se registraron el número de avisos de cada PRM generado, los fármacos implicados en cada aviso y la aceptación o rechazo del aviso. Cada mes se fueron acumulando los avisos generados y aceptados por los clínicos en un repositorio informático. Anualmente se analizaron el conjunto de datos a través de las extracciones informáticas de las bases de datos del ECAP. La trazabilidad de los avisos se guardó y organizó en los servidores informáticos considerando la estructura organizativa del ICS, es decir diferenciando los territorios sanitarios en que se organiza la institución y los diferentes niveles estructurales.

Se realizó un análisis descriptivo de los avisos generados y aceptados de los distintos PRM en los años 2016, 2017 y 2018. Inicialmente, el análisis fue anual porque los contenidos clínicos cambiaban anualmente. Los cambios de contenidos se dieron por situaciones diversas: inclusión de nuevos medicamentos comercializados, modificaciones en la definición de los avisos de PRM existentes para hacerlos más específicos, abordaje de más grupos farmacológicos, entre otros. A pesar de los cambios de contenidos, dado que los datos eran acumulados, también se realizó un análisis global de los avisos generados y aceptados en los tres años estudiados.

Variables e indicadores relacionados con Self Audit

La variable principal del estudio del uso de Self Audit fue el número de PRM resueltos. Un PRM se consideró "resuelto" cuando: (1) el medicamento o los medicamentos que causaron el PRM se eliminaron de la prescripción activa del paciente, o (2) el diagnóstico se registró como resuelto.

Se analizaron los principales tipos de PRM de seguridad detectados por Self Audit, y se estudiaron más detalladamente los PRM clínicamente relevantes que habían sido vinculados al indicador de seguridad incentivado. Este indicador de seguridad incluía 3 PRM: (1) Duplicidades terapéuticas; (2) alertas de seguridad de la Agencia Española de Medicamentos y Productos Sanitarios (AEMPS), y (3) polimedicación en pacientes mayores de 65 años con algunos PRM específicos.

El PRM relacionado con las duplicidades terapéuticas detectó pacientes con prescripción no beneficiosa de dos o más fármacos que presentan el mismo principio activo (solo o en combinación) y/o la misma acción farmacológica. Además, se diferenciaron claramente las "duplicidades clínicamente relevantes" y las "duplicidades de ajustes de dosis" (es decir, combinaciones buscadas con un objetivo terapéutico), y solo se vincularon al indicador de seguridad aquellas consideradas relevantes.

Durante el periodo de estudio, las alertas de seguridad de la AEMPS incluían las siguientes contraindicaciones: El "Triple Whammy"; coxibs, diclofenaco y aceclofenaco; cilostazol; ivabradina; escitalopram y citalopram; trimetazidina; raloxifeno y bazedoxifeno; ranelato de estroncio; aliskirén; y canagliflozina.

Tabla 4. Resumen de los distintos criterios de alerta de seguridad de la AEMPS

FÁRMACO	**CRITERIOS ALERTA**
Citalopram	Altas dosis:
	- Por encima de 40 mg/día.
	- Por encima de 20 mg/día en pacientes >65 años.
	- Por encima de 20 mg/día en pacientes que padezcan disfunción hepática.
	Administrado en combinación con otros fármacos que también prolongan el intervalo QT del electrocardiograma.

Escitalopram	Dosis altas (>10 mg/día en pacientes >65 años).
	Administrado en combinación con otros fármacos que también prolongan el intervalo QT del electrocardiograma.
Aliskiren	En pacientes con diagnóstico de diabetes mellitus II o en tratamiento con fármacos antidiabéticos.
	Administrado conjuntamente con inhibidores de la ECA
Cilostazol	En pacientes que padezcan algún problema de salud en el que esté contraindicado su uso, por ejemplo, hemorragia cerebral, arritmias ventriculares graves o insuficiencia cardiaca.
	O, en tratamiento concomitante con:
	- 2 Antiagregantes plaquetarios
	- Antiagregante plaquetario y anticoagulante
Trimetazidina	En pacientes con diagnóstico de trastornos extrapiramidales y del movimiento.
Raloxifeno o bazedoxifeno	En pacientes que padezcan cualquier problema de salud en el que esté contraindicado, por ejemplo, tromboembolismo venoso, saco uterino, cáncer de endometrio o insuficiencia hepática de cualquier grado.
COXIBS	En pacientes que padezcan cualquier problema de salud en el que esté contraindicado, por ejemplo, cardiopatía isquémica, enfermedad arterial periférica, enfermedad cerebrovascular, insuficiencia cardíaca o enfermedad inflamatoria intestinal.
Diclofenaco o Aceclofenaco	En pacientes que padezcan algún problema de salud en el que esté contraindicado su uso, por ejemplo, cardiopatía isquémica, enfermedad arterial periférica, enfermedad cerebrovascular o insuficiencia cardiaca.
Agomelatina	En pacientes ≥75 años de edad.
Ivabradina	Coadministración con verapamilo.
"Triple Whammy" [82] (AINE + ISRA + diureticos)	En pacientes ≥ 75 años o en tratamiento para la diabetes.
Canagliflozina	En pacientes que padezcan algún problema de salud en el que sea necesario ser más cuidadoso debido a un mayor riesgo de amputación.

El PRM relacionado con incidencias de polimedicación detectó pacientes mayores de 65 años con 10 o más medicamentos prescritos (en 2016 o 2017) y con algunos PRM específicos, como doble antiagregación plaquetaria durante más de 12 meses, combinación de fármacos anticolinérgicos, u otros medicamentos evitables. En 2018 cambió el denominador y se definió polimedicación como un paciente con 8 o más medicamentos prescritos.

Recogida y análisis de datos relacionados con Self Audit:

Los datos analizados proceden de la estación clínica ECAP que alberga la prescripción activa de los pacientes, sin embargo, no se han analizado datos de pacientes concretos. El estudio se restringió a los medicamentos prescritos y financiados por el Sistema Nacional de Salud, y de uso en la AP.

Mensualmente y de manera automática se realizó una extracción de datos de prescripción activa que identificaba el número de pacientes con cada tipo de PRM que detectaba Self Audit.

A lo largo de los tres años analizados (2016, 2017 y 2018) se estudiaron 6 momentos o cortes transversales de información. Dentro de cada año se calcularon las variaciones en el número de PRM entre los datos considerados basales y los datos finales y así se estableció el % de variación. No se pudieron comparar datos entre diferentes años porque los criterios que definían la detección de PRM eran diferentes de un año a otro y por lo tanto no medían lo mismo. Así, por ejemplo, si en el PRM de duplicidades en un año se añadió un nuevo grupo farmacológico o bien se introdujeron más fármacos en algún grupo de duplicidad existente, eso generó que las detecciones de duplicidades aumentaran, ya que en años anteriores no se detectaban esas duplicidades.

Los datos de las extracciones del mes de abril se consideraron datos basales porque era el momento en que se habían actualizado los criterios que definían la detección de PRM y se proponían las metas a alcanzar ligadas al indicador incentivado. Los datos del mes de diciembre se consideraron los datos finales porque eran los datos del último mes del año natural y coincidían con en el último momento o corte de evaluación del indicador de seguridad. La diferencia entre el basal y el final nos indicaba el número de PRM resueltos respecto el inicio o

bien el número de PRM incrementados. No se siguieron en el tiempo los PRM de pacientes concretos.

El indicador de seguridad media la variación de una selección de PRM mencionados anteriormente. El efecto del indicador asistencial incentivado se evaluaba por la reducción de los PRM a nivel de la AP durante un año, que era el tiempo en que el indicador permanecía sin cambios y que coincidía con la vigencia del contrato de gestión que firmaban los médicos de AP.

Para evaluar el indicador se midió si en unos meses concretos los médicos habían conseguido llegar a una meta establecida a principios de año, calculada a partir del dato basal. La meta para cada médico correspondía a un número concreto de PRM menor que el de inicio de año. En los años estudiados hubo 2 o 3 cortes transversales en meses concretos en que la extracción de información de los PRM de prescripción activa fue evaluada y se midió si los médicos habían conseguido llegar a la meta. En 2016 la evaluación se realizó en el mes de setiembre y diciembre, mientras que en el 2017 y 2018 la evaluación se realizó en el mes de junio, setiembre y diciembre.

RESULTADOS

ARTÍCULO 1. Safer prescription of drugs: Impact of the PREFASEG System to Aid Clinical Decision-making in Primary Care in Catalonia

Title:

Safer prescription of drugs: Impact of the PREFASEG System to Aid Clinical Decision-making in Primary Care in Catalonia

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Abstract

Background: In 2008, the Institut Català de la Salut (ICS, Catalan Health Institute) implemented a prescription decision support system in its electronic clinical workstation (ECW), which automatically generates online alerts for general practitioners when a possible medication-related problem (MRP) is detected. This tool is known as PREFASEG, and at the time of beginning a new treatment, it automatically assesses the suitability of the treatment for the individual patient. This analysis is based on ongoing treatments, demographic characteristics, existing pathologies, and patient biochemical variables. As a result of the assessment, therapeutic recommendations are provided. The objective of this study is to present the PREFASEG tool, analyse the main alerts that it generates, and determine the degree of alert acceptance.

Methods: A cross-sectional descriptive study was carried out to analyse the generation of MRP-related alerts detected by PREFASEG during 2016, 2017, and 2018 in primary care (PC) in Catalonia. The number of MRP alerts generated, the drugs involved, and the acceptance/rejection of the alerts were analysed. An alert was considered "accepted" when the medication that generated the alert was not prescribed, thereby following the recommendation given by the tool. The MRP alerts studied were therapeutic duplications, safety alerts issued by the Spanish Medicines Agency, and drugs not recommended for use in geriatrics. The prescriptions issued by 6,411 ICS PC physicians who use the ECW and provide their services to 5.8 million Catalans through 288 PC teams were analysed.

Results: During the 3 years examined, 67.2 million new prescriptions were analysed, for which PREFASEG generated 4,379,866 alerts (1 for every 15 new treatments). A total of 1,222,159 alerts (28%) were accepted. Pharmacological interactions and therapeutic duplications were the most detected alerts, representing 40 and 30% of the total alerts, respectively. The main pharmacological groups involved in the safety alerts were nonsteroidal anti-inflammatory drugs and renin-angiotensin system inhibitors.

Conclusions: During the period analysed, 28% of the prescriptions wherein a toxicity-related PREFASEG alert was generated led to treatment modification, thereby helping to prevent the generation of potential safety MRPs. However, the tool should be further improved to increase alert acceptance and thereby improve patient safety.

Keywords: Clinical decision support system, primary care, clinical safety, electronic prescription, pharmacovigilance, medicines use

BACKGROUND

According to a European Commission report, 3–10% of hospital admissions between 2012 and 2014 were caused by adverse drug events (ADEs), totalling 2.5–8.4 million cases annually. In addition, approximately 2.1–6.5% of hospitalised patients experienced an ADE, corresponding to 1.8–5.5 million annually [1]. Thus, since the late 1990s, patient safety has become a priority of health systems [2,3], and several initiatives have identified the need for a new culture of safety in the health and policy environment [4–6]. To achieve this, and according to the definition of clinical safety, it is essential to define actions to avoid, prevent, and improve adverse effects or injuries from healthcare processes where possible, since it should be acknowledged that some adverse events are inherent in treatment, and cannot always be avoided or minimised.

In this context, the 1999 technical report 'To err is human' by the Institute of Medicine (OIM) highlighted the need to develop new information and communications technologies to reduce medical errors [2], and, beyond this, prescriptions which could increase the risk of developing adverse effects. Subsequent reports later affirmed that the electronic record of healthcare activity that is typical of an electronic health record (EHR), together with the integration of clinical decision support systems (CDSSs) into these EHRs, should contribute to guaranteeing quality in the healthcare system [7,8] by helping to reduce preventable adverse effects.

In the scientific literature we find different definitions of a CDSS [9,10]. According to Kawamoto et al. [11], a CDSS can be considered any electronic system designed to help clinical decision making, which takes into account the characteristics of the patient to generate a specific evaluation and provide a recommendation to be evaluated by the practicing clinician. The design and functionalities of these CDSSs can be very varied. Some authors consider that CDSSs aimed at the initial prescription phase may have the greatest impact on improving patient safety [12], while others discuss the fact that integration of a CDSS into the HER renders it possible to provide patient histories along with interactive signals that alert professionals to situations of risk for the patient [13]. As a result, the prescription process can be improved and the clinical safety of patients enhanced [12,14,15].

CDSSs have been found to bring multiple benefits to patient care [16–19], wherein it has been reported that they contribute to improving the dosage and selection of drugs, while also encouraging patients to take part in preventive activities, improving test results, decreasing morbidity, and improving the quality of care [20]. In contrast, the main risk of CDSSs is the alert fatigue experienced by physicians who are faced with a multitude of prompts and reminders on-screen, which can lead to important alerts being ignored [21,22].

The Catalan Health Institute (ICS) is a public entity that provides health services to 80% of the population of Catalonia. In 2008, in line with promoting the clinical safety of the patient, it designed and integrated a CDSS into its primary care electronic clinical workstation (ECW) that made it possible to detect certain medication-related problems (MRPs) online. This CDSS, which is known as PREFASEG (PREscripción FArmacéutica SEGura, i.e., safe pharmaceutical prescription), is a computer tool that acts interactively to alert clinicians to any potential drug use-related problems during the process of deciding the most appropriate treatment for their patient.

To understand the means by which PREFASEG functions, we consider the prescription of a new drug to a specific patient. At the point at which the prescription is requested by the clinician, PREFASEG is activated and performs an assessment of the prescription to verify that it is safe for the patient, and that it does not pose a potential risk to their health. This evaluation is carried out based on the different MRPs detected by the tool, which include: (1) Drug interactions; (2) Therapeutic duplications; (3) Drugs advised against for use in geriatrics; (4) Contraindications with a safety alert published by the Spanish Agency for Medicines and Health Products (AEMPS, Agencia Española del Medicamentos y Productos Sanitarios); (5) Contraindications due to health problems and/or clinical variables; (6) Drugs that are known to be teratogens during pregnancy; (7) Anticholinergic drug combinations; (8) Patient history of hypersensitivity or suspected hypersensitivity reactions (suspected, not confirmed); and (9) Adverse drug events. To carry out this evaluation, a number of factors are taken into account, such as any active prescriptions that the patient already has on their record, other medical diagnoses or active health problems, the presence of any clinical variables with altered values, and the age and/or sex of the patient. In the event of a safety alert being generated following the above evaluation, the corresponding warnings are shown to the clinician (e.g., the risk to the patient and any therapeutic alternatives) so that he can decide whether to continue with the prescription or change the medication. These safety alerts are displayed in a simple manner on a single screen to permit their rapid consultation and understanding, as shown in Figure 1, which presents an example relating to

the prescription of a product that is not recommended for patients over 75 years of age. The information displayed includes the severity icon (two degrees, moderate or severe), the drug or active ingredient causing the alert, the cause of conflict (i.e., medication or active ingredient conflict, patient age, or pre-existing health problem), the risk to the patient, and any therapeutic alternatives. Each MRP alert is classified as either high (red indicator) or medium-low (orange indicator) clinical relevance, according to previously described recommendations [23].

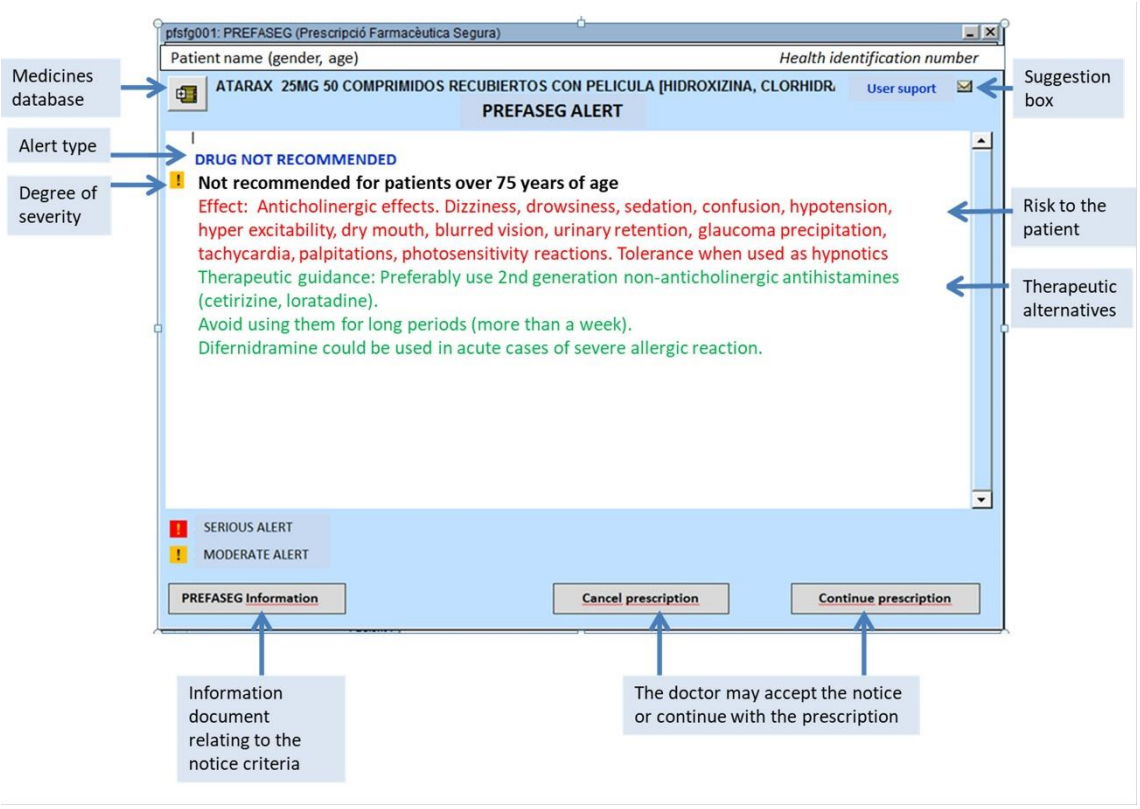

Figure 1. Example PREFASEG screen showing the various informative elements presented by the tool.

It is also possible that more than one alert is generated by the tool, and in such a case, the clinician is informed of all warnings associated with the different potential safety issues, as can be seen in Figure 2.

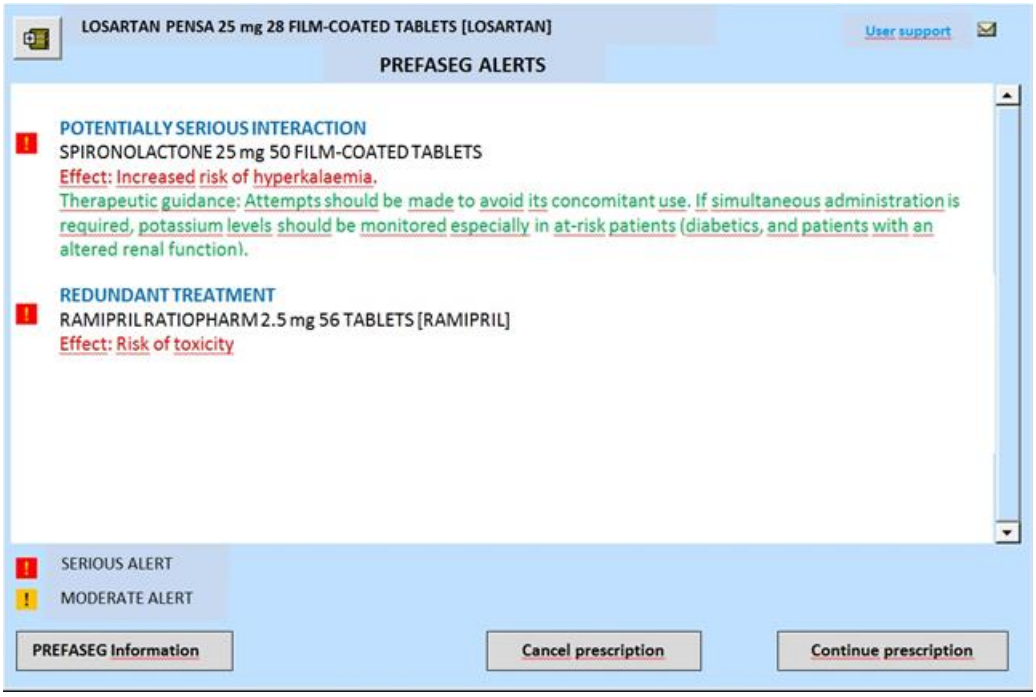

Figure 2. Example screen of the PREFASEG system with various included safety alerts and therapeutic recommendations.

Each alert generated by PREFASEG is recorded as "audit data" along with the information related to whether it has been accepted or whether prescription of the product was continued. The evaluation of these data allows us to determine if certain types of alerts are accepted to a greater degree than others, thereby improving the clinical content definitions to adapt the tool to the healthcare reality. PREFASEG consists of a calculation core in the Oracle PL/SQL, in which the calculations that access the tables of clinical contents have been optimised, and in which there is a minimum visual interface for the communication of safety alerts. This interface was developed using Developer Forms, which is the same technology employed to produce the ECW. As a result, the look and feel of the alert screens are comparable to those of the original ECW, and so maximum integration is achieved.

The contents of the MRP alerts are defined and maintained as described by a multidisciplinary group of expert professionals from the ICS (i.e., primary care (PC) physicians, pharmacists, and clinical pharmacologists) according to previous literature [9,24]. The MRP alerts are reviewed and updated each year according to the available scientific evidence, and as a result, the clinical content undergoes some changes from one year to the next. For example, references to the more current STOPP/START and Beers criteria were included in updates for drugs advised

against for use in geriatrics. Importantly, the clinical content can be revised at any time, and are updated from a specific maintenance platform known as 'Know How.'

In general terms, to provide the PREFASEG with clinical and pharmacological content, the following methodology was followed during its development:

1. Bibliographic search. Initially a bibliographic search was carried out in the PubMed database for the different MRPs addressed by PREFASEG, wherein national and international articles that were considered to be the most relevant and best adapted to our healthcare environment were reviewed. The safety alerts included in the ICS Clinical Practice Guidelines [25] were also considered.

2. Consensus with a group of experts. Following a literature review, the pharmacological groups to be included were selected and the messages to be presented to the prescribing physicians were defined. Each MRP alert was classified as high (red) or medium-low (orange) clinical relevance, as mentioned above [23]. The red alerts reflected situations of absolute contraindications, while the orange alerts were considered precautionary.

3. Adaptation of the clinical content to the table formats necessary for the PREFASEG computer program. The clinical content was transferred into a computer-readable language from various configuration tables presented in Excel, and for this purpose, it was necessary to code the active ingredients according to the Anatomical Therapeutic Chemical (ATC) classification. Similarly, the various health issues were coded according to the International Classification of Diseases ICD-10 system. To produce the clinical contents, ATC groups or groups of health problems were built. Each alert type was then defined and configured using a combination of various attributes, as outlined in Table 1.

Table 1. Combinable attributes in the configuration of each PREFASEG notice

Type of Alert	Combinable attributes in the PREFASEG message configuration
Interactions	▪ Active ingredient grouping based on the ATC
Duplicate therapies	▪ Active ingredient grouping based on the ATC
AEMPS safety alerts	▪ Age ▪ Active ingredient grouping based on the ATC ▪ Grouping based on health problems ▪ Dose of the active ingredient that generates the warning
Advised against for use in geriatrics	▪ Age

Contraindications due to health issues	▪ Grouping based on the ATC ▪ Grouping based on health problems ▪ Labelling of clinical variables (e.g., glomerular filtration and potassium levels)
Contraindications due to clinical variables	
Teratogens in pregnancy	
Combinations of anticholinergic drugs	▪ Grouping based on the ATC
Suspicions of hypersensitivity	▪ Grouping based on the ATC
Adverse drug reactions	▪ Grouping based on the ATC

The purpose of this study is therefore to describe the principal characteristics of the PREFASEG tool, the main safety alerts generated by PREFASEG in the Catalan PC system, the degree of acceptance of these alerts by physicians, and the main pharmacological groups implicated in the alerts. Furthermore, three of the most frequent alerts are also described in greater detail.

METHODS

A descriptive, cross-sectional study was designed, which began in January 2016 and continued until December 2018. This study was developed within the scope of the PC system of the ICS, which is the main entity that provides health services in Catalonia, and which covers a population of 5.8 million inhabitants of the different Catalan territories through a network of 288 PC teams and 8 hospitals. The ICS is a public company with a total of 42,374 professionals who provide services to 80% of the population of Catalonia.

Study sample

The sample studied consisted of all prescriptions issued by the 6,411 ICS PC physicians who used the EHR during the study period.

Variables and indicators

The main variable of the study was the number of MRP alerts generated by PREFASEG. Another of the variables studied was the number of accepted alerts. An alert was considered "accepted" when the medicine that generated the safety alert was not prescribed.

Some PREFASEG alerts are associated with recommendations for clinical follow-ups or dose reductions. Therefore, following these recommendations does not entail the withdrawal of the

treatment that has generated the alert. Consequently, these alerts are not considered "accepted" alerts.

Description of the MRPs included in PREFASEG

Box 1 includes the MRPs that are defined in the PREFASEG system (further details can also be found in Annex 1):

(1) Drug interactions

(2) Therapeutic duplications

(3) Drugs advised against for use in geriatrics

(4) Contraindications with a safety alert published by the Spanish Agency for Medicines and Health Products (AEMPS, Agencia Española del Medicamentos y Productos Sanitarios)

(5) Contraindications due to health problems and/or clinical variables

(6) Drugs that are known to be teratogens during pregnancy

(7) Anticholinergic drug combinations

(8) Patient history of hypersensitivity or suspected hypersensitivity reactions (suspected, not confirmed)

(9) Adverse drug events

The global MRP alerts generated and accepted by PREFASEG were analysed. More specifically, the safety MRPs related to therapeutic duplications, medicines not recommended for use in geriatrics, and safety alerts from the AEMPS were examined in greater detail.

The contents of the MRP alerts were defined and maintained as described by a multidisciplinary group of expert professionals from the ICS according to previous literature [9,24]. The MRP alerts were reviewed and updated each year according to the available scientific evidence, and as a result, the clinical content underwent some changes from one year to the next. Each MRP alert was classified as either high or medium-low clinical relevance, as described above [23].

The MRP alerts corresponding to "therapeutic duplications" detected patients with a non-beneficial prescription of two or more medicines based on the same active ingredient (alone or in combination) and/or with the same pharmacological action (further details can be found in Annex 2). Duplications of more than 60 different pharmacological groups commonly used in PC were addressed. In each group, "clinically relevant duplications" and "dose adjustments duplications" (combinations sought with a therapeutic objective) were clearly differentiated.

Depending on their relevance, alerts marked with different colours were generated, as indicated above.

During the study period, MRP alerts associated with "AEMPS safety alerts" reported contraindications for the "Triple Whammy," COXIBS, diclofenac, aceclofenac, cilostazol, ivabradine, agomelatine, escitalopram, citalopram, trimetazidine, raloxifene/bazedoxifene, strontium ranelate, aliskiren, and canagliflozin (further details can be found in Annex 3). These alerts were considered to be highly relevant because they were absolute contraindications, in addition to having a specific safety alert originating from the AEMPS, and so they were indicated in red.

The MRP alerts corresponding to "medicines not recommended for use in geriatrics" detected patients ≥75 years of age who had been prescribed inappropriate medication that posed a more unfavourable risk-benefit profile due to their age. The selection of medications considered inappropriate for this age group was based on the Beers (2015) [26], EU-PIM (European Consensus) [27], STOPP/START [28], and PRISCUS [29] criteria (further details can be found in Annex 1). These alerts were displayed on-screen as alerts of medium-low relevance (i.e., orange colour) since the literature indicates that they should be administered with caution.

Data collection and analysis

The analysed data were obtained from the ECW that stores the active prescriptions of all patients; however, data from specific patients were not analysed. The study was restricted to drugs prescribed and financed by the National Health System for use in the PC setting.

In January 2016, information began to be extracted regarding the different types of MRP alerts generated by PREFASEG, which were internally identified in the patient's EHR. Thus, the number of advisories for each MRP generated, the medicines involved in each alert, and the acceptance or rejection of the alert were recorded. Each month, the alerts generated by the system and accepted by the clinicians were accumulated in a computer repository. The data set was analysed annually through computerised extractions from the ECW databases. The alert traceability was stored and organised on computer servers according to the organisational structure of the ICS, i.e., with differentiation between the health territories in which the institution is organised.

A descriptive analysis was carried out of the generated and accepted alerts of the different MRPs from January 2016 to December 2018. Initially, the analysis was carried out on an annual basis

because the clinical contents changed annually. These content changes occurred for a number of reasons, including the inclusion of new marketed drugs, modifications in the definitions of existing MRP alerts to render them more specific, and the inclusion of additional pharmacological groups. Despite these content changes, the data were accumulated, and a global analysis of the alerts generated and accepted during the three-year study period was also carried out.

RESULTS

General analysis of the MRP alerts generated by PREFASEG

During the period of study, 22.5, 22.3, and 22.4 million new prescriptions were issued in the ICS PC system in 2016, 2017, and 2018, respectively, while the number of alerts generated by PREFASEG were 1.17 million in 2016, 1.43 million in 2017, and 1.77 million in 2018. Thus, the percentage of MRP alerts generated by the tool with respect to the number of new prescriptions issued were 5% in 2016, 6% in 2017, and 8% in 2018.

The global acceptance of these alerts varied throughout the three years studied, ranging from 31% (362,732) in 2016 to 26% (457,976) in 2018 (see Table 1), which corresponds to 69–74% of the MRP alerts generated by PREFASEG during the years of study. Analysis of the accumulated number of alerts issued over the three-year study period (i.e., 4.38 million alerts) gave a 28% degree of acceptance (i.e., 1.22 million accepted alerts).

Table 2. MRP alerts generated and accepted by PREFASEG between January 2016 and December 2018

PREFASEG	2016			2017			2018			Sum 2016–2018		
TYPE OF MRP ALERT	Alerts generated	Alerts accepted	% Accepted alerts	Alerts generated	Alerts accepted	% Accepted alerts	Alerts generated	Alerts accepted	% Accepted alerts	Alerts generated	Alerts accepted	% Accepted alerts
Interactions	439,507	118,485	27%	550,692	138,947	25%	701,687	166,452	24%	1,691,886	423,884	25%
Duplicate therapies	426,506	141,371	33%	463,418	136,097	29%	546,797	148,943	27%	1,436,721	426,411	30%
Advised due to age (>75 years)	108,974	32,345	30%	144,807	41,740	29%	188,139	50,299	27%	441,920	124,384	28%

AEMPS safety alerts	59,146	18,301	31%	86,308	21,958	25%	84,158	18,720	22%	229,612	58,979	26%
Contraindications due to health issues	35,164	13,771	39%	67,452	21,330	32%	105,749	28,390	27%	208,365	63,491	30%
Teratogens in pregnancy	11,721	4,200	36%	10,938	3,830	35%	11,404	3,709	33%	34,063	11,739	34%
Combinations of anticholinergic drugs	1,077	423	39%	2,619	863	33%	3,171	877	28%	6,867	2,163	31%
Suspicions of hypersensitivity	76,883	28,952	38%	84,099	29,759	35%	93,852	30,568	33%	254,834	89,279	35%
Adverse drug reactions	15,397	4,884	32%	23,712	6,927	29%	36,489	10,018	27%	75,598	21,829	29%
TOTALS	**1,174,375**	**362,732**	**31%**	**1,434,045**	**401,451**	**28%**	**1,771,446**	**457,976**	**26%**	**4,379,866**	**1,222,159**	**28%**

When analysing the alerts generated from the different MRPs throughout the study period (2016–2018), it was observed that those related to drug interactions, therapeutic duplications, and drugs advised against for use in geriatrics were the most common. Taking the data collected over the three years, 39% (1,691,886) of the 4,379,866 million alerts generated were for drug interactions, 33% (1,436,721) were for therapeutic duplications, and 10% (441,920) were for the use of drugs advised against in geriatrics. Thus, these three types of MRP alerts accounted for more than three-quarters of the PREFASEG alerts (3,570,527; 82%). Of these, 27% were accepted and 73% were ignored. In addition, of the 34,063 alerts related to teratogens in pregnancy, 22,324 (66%) were ignored.

The types of alerts with the highest percentage of acceptance were those related to a history of suspected (unconfirmed) drug hypersensitivity, with 35% (89,279) of these alerts being accepted over the three years studied. Detailed analyses indicated that four non-steroidal anti-inflammatory drugs (NSAIDs, i.e., ibuprofen, naproxen, desketoprofen, and diclofenac) represented 45% (113,936) of the suspected hypersensitivity reactions reported by PREFASEG, with ibuprofen generating the highest number of alerts (61,026). In addition, during the study period, the number of suspected hypersensitivity reaction alerts for β-lactam antibiotics alone or in combination fell into the second largest group, with 39,622 alerts and an acceptance level of 63% (25,153).

In contrast, the alerts related to potential teratogenic compounds during pregnancy had a lower degree of acceptance (i.e., 34%, 11,739). It was observed that the active ingredients that generated the most alerts were ibuprofen (10,864) and acetylsalicylic acid (4,336) out of a total of 34,063.

Overall, the alerts with the lowest degree of acceptance were those attributed to interactions between treatments, with 25% (423,884) of a total of 1,691,886 being accepted. More specifically, the interactions of NSAIDs with acetylsalicylic acid generated the greatest number of alerts, reaching 220,507 alerts with an acceptance level of 18% (40,227). Table 3 outlines the 10 main interactions at the active ingredient level, which represent 30% (506,082) of all alerts of this type.

Table 3. Top 10 alerts related to drug interactions between January 2016 and December 2018

Original active ingredient	Conflicting active ingredient	Alerts generated	Acceptance
Ibuprofen	Acetylsalicylic acid	97,847	19%
Amlodipine	Simvastatin	85,358	24%
Naproxen	Acetylsalicylic acid	64,913	16%
Simvastatin	Amlodipine	59,453	26%
Dexketoprofen	Acetylsalicylic acid	32,455	16%
Acenocoumarol	Simvastatin	31,349	29%
Simvastatin	Acenocoumarol	31,349	26%
Tramadol and paracetamol	Citalopram	27,479	24%
Tramadol and paracetamol	Sertraline	26,872	24%
Diclofenac	Acetylsalicylic acid	25,292	24%
Enoxaparin	Acetylsalicylic acid	23,715	16%

Analysis of the PREFASEG alerts related to therapeutic duplication

In the three years studied, the four groups of duplications that generated the most alerts were the NSAIDs, paracetamol-type analgesics, renin-angiotensin system (RAS) inhibitors and gastric protectors (see Figure 2). Out of a total of 65 groups, these 4 duplication groups represented 42% (600,930) of the total alerts generated (1,436,721). Duplications related to analgesics and gastric protectors had the highest levels of acceptance during the study period, reaching 42% (88,435) and 32% (33,245), respectively. In contrast, duplications related to the SSRI antidepressants and the RAS inhibitor antihypertensives had the lowest degrees of acceptance, i.e., 20% (10,753) and 21% (20,940), respectively.

Furthermore, the pairs of active ingredients with the greatest numbers of alerts generated for duplications during the three years studied were paracetamol-paracetamol, paracetamol-paracetamol with tramadol, omeprazole-omeprazole, ibuprofen-ibuprofen, and metamizole-metamizole. These 5 pairs represented 22% (317,390) of the duplications, of which 144,450 (46%) were accepted.

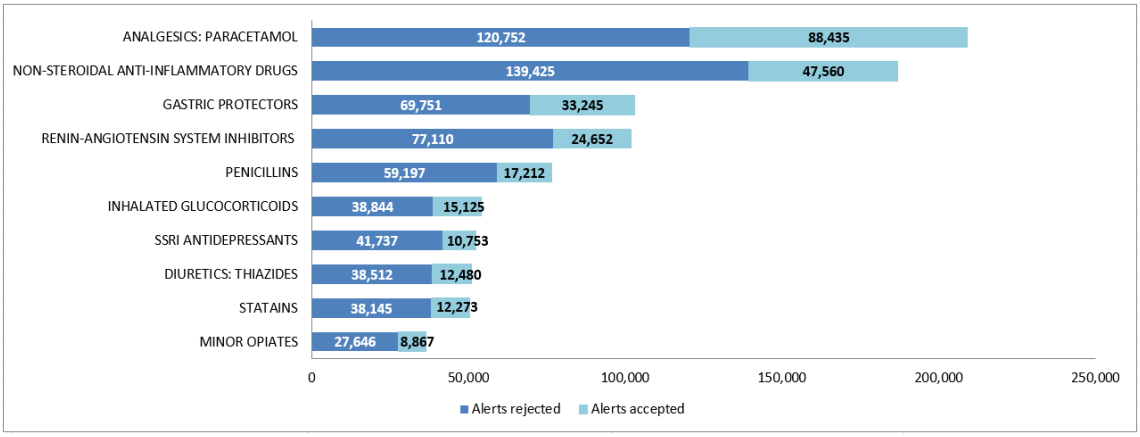

Figure 3. Degrees of detection and acceptance of the main types of duplication from January 2016–2018.

Moreover, the duplications related to antibiotics such as amoxicillin generated a considerable number of alerts, i.e., 76,409 over the three years studied, and their acceptance rate was relatively low at 23%. Upon the analysis of other groups of potentially dangerous duplications, such as those related to oral anticoagulants, it was observed that PREFASEG generated 14,903 alerts of duplications for this group, of which 42% (6,314) were accepted, and the prescriptions were not continued.

Analysis of PREFASEG alerts related to AEMPS safety alerts

It was found that the number of alerts related to AEMPS safety alerts increased throughout the study period, i.e., from 59,146 in 2016 to 84,158 in 2018. This was accompanied by a reduction in the degree of acceptance of these alerts from 31% (18,301) to 22% (18,720), respectively.

Analysing the details of these AEMPS alerts (see Table 4), it was apparent that the Triple Whammy, which considered the concomitant therapy of NSAIDs, diuretics, and RAS inhibitors, generated the highest degree of alerts, representing 85% (195,987) of the total alerts. The

degree of acceptance of this type of alert varied, ranging from 30% (13,867) in 2016 to 22% (15,988) in 2018, thereby indicating a decrease in acceptance over this three-year period. Reviewing the main anti-inflammatory drugs that generated the Triple Whammy alerts, it was observed that in 65% of the cases, the NSAIDs involved were ibuprofen and naproxen.

Table 4. Degree of detection and acceptance of the AEMPS safety alerts in 2016, 2017, and 2018

	2016			2017			2018		
AEMPS Alert	**Alerts**	**Alerts accepted**	**% Accepted**	**Alerts**	**Alerts accepted**	**% Accepted**	**Alerts**	**Alerts accepted**	**% Accepted**
"TRIPLE WHAMMY"*	46,020	13,867	30%	76,107	18,992	25%	73,860	15,988	22%
DICLOFENAC	7,288	2,588	36%	5,734	1,774	31%	5,137	1,511	29%
COXIBS	3,131	888	28%	2,535	616	24%	2,986	644	22%
ACECLOFENAC	805	204	25%	665	127	19%	487	101	21%
ESCITALOPRAM	645	204	32%	270	95	35%	305	72	24%
CITALOPRAM	495	189	38%	217	67	31%	302	104	34%
CILOSTAZOL	193	70	36%	181	66	36%	289	65	22%
AGOMELATINE	133	54	41%	175	54	31%	249	72	29%
IVABRADINE	130	51	39%	153	56	37%	200	48	24%
CANAGLIFLOZIN	-	-	-	128	42	33%	177	40	23%
TRIMETAZIDINE	115	62	54%	82	36	44%	111	47	42%
RALOXIFENE and BAZEDOXIFENE	106	64	60%	23	11	48%	30	20	67%
STRONTIUM RENALATE	53	39	74%	21	11	52%	22	5	23%
ALISKIREN	32	21	66%	17	11	65%	3	3	100%
Total	**59,146**	**18,301**	**31%**	**86,308**	**21,958**	**25%**	**84,158**	**18,720**	**22%**

* Triple Whammy: NSAIDs + RAS inhibitors + diuretics

As indicated in Table 4, the number of alerts generated by diclofenac decreased over time. More specifically, in 2016, diclofenac generated 7,288 alerts, while by 2018 this number had reduced to 5,137. However, the degree of acceptance also decreased from year to year, dropping from 36% (2,588) in 2016 to 29% (1,511) in 2018.

The alerts with the highest degree of acceptance were those related to strontium ranelate, raloxifene/bazedoxifene, and aliskiren; however the number of such alerts was low since these are drugs that are being gradually withdrawn from the market, or tend to be unused in daily practice.

Analysis of the PREFASEG alerts related to medicines not recommended for use in geriatrics between January 2016 and December 2018

The alerts generated by PREFASEG that were related to drugs advised against for use in geriatrics increased throughout the study period, i.e., from 108,974 in 2016 to 188,139 in 2018. However, a reduction in the degree of acceptance from 30% (32,345) to 27% (50,299), respectively, was also observed.

The two pharmacological groups that generated the highest number of alerts within this category were the benzodiazepines and the NSAIDs, representing 39% (172,574) and 21% (47,966) of a total of 441,920 alerts in the three years studied (see Table 5). More specifically, the alerts related to benzodiazepine usage in geriatrics increased by 55% during the study period, i.e., from 30,662 in 2016 to 68,974 in 2018. Alprazolam represented 44% (65,910) of the alerts generated for benzodiazepines in this group of patients (see Table 6), and overall, the benzodiazepine group showed an acceptance rate of 27% over the three years.

Within the NSAID alerts, it was observed that desketoprofen represented 48% (45,293) of the total alerts in this group, and this group showed one of the lowest levels of acceptance (i.e., 22%).

In general, analysis of the degrees of acceptance in this class of alerts shows a significant level of variation (see Table 5), and the pharmacological groups with the highest degree of acceptance (i.e., where no prescription was issued for the corresponding treatment) were the muscle relaxants (41%, 7,521) and the peripheral vasodilators (39%, 6,621).

Table 5. Pharmacological groups not recommended in the elderly that generated PREFASEG alerts from January 2016–December 2018

Not recommended pharmacological groups	Alerts generated	Total accepted	% Accepted
Benzodiazepines, hypnotics, and sedatives	172,574	47,966	27%
Anti-inflammatory and anti-rheumatic (NSAIDs, COXIBS)	94,034	20,627	22%
Antihypertensives	34,542	10,310	30%
Digestive system (otilonium, metoclopramide, glibenclamide, chlorporpamide)	31,496	8,945	28%
Chronic obstructive pulmonary disease treatments (theophylline)	19,285	4,758	25%
Central action muscle relaxants (cyclobenzaprine)	18,170	7,521	41%
Tricyclic antidepressants and Fluoxetine	17,289	5,654	33%

Peripheral vasodilators (pentoxifilline, nicergoline, nafthydrofuril)	16,958	6,621	39%
Respiratory system (systemic antihistamines)	14,219	4,917	35%
Hormone therapy (megestrol)	10,776	2,631	24%
Urinary antispasmodics (oxybutynin)	7,018	2,495	36%
Antithrombotics (cilostazol)	3,270	1,100	34%
Beta-blockers (sotalol)	1,105	392	35%
Opioid and anti-migraine pain relievers	868	342	39%
Antiparkinsonian drugs	316	105	33%

Table 6. Top 10 alerts for drugs advised against for use in geriatrics between January 2016 and December 2018

Active ingredient responsible for the alert	Alerts generated	Acceptance
Alprazolam	65,910	24%
Dexketoprofen	45,293	24%
Doxazosin	33,867	30%
Clonazepam	23,887	35%
Zolpidem	23,314	25%
Pentoxifylline	20,395	31%
Metoclopramide	19,098	28%
Hydroxyzine	18,328	29%
Etoricoxib	15,729	18%
Potassium clorazepate	15,468	29%

DISCUSSION

The main finding of this study was that the PREFASEG system appears to adopt the role of a CDSS that assists in preventing potential safety MRPs for patients by generating online alerts when starting a new treatment. During the period studied, it was observed that 28% of the generated security alerts led to a modification of the prescription (i.e., acceptance of the alert). In absolute terms, between 2016 and 2018, a total of 1,222,159 recommendations were accepted globally, which likely led to the avoidance of numerous potential MRPs in patients. Overall, PREFASEG reported a safety MRP in 1 out of every 15 new prescriptions. The degrees of acceptance of the recommendations were relatively high when compared with a similar study into a different online preventive alert system, where the percentages of acceptance ranged

from 12 to 14% [30]. However, the variability between studies was considerable; in a 2009 Cochrane review on the effects of online prompts/reminders, an improvement of only 4.2% was reported [18], while other studies described omissions of recommendations in between 49 and 96% of the cases [31]. In general, subsequent systematic reviews [32,33] concluded that online notification systems had only a small or moderate effect.

Despite the high number of potential MRPs avoided in patients in Catalonia, it should be noted that in the case of safety alerts relating to the use of medicines, it was striking that globally, >70% of the alerts generated by PREFASEG were ignored, which amounts to 3.16 million over the three-year study period. However, it must be taken into account that, on occasions, the recommendations given by PREFASEG involved modification of the drug dosage, or the following up of some clinical variable. This could translate into a higher degree of acceptance than registered by the system, since PREFASEG was only capable of measuring whether or not the prescription was continued. It should also be considered that not all alerts had the same degree of clinical relevance, with alerts being accompanied by either an orange or a red icon, depending on the importance of the recommendation, as also described in a previous study [23].

Over the course of the three years studied, the number of generated alerts increased. This was partly related to the fact that new and updated content was introduced into the PREFASEG system on an annual basis. The existence of a direct relationship between the increased consumption of certain drugs (e.g., the benzodiazepines) was also considered, in addition to the probability that greater numbers of MRP alerts could be generated from such drugs due to their increased use among the population. At the same time, it should be noted that the degree of acceptance of the alerts tended to decrease over time, with practitioners gradually ignoring the recommendations. This decline in acceptance could be partly attributed to alert fatigue; however, it will be necessary to further investigate the reasons behind the rejection of alerts, in addition to separately analysing the high and medium-low relevance alerts, while also considering the cases where the recommendation does not suggest a change of drug. It will also be essential to collect the opinions of the professionals who use the PREFASEG tool. According to various reports, the main reasons for low acceptance by clinicians are the large number of low-relevance alerts they receive and their poor content [21,22,34]. To reduce the risk of fatigue, it is therefore necessary to increase the specificity of the alerts, provide clear and concise information, and not impact on the clinician's workflow.

In relation to the ignored alerts regarding suspicions of a history of hypersensitivity to certain drugs, it is known that general practitioners tend to register cases of hypersensitivity that are reported by patients, despite the fact that such hypersensitivity has not been confirmed, and in many cases, are not real [35–37]. To address this issue, a number of hospitals are now working on a project to de-label patients with a supposed hypersensitivity reported in their clinical history unless it is confirmed by the corresponding tests.

Another type of MRP that drew significant attention due to its severity was that of teratogenic drugs, for which 66% of the generated alerts were ignored. However, it must be considered that not all medicines act as teratogens in all trimesters of pregnancy, and PREFASEG is unable to distinguish between such cases. It is also possible that some alerts were generated for women who were no longer pregnant but who, by some registration error, maintained a pregnancy status in their health records.

Regarding the alerts related to therapeutic duplications, it was observed that approximately 70% of these alerts were ignored by clinicians. However, many such alerts were related to adjustment of the daily dose of treatment, and so it was necessary to combine presentations at different doses; this was common in the groups of antihypertensive RAS inhibitors and antidepressants, and in the replacement of amoxicillin with amoxicillin-clavulanate. In terms of the NSAIDs and paracetamol-type analgesics, it was observed that prescriptions were authorised for issuing on demand if necessary, which often generated alerts related to duplication if an attempt was made to prescribe a drug from the same pharmacological group. Another group of duplications that drew attention due to their association with a high risk of serious adverse effects that motivate hospital admissions were the oral anticoagulants [38]. During the three-year study period, PREFASEG produced 14,903 alerts related to duplications in this group of drugs, which translated to an acceptance of 42% (6,314), wherein the prescription was not continued.

In the case of the AEMPS safety alerts, an unexpected low degree of acceptance was recorded considering that these constituted specific alerts from a regulatory agency [39]. In fact, throughout the three-year study period, the degree of acceptance of the AEMPS safety alerts decreased, and in 2018 they reflected the lowest percentage of acceptance (22%) of all alerts throughout that year. Among these notices, the Triple Whammy, which is associated with a significant increase in the risk of kidney failure [40], represented the largest number of alerts.

Upon examination of the alerts related to the use of drugs advised against in geriatrics, it was observed that the degree of acceptance ranged from 30% in 2016 to 27% in 2018. Despite the

fact that this alert category is considered of low clinical relevance, wherein use of a specific drug may not be recommended in older patients but is not totally contraindicated, it produced similar or even superior acceptance results compared to the AEMPS safety alerts. It was therefore considered that this level of acceptance was due to physicians being somewhat more sensitive to safety alerts related to elderly patients. However, we must not lose sight of the fact that >70% of these alerts were discarded and the corresponding prescriptions was generated, which could lead to potential adverse reactions in patients. In this context, it is estimated that drug-associated adverse effects produce approximately 6.5% of hospital admissions, of which more than half of these could be prevented [41–44].

The pharmacological groups that generated the highest number of alerts in geriatric patients were the benzodiazepines and the NSAIDs, which are also widely used drugs throughout the population. The significant increase in the number of alerts for benzodiazepines (i.e., from 30,662 in 2016 to 68,974 in 2018) was particularly surprising, and these were mainly attributed to alprazolam. It is known that both an advanced age, which is linked to metabolic and pharmacokinetic changes, and the number of drug treatments that a patient is receiving, are two of the situations that increase the risk of adverse drug effects to the greatest extent [45–47]. In addition, it must be considered that the world population is constantly aging, which is accompanied by a greater degree of pathologies, and an increase in the use of pharmaceuticals [48–50].

Analysing the percentages of acceptance for alerts related to the use of drugs advised against in geriatrics, significant variation was observed between the different pharmacological groups. More specifically, muscle relaxants and peripheral vasodilators were the groups with the highest degrees of acceptance. According to a previous study, physicians tend to prioritise alerts that are more clinically relevant, or that can be resolved with the least amount of time or effort [51].

In a classic study looking at hospitalisations caused by adverse effects, it was found that the majority occurred in the elderly, and were due to commonly used drugs with well-known safety profiles [52]. Considering this point, which can likely be extrapolated to other countries, it would be interesting to analyse the situation of patients for whom PREFASEG detected a possible MRP that was not addressed.

In terms of limitations to the current study, it should be noted that the moderate percentage of alert acceptance highlights the need to investigate the causes that lead clinicians to discard such a high number of recommendations. Thus, to maximise the usefulness of PREFASEG and to avoid

possible alert fatigue, it will be necessary to carry out a detailed review into the traceability data of the tool to eliminate low-relevance alerts that are generated but not accepted, and to highlight any alerts related to therapeutic orientations while providing one or more alternative active ingredients. The introduction of a block to prevent the continuation of a prescription associated with a severe MRP could also be considered.

On the other hand, essential future work should also focus on analysing the acceptance of MRP alerts based on their clinical relevance and the type of recommendation, which are key aspects to consider in the case of drug interactions. In addition, a satisfaction survey should be carried out to request feedback and suggestions from practitioners with regards to improving the PREFASEG system in terms of its clinical content and technological aspects.

The future development of PREFASEG also involves the inclusion of medicines that can only be prescribed in hospitals and their corresponding contraindications, which will allow the program to be extended to different levels of care. The technological evolution of the tool is also necessary to render it more specific when generating alerts. For example, this could be achieved using the terminology common to all SNOMED CT systems (Systematised Nomenclature of Medicine – Clinical Terms) that determine the active ingredient, the dose, the pharmaceutical form, and the number of packaging units [53–55]. To optimise the use of PREFASEG and improve the management of clinical information, intelligent systems such as natural language processing could be applied that would allow the clinician to obtain and interact with the information recorded in text format in the patient's clinical history [56,57]. An improved follow-up and monitoring of the PREFASEG alerts would also be desirable, wherein details regarding the professional receiving the alert are registered and made visible, in addition to whether this alert is ignored, and the level of care of the corresponding professional.

In summary, PREFASEG appears to be a feasible and efficient strategy to improve some aspects of clinical safety related to the prescription of drugs, and as a result, in the health care received by patients.

CONCLUSIONS

Our study demonstrated that the PREFASEG (PREscripción FArmacéutica SEGura, i.e., safe pharmaceutical prescription) clinical decision support system contributes to the prevention of potential safety medicine-related problems in patients. In 28% of the cases in which the tool

generated a safety alert, primary care physicians modified their prescriptions by some means. The main drug groups implicated in the PREFASEG alerts were the non-steroidal anti-inflammatory drugs, the benzodiazepines, and the renin-angiotensin system inhibitors; groups that frequently cause adverse effects and motivate hospital admissions.

In future, it will be necessary to study in detail the reasons behind the fact that >70% of the generated alerts were ignored by physicians. In addition, the possibility of reducing the number of alerts should be assessed to avoid alert fatigue. Moreover, it is evident that strategies must be designed to make the prescriber aware of the importance of patient safety, as well as to technologically improve the tool and render it more robust and specific.

LIST OF ABBREVIATIONS

ADE, adverse drug event; AEMPS, Spanish Agency for Medicines and Health Products (Agencia Española del Medicamentos y Productos Sanitarios); CDSS, clinical decision support system; ECW, electronic clinical workstation; EHR, electronic health record; ICS, Institut Català de la Salut (Catalan Health Institute); MRP, medication-related problem; NSAIDs, non-steroidal anti-inflammatory drugs; PC, primary care; PREFASEG, PREscripción FArmacéutica SEGura, i.e., safe pharmaceutical prescription; RAS, renin-angiotensin system.

DECLARATIONS

Ethics approval and consent to participate

Not applicable.

This manuscript does not report studies involving human participants, human data or human tissue.

This manuscript does not report studies involving animals.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

Funding

The primary care component of this study was funded by the Institut Universitari d'Investigació en Atenció Primària (IDIAP Jordi Gol) Scholarship to complete a PhD thesis in primary care.

Authors' contributions

MAP extracted, analysed, and interpreted the data on the use of the PREFASEG tool. She also wrote the majority of the manuscript. MO helped to interpret the data on the use of the PREFASEG tool, in addition to giving support and making contributions to the writing of the manuscript. AF and ED reviewed the data analysis process, reviewed the various parts of the manuscript, and made the relevant contributions to give clarity and understanding to the study.

Acknowledgements

This study has been prepared within the framework of the Doctorate in Pharmacology at the Universitat Autònoma de Barcelona (UAB). We would like to thank ICS Information Systems for supporting us during acquisition of the information required to conduct this study. We would also like to thank the PREFASEG working group for helping to maintain a useful and up-to-date tool.

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TABLE LEGENDS

Table 1. Combinable attributes in the configuration of each PREFASEG notice

Table 2. MRP alerts generated and accepted by PREFASEG between January 2016 and December 2018

Table 3. Top 10 alerts related to drug interactions between January 2016 and December 2018

Table 4. Degree of detection and acceptance of the AEMPS safety alerts in 2016, 2017, and 2018

Table 5. Drug groups not recommended in geriatrics that generated PREFASEG alerts from January 2016−December 2018

Table 6. Top 10 alerts for drugs advised against for use in geriatrics between January 2016 and December 2018

FIGURE LEGENDS

Fig. 1 Example PREFASEG screen showing the various informative elements presented by the tool.

Fig. 2 Example screen of the PREFASEG system with various included safety alerts and therapeutic recommendations.

Fig. 3 Degrees of detection and acceptance of the main types of duplication from January 2016–2018.

ANNEXES

Annex Table 1. Description of the types of PREFASEG alerts

MRP alert	**Description**
Interactions	
Contraindications for health problems	Detection of patients with absolute contraindications defined in the ICS Clinical Practice Guidelines and the CatSalut Harmonisation Guidelines for the following pathologies: Diabetes mellitus II, heart failure, chronic kidney disease, hypercholesterolemia, and depression.
Contraindications for clinical variables	Detection of patients with contraindications due to renal insufficiency: • Severe renal insufficiency: glomerular filtration of 15 or 30 mL/min/1.73 m^2 • End-stage renal failure: glomerular filtration <15 mL/min/1.73 m^2 Detection of patients with contraindications due to abnormal potassium levels: • Hypokalaemia <3.5 mmol/L • Hyperkalaemia >5.5 mmol/L.
Contraindications with a specific AEMPS alert	Detection of patients with contraindications due to the use of an active ingredient that has a relevant safety alert from the Spanish Agency for Medicines and Health Products (AEMPS). The active ingredients included are: Aliskiren, citalopram, escitalopram, cilostazol, trimetazidine, raloxifene and bazedoxifene, COXIBS, diclofenac, aceclofenac, ivabradine, agomelatine, canagliflozin, and the "Triple Whammy" (i.e., NSAIDs + diuretics + RAS inhibitors).
Teratogenic pharmaceuticals	Detection of female patients with contraindications based on the use of active ingredients in pregnancy (diagnoses registered in the ECW). Teratogenic drugs are considered those who fall into categories D and X of the old FDA Reproductive Risk Classification. It should be noted that in June 2015, the FDA decided to remove this classification.
Drugs advised against for use in geriatrics	Detection of patients >75 years of age who are taking any inappropriate medication that exhibits a more unfavourable risk-benefit profile due to their age.

Duplicate therapies	Detection of patients who are classed as receiving a non-beneficial prescription of two or more drugs with the same active ingredient (alone or in combination) and/or with the same pharmacological action. Duplicities considered relevant and duplicities considered dose adjustments (i.e., combinations sought at the therapeutic level) are clearly differentiated.
Anticholinergic drug combinations	Detection of patients receiving a prescription of any urinary antispasmodic together with another drug that exhibits significant anticholinergic effects (e.g., antihistamines, tricyclic antidepressants, etc.).
History of suspected hypersensitivity	Detection of patients for whom a history of unconfirmed hypersensitivity has been recorded.
Adverse drug events (ADEs)	Detection of patients for whom an ADE has been registered.

ANNEX Table 2. Groups of pharmacological duplications included in PREFASEG in 2018

TYPE OF DRUG OR SYSTEM UPON WHICH THE DRUG ACTS	**TYPE OF DUPLICATION**
CARDIOVASCULAR SYSTEM	1. Antithrombotic agents: acetylsalicylic acid (Aspirin) 2. Antiplatelet agents: clopidogrel 3. Oral anticoagulants 4. Digitalis 5. Antiarrhythmics
ANTIHYPERTENSIVES	6. Diuretics: thiazides 7. Loop diuretics 8. Potassium sparing diuretics 9. β-Blockers 10. Non-dihydropyridine calcium antagonists 11. Dihydropyridine calcium antagonists 12. High blood pressure medications: renin-angiotensin system inhibitors (ACEIs, AIIRAs) 13. α-Adrenergic antagonists
ANTIULCER AGENTS	14. Gastric protectors 15. Antacids
MUSCULOSKELETAL SYSTEM	16. Anti-inflammatories 17. Anti-gout agents: allopurinol 18. Anti-gout agents: uricosuric 19. Anti-gout agents: colchicines 20. Analgesics: metamizole 21. Analgesics: paracetamol 22. Minor opiates 23. Triptans
ANTIBIOTICS	24. Penicillins 25. Tetracyclines 26. Macrolides 27. Quinolones
HYPOLIPIDEMIC AGENTS	28. Statins 29. Other lipid-modifying agents

	30. Fibrates
ANXIOLYTICS AND HYPNOTICS	31. Long-acting benzodiazepines 32. Intermediate-acting benzodiazepines 33. Short-acting benzodiazepines 34. Z-Drugs and others
ANTIEPILEPTICS	35. Barbiturates 36. Other antiepileptics
ANTIDEPRESSANTS	37. Tricyclic antidepressants 38. SSRI antidepressants 39. Other antidepressants (I) 40. Other antidepressants (II) 41. Bupropion and naltrexone
ORAL ANTIDIABETICS	42. Biguanides 43. Secretagogues (sulfonylureas and glinides) 44. Glitazones 45. Incretins (glyptins and GLP-1 analogues) 46. Type 2 sodium-glucose cotransporter inhibitors (ISGLT-2) 47. Long-acting insulin (injected form)
GENITOURINARY SYSTEM	48. Urinary antispasmodics 49. Prostate drugs: testosterone inhibitors
SYSTEMIC HORMONAL PREPARATIONS	50. Systemic corticosteroids 51. Aromatase inhibitors 52. Osteoporosis treatments 53. Oestrogens and progestogens
RESPIRATORY SYSTEM	54. Long-acting β2-agonists 55. Anticholinergics 56. Inhaled glucocorticoids
OTHERS	57. Calcium supplements 58. Potassium supplements 59. Iron supplements 60. Magnesium supplements 61. Vitamin D

ANNEX Table 3. Definitions of the AEMPS safety alerts included in PREFASEG in 2018

DRUG	**ATC**	**YEAR OF ALERT PUBLICATION**	**ALERT CRITERIA**
Citalopram	N06AB04	2011	High doses: - Above 40 mg/day. - Above 20 mg/day in patients >65 years of age. - Above 20 mg/day in patients suffering from liver dysfunction. Administered in combination with other drugs that also prolong the QT interval of the electrocardiogram.
Escitalopram	N06AB10	2011	High doses (>10 mg/day in patients >65 years of age). Administered in combination with other drugs that also prolong the QT interval of the electrocardiogram.
Aliskiren	Aliskiren alone (C09XA02) Aliskiren + hydrochlorothiazide (C09XA52) Aliskiren + amlodipine (C09XA53) Aliskiren + hydrochlorothiazide + amlodipine (C09XA54)	2014	In patients with a diagnosis of diabetes mellitus II or undergoing treatment with antidiabetic drugs (ATC A10). Jointly administered with ACE inhibitors (ATC: C09AA, C09BA, C09BB) and/or ARA-IIs (ATC: C09CA, C09DA, C09DB, C09DX).

Cilostazol	B01AC23	2013	In patients suffering from a health problem where its use is contraindicated, i.e., cerebral haemorrhage, severe ventricular arrhythmias, or heart failure. Or, in concomitant treatment with: - 2 Antiplatelet agents - Antiplatelet + oral anticoagulant
Trimetazidine	C01EB15	2012	In patients with a diagnosis of extrapyramidal and movement disorders.
Raloxifene or bazedoxifene	Raloxifene (G03XC01) Bazedoxifene (G03XC02)		In patients suffering from any health problem where it is contraindicated, e.g., venous thromboembolism, uterine sac, endometrial cancer, or liver failure of any degree.
COXIBS	Celecoxib (M01AH01) Etoricoxib (M01AH05)		In patients suffering from any health problem where it is contraindicated, e.g., ischemic heart disease, peripheral arterial disease, cerebrovascular disease, heart failure, or inflammatory bowel disease.
Diclofenac or Aceclofenac	Diclofenac alone (M01AB05) or combined (M01AB55) Aceclofenac (M01AB16)	2013, 2014	In patients suffering from any health problem where its use is contraindicated, e.g., ischemic heart disease, peripheral arterial disease, cerebrovascular disease, or heart failure.
Agomelatine	N06AX22	2014	In patients ≥75 years of age.
Ivabradine	N06AX22	2014	Co-administration with verapamil (C08DA01, C08DA51, C09BB10) or (C08DB01).

"Triple Whammy" (NSAIDs + RAS inhibitors + diuretics)	NSAIDs alone and in combination	2014	In patients ≥75 years of age or undergoing treatment for diabetes (ATC A10).
Canagliflozin	A10BK02 Metformin + canagliflozin (A10BD16)	2016, 2017	In patients suffering from a health problem in which it is necessary to be more careful due to an increased risk of amputation.

ANNEX Table 4. List of drugs not recommended for use in geriatrics in 2018

A03A: AGENTS AGAINST FUNCTIONAL ALTERATIONS OF THE STOMACH		**M03B: CENTRAL ACTION MUSCLE RELAXANTS**	
A03AB06	Otilonium bromide	M03BA03	Methocarbamol
A03F: PROKINETIC AGENTS		M03BX02	Tizanidine
A03FA01	Metoclopramide	M03BX07	Tetrazepam
A10B: HYPOGLYCEMANTS (EXCEPT INSULINS)		M03BX08	Cyclobenzaprine
A10BB01	Glibenclamide	**N02A: OPIOIDS**	
A10BB02	Clorpropamide	N02AB02	Pethidine
B01A: ANTITHROMBOTICS		N02AD01	Pentazocine
B01AC05	Ticlopidine	**N02C: ANTIMIGRANE AGENTS**	
B01AC07	Dipyridamole	N02CA01	Dihydroergotamine
B01AC22	Prasugrel	N02CA51	Combinations with Dihydroergotamine
B01AC24	Ticagrelor	N02CA52	Combinations with ergotamine
B01AC23	Cilostazol	**N04A: ANTIPARKINSONIAN AGENTS**	
C02A: CENTRAL ACTION ANTIADRENERGICS		N04AA01	Trihexyphenidyl
C02AB01	Methyldopa	**N05B: ANSIOLYTICS and N05C: HYPNOTICS AND SEDANTS**	

C02AC01	Clonidine	**SHORT- AND INTERMEDIATE-ACTING BENZODIAZEPINES**	
C02AC05	Moxonidine	N05BA08	Bromazepam (INTERMEDIATE)
C02C: PERIPHERAL ACTION ANTIADRENERGICS		N05BA12	Alprazolam
C02CA01	Prazosine	N05BA14	Pinazepam (INTERMEDIATE)
C02CA04	Doxazosin	N05BA21	Clotiazepam
G04CA03	Terazosin	N05BA91	Bentazepam
C04A: PERIPHERAL VASODILATORS		N05CD05	Triazolam
C04AD03	Pentoxifylline	N05CD08	Midazolam
C04AE02	Nicergoline	N05CD09	Brotizolam
C04AX21	Naftidrofuryl	N05CD11	Loprazolam
C07A: BETA-BLOCKING AGENTS		**LONG-ACTING BENZODIAZEPINES**	
C07AA07	Sotalol	N03AE01	Clonazepam (N03A)
G04B: OTHER UROLOGICAL PRODUCTS, INCLUDING ANTI-SPASMODIC PRODUCTS		N05BA02	Clordiazepoxid
G04BD04	Oxybutynin	N05BA05	Clorazepat dipotassium salt
L02A: HORMONES AND RELATED AGENTS		N05BA09	Clobazam
L02AB01	Megestrol	N05BA10	Ketazolam
M01A: NSAIDs: NON-STEROIDAL ANTI-INFLAMMATORY AND ANTI-RHEUMATIC		N05BA13	Halazepam
M01AA01	Phenylbutazone	N05BA51	Combinations with diazepam
M01AB01	Indomethacin	N05BA55	Combinations with clorazepat dipotassium salt
M01AB15	Ketorolac (H)	N05CD01	Flurazepam
M01AB16	Aceclofenac	N05CD03	Flunitrazepam
M01AB05	Diclofenac	N05CD10	Quazepam
M01AB55	Combinations with diclofenac	**NON-BENZODIAZEPINE HYPNOTICS**	
M01AC01	Piroxicam	N05CF02	Zolpidem

M01AC02	Tenoxicam	N05CF01	Zopiclone
M01AC05	Lornoxicam	**R06A: ANTIHISTAMINES FOR SYSTEMIC USE**	
M01AC06	Meloxicam	**H1 ANTIHISTAMINES 1ST GENERATION**	
M01AE03	Ketoprofen	R06AB06	Dexbrompheniramine
M01AE09	Flurbiprofen	R06AB56	Combinations with dexbrompheniramine
M01AE14	Dexibuprofen	R06AB01	Brompheniramine
M01AE17	Dexketoprofen	R06AB51	Combinations with brompheniramine
M01AG01	Mefenamic acid	R06AX07	Triprolidine
M01AH01	Celecoxib	R06AA02	Dimenhydrinate
M01AH05	Etoricoxib	R06AA09	Doxylamine
M01AX01	Nabumetone	R06AA52	Combinations with diphenhydramine
N06A: ANTIDEPRESSANTS		R06AB02	Dexchlorpheniramine
TRICYCLIC ANTIDEPRESSANTS		R06AC01	Mepyramine
N06AA12	Doxepine >6mg/d	R06AD01	Alimemazine
N06AA02	Imipramine	R06AD02	Promethazine
N06AA04	Clomipramine	R06AD03	Tiethylperazine
N06AA06	Trimipramine	R06AD07	Mequitazine
N06AA21	Maprotiline	R06AE05	Meclozine
SSRIs		R06AE92	Combinations with clocinizine
N06AB03	Fluoxetine	R06AX02	Cyproheptadine
N06B:PSYCHOSTIMULANTS AND NOOTROPICS		R06AX17	Ketotifen
N06BX03	Piracetam	R06AX19	Azelastine
R03D: OTHER SYSTEMIC AGENTS AGAINST OBSTRUCTION OF THE RESPIRATORY TRACT		H02BX92	Clemastine
R03DA04	Theophylline	N05BB01	Hydroxyzine

ARTÍCULO 2. Impact of a System to Assist in Clinical Decision-Making in Primary Healthcare in Catalonia: Prescription Self Audit

Title:

Impact of a System to Assist in Clinical Decision-Making in Primary Healthcare in Catalonia: Prescription Self Audit

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Abstract

Background: In 2008, in the context of a complete computerisation of medical records, the Institut Català de la Salut (ICS, Catalan Health Institute) implemented a system in its electronic clinical workstation (ECW) to assist decision-making at the prescription level. This system is known as Self Audit, and it supports physicians in reviewing the medication of their patients. Self Audit provides lists of patients presenting medication-related problems (MRPs) that have potential for improvement, and provides therapeutic recommendations that are easy to apply from the system itself. The aim of this study was to analyse the main results derived from the use of Self Audit in primary care (PC) in Catalonia, and the effect of an incentive-based safety indicator on the results obtained.

Methods: A descriptive cross-sectional study was carried out to analyse variations in the MRPs detected by Self Audit during 2016, 2017, and 2018 in PC in Catalonia. The effect of a safety indicator on the results obtained was also studied. This safety indicator includes the most clinically relevant MRPs (i.e., therapeutic duplications, safety alerts from the Spanish Medicines Agency, and incidences of polymedication in patients over 65 years of age). Variation in the MRPs was measured using the differences between two evaluation points (initial and final). An MRP was considered resolved if the recommendation specified in the alert was followed. The prescriptions of 6,411 PC doctors of the ICS who use the ECW and provide their services to 5.8 million Catalans through 288 PC teams were analysed.

Results: Analysis of the total safety-based MRPs detected by Self Audit gave overall resolutions from April to December of 9% (21,547) in 2016, 7% (15,924) in 2017, and 1% (2,392) in 2018 out of the total number of MRPs recorded in April each year. Examination of the 3 types of MRPs with the highest clinical relevance that were linked to the safety indicator gave overall resolutions of 41% in 2016 (17,358), 20% in 2017 (7,655), and 21% in 2018 (8,135).

Conclusions: The ICS Self Audit tool assists in reducing the number of safety-based MRPs in a systematic manner, and yields superior results for the MRPs linked to a safety indicator included in the incentives of PC physicians.

Keywords: Decision support system, primary care, clinical safety, electronic prescription

BACKGROUND

In the past few decades, the development of new information and communication technologies in the field of healthcare has potentially contributed to improving the cost-effectiveness and quality of patient care. In this context, a range of technical reports from the American National Institute of Medicine have confirmed that an electronic record of healthcare activity, such as an electronic health record (EHR), together with the integration of clinical decision support systems (CDSSs) in such EHRs, constitute a guarantee of quality for the health system [1,2]. According to several authors, CDSSs aimed at the prescription of medications have the greatest impact on improving patient safety [3]. Although a variety of different designs and functionalities exist, these systems have a common role in intelligently combining clinical knowledge and patient information, with the aims of ultimately improving the overall prescribing process. The possibility of integrating a CDSS into the EHR system has made it possible to provide medical histories with interactive signals that alert professionals to situations of risk for their patients [4], thereby helping to improve the prescription process and the overall clinical safety of patients [3,5,6]. Indeed, several Spanish studies have indicated that 50% of adverse events related to medication errors are avoidable [7,8], and that the implementation of such technologies can help to reduce them.

With this background in mind, in 2008, the Institut Català de la Salut (ICS, Catalan Health Institute) integrated a combination of CDSSs into its electronic clinical workstation (ECW), namely PREFASEG, which generates online notifications when starting a treatment to prevent medication errors [9], and the Self Audit tool, which generates lists of patients presenting with active medication-related problems (MRPs). This study focuses on the Self Audit tool.

The Self Audit tool is a computerised system that is integrated into the EHR, and based on the combination of clinical with therapeutic data, it simplifies the search for patients with an MRP related to an ongoing medication, thereby facilitating changes and/or suspensions of treatment. In an agile and visual manner, it provides the professional with a list of patients with an MRP, such as a therapeutic duplication or a drug contraindicated by a previous or current pathology, thereby allowing the review and assessment of any possible change in treatment. The tool itself provides a therapeutic recommendation in each case and facilitates the management of changes and/or suspensions of treatment, without the need to leave the program. Thus, in this system, a number of aspects related to the review of a patient's medication are systematised based on an optional and individual self-evaluation exercise. Any changes carried out are recorded in the EHR.

The MRPs are defined by a group of expert professionals from the ICS. Each year, the clinical content of the MRPs is reviewed according to the scientific information available, and, for this reason, they may vary from year to year. Each MRP is classified as high or low clinical relevance, as recommended in the literature [10].

The Self Audit tool is activated voluntarily, wherein the practitioner can use the ECW to consult the lists of patients with an MRP in his assigned population. All primary care (PC) practitioners (i.e., 100% of practitioners) use this tool at some point over the course of a year. The practitioner can also check the schedule of visits for the day, which will indicate any patients who have an MRP, and allow the doctor to take advantage of the visit to review the medication. This system therefore does not alter the workflow during the consultation [11,12], and allows the professional to decide when is the most appropriate time to review the MRP.

From 2008 to 2016, Self Audit evolved both at the technological level and at the level of its clinical content. Initially, the tool only allowed the detection of patients with certain therapeutic duplications and/or cases of polymedication (i.e., >10 drugs). During this period, a number of new MRP detections were incorporated into the tool, and the detection specificity was improved overall. Thus, it was not until approximately 2014 that this tool was completed in its current Self Audit configuration. In addition, the process of obtaining data to monitor the use of the tool was expensive, taking a long time to validate and debug the data until the level of quality and detail required for analysis was obtained.

Linked to the Self Audit prescription system, an incentive-based safety indicator was designed in 2008, which selected some of the most clinically relevant MRPs, and was included in the “payment for objectives” program for ICS PC physicians (N.B. according to this program, objectives are linked to annual economic incentives up to approx. 6000 €). The aim of this indicator was to promote a culture of safety in the use of medicines, and also to encourage the use of the Self Audit tool.

The aims of this study are therefore to determine the main results derived from the use of Self Audit in the Catalan PC system, and to evaluate the effect of the safety indicator on the results obtained. A further aim of this article is to provide the international audience with details regarding a computer tool aimed at improving clinical safety, which has been widely managed in the Catalan PC system by 6,411 users with more than 10 years of experience. This tool is of particular importance since it helps doctors to detect patients with potential MRPs, and as a result, any ongoing treatments related to these MRPs can be reviewed and modified to benefit the health of the patient. Self Audit is a versatile and dynamic tool that can be updated with new or modified warnings as desired. Due to the considered importance of this tool to provide

improvements in healthcare practice, its implementation was essentially immediate for all PC teams and professionals. Physicians refer to Self Audit as a useful tool whose usability needs, nevertheless, to be assessed.

METHODS

A descriptive, cross-sectional study was designed that began in April 2016 and continued until December 2018. This study was developed within the scope of the PC system of the ICS, which is the main provider of health services in Catalonia, a region in the northeast of Spain, and covers a population of 5.8 million inhabitants over the different Catalan territories. Overall, it serves the population through a network of 288 PC teams and 8 hospitals. The ICS is a public company that has a total of 42,374 professionals, who provide services to 80% of the population of Catalonia. Since all PC doctors of the ICS employed the Self Audit tool during routine practice, no control group was available to establish a comparison. We therefore analysed the evolution of the results over time.

Study sample

The sample studied consisted of all the prescriptions of the 6,411 ICS PC physicians (i.e., 100% of the physician staff) who used the EHRs during the study period.

Variables and indicators

The main variable was the number of resolved MRPs. An MRP was considered “resolved” when: (1) the drug or drugs causing the MRP had been dropped from the patient's active prescription, or (2) the diagnosis was registered as resolved.

The main types of safety MRPs detected by the Self Audit tool were analysed, wherein clinically relevant MRPs that had been linked to the incentive-based safety indicator were emphasised. This safety indicator included 3 MRPs: (1) Therapeutic duplications; (2) safety alerts from the Spanish Agency for Medicines and Health Products (AEMPS, Agencia Española de Medicamentos y Productos Sanitarios), and (3) polymedication in patients over 65 years of age with some specific MRPs, wherein polymedication is defined as the case where more than 10 medicines were prescribed in 2016 and 2017, and more than 8 medications were prescribed in 2018.

The MRP related to therapeutic duplication detected patients with a non-beneficial prescription of two or more drugs that exhibit the same active principle (alone or in

combination) and/or the same pharmacological action. In addition, “clinically relevant duplications” and “duplications of dose adjustments” (i.e., combinations sought with a therapeutic objective) were clearly differentiated, and only those considered relevant were linked to the safety indicator.

During the study period, the AEMPS safety alerts included the following contraindications: The “Triple Whammy”; coxibs, diclofenac, and aceclofenac; cilostazol; ivabradine; escitalopram and citalopram; trimetazidine; raloxifene and bazedoxifene; strontium ranelate; aliskiren; and canagliflozin (see Table 1).

Table 1. Summary of the various AEMPS safety alert criteria

DRUG	ALERT CRITERIA
Citalopram	High doses: - Above 40 mg/day. - Above 20 mg/day in patients >65 years of age. - Above 20 mg/day in patients suffering from liver dysfunction. Administered in combination with other drugs that also prolong the QT interval of the electrocardiogram.
Escitalopram	High doses (>10 mg/day in patients >65 years of age). Administered in combination with other drugs that also prolong the QT interval of the electrocardiogram.
Aliskiren	In patients with a diagnosis of diabetes mellitus II or undergoing treatment with antidiabetic drugs. Jointly administered with ACE inhibitors
Cilostazol	In patients suffering from a health problem where its use is contraindicated, i.e., cerebral haemorrhage, severe ventricular arrhythmias, or heart failure. Or, in concomitant treatment with: - 2 Antiplatelet agents - Antiplatelet + oral anticoagulant
Trimetazidine	In patients with a diagnosis of extrapyramidal and movement disorders.
Raloxifene or bazedoxifene	In patients suffering from any health problem where it is contraindicated, e.g., venous thromboembolism, uterine sac, endometrial cancer, or liver failure of any degree.
COXIBS	In patients suffering from any health problem where it is contraindicated, e.g., ischemic heart disease, peripheral arterial disease, cerebrovascular disease, heart failure, or inflammatory bowel disease.
Diclofenac or Aceclofenac	In patients suffering from any health problem where its use is contraindicated, e.g., ischemic heart disease, peripheral arterial disease, cerebrovascular disease, or heart failure.
Agomelatine	In patients ≥75 years of age.
Ivabradine	Co-administration with verapamil.

"Triple Whammy" (NSAIDs + RAS inhibitors + diuretics)	In patients ≥75 years of age or undergoing treatment for diabetes.
Canagliflozin	In patients suffering from a health problem in which it is necessary to be more careful due to an increased risk of amputation.

The MRP related to incidences of polymedication detected patients older than 65 years of age with 10 or more prescribed medications (in 2016 or 2017) and with some specific MRPs, such as double antiplatelet therapy for more than 12 months, a combination of anticholinergic drugs, or other avoidable medications. In 2018, the denominator changed, and polymedication was defined as a patient with 8 or more prescribed medications.

Data collection and analysis

The data were collected from the ECWs, where the active prescriptions of the patients are stored. The study was restricted to drugs prescribed and financed by the National Health System and employed in PC centres. The extraction of active prescription data was carried out automatically on a monthly basis, and identified the MRPs out of the prescritions of each physician detected by Self Audit.

Throughout the three years analysed (2016, 2017, and 2018), 6 points or cross-sections of information were studied. Within each year, the variations in the number of MRPs between the considered baseline data and the final data were calculated and thus the percentage variation was established. Data could not be compared between different years because the criteria that defined the detection of an MRP were different from year to year, and so such a comparison would not have been appropriate. For example, if a new pharmacological group was to be added to the "duplicate therapy" MRP in a particular year, or additional drugs were to be included in an existing duplication group, the number of MRPs related to duplicate therapies would increase.

The data obtained from the extractions carried out for the month of April were considered as the baseline data because this was the point at which the MRP detection criteria were defined and updated, and the incentive-based goals were proposed. The data obtained for the month of December were considered to be the final data since they correlated to the final month of the calendar year, and they coincided with the last evaluation point of the safety

indicator. The difference between the baseline and the final data points reflected the number of resolved MRPs and the number of generated PRMs. The MRPs of individual patients were not followed over time.

The safety indicator averages the variation in the selection of the MRPs mentioned above. The effect of the incentive-based care indicator was therefore evaluated by the reduction in the number of MRPs at the PC level over a year, which was the time that the indicator remained unchanged, and which coincided with the validity of the management contract signed by the PC doctors.

To evaluate the indicator, the ability of the PC doctors to reach the goal established at the beginning of the year was measured for specific months, and was calculated from the baseline data. More specifically, the goal for each physician corresponded to a specific number of MRPs less than that existing at the beginning of the year. In the years studied, there were 2 or 3 months of the year in which the extraction of information from the active prescription MRPs was evaluated, and the ability of the doctors to reach the goal was measured. In 2016, the evaluation was carried out in September and December, while in 2017 and 2018 the evaluations were carried out in June, September, and December.

RESULTS

General analysis of the MRPs of the Self Audit tool

The data extractions corresponding to the months of December 2016, December 2017, and December 2018 showed that the ECW had registered 9.5, 9.6, and 9.7 million active prescriptions, respectively. In these months, 210,916 MRPs (December 2016), 227,856 MRPs (December 2017), and 230,959 MRPs (December 2018) were identified. Based on these data, it was observed that the percentage of MRPs studied with respect to the total number of active prescriptions represented 2.2% in 2016 and 2.4% in 2017 and 2018.

Upon analysis of the total clinical safety MRPs detected by Self Audit, an overall resolution of 9% (21,547) was observed in 2016, while resolutions of 7% (15,924) and 1% (2,392) were found in 2017 and 2018, respectively (see Table 2).

Table 2. Problems related to medications detected by Self Audit: April 2016–December 2018

		YEAR 2016*			
PROBLEM DETECTED BY SELF AUDIT		Apr 2016	Dec 2016	Variation	Percentage
Duplicate therapies		46,242	41,589	−4,653	−10%
AEMPS safety alerts		13,521	6,849	−6,672	−49%
Contraindications due to medical devices and/or clinical variables		37,359	37,421	62	0%
Treatment duration	Bisphosphonates ≥5 years	8,246	7,434	−812	−10%
	Double anti-aggregation ≥12 months	4,805	4,332	−473	−10%
Drugs advised against in geriatrics		88,393	83,638	−4,755	−5%
Combination of anticholinergic drugs		2,913	2,320	−593	−20%
Avoidable medication		30,984	27,333	−3,651	−12%
TOTAL NUMBER OF PROBLEMS DETECTED		232,463	210,916	−21,547	−9%
		YEAR 2017			
PROBLEM DETECTED BY SELF AUDIT		Apr 2017	Dec 2017	Variation	Percentage
Duplicate therapies		65,679	59,536	−6,143	−9%
AEMPS safety alerts		11,212	9,935	−1,277	−11%
Contraindications due to medical devices and/or clinical variables		44,687	44,000	−687	−2%
Treatment duration	Bisphosphonates ≥5 years	6,386	4,964	−1,422	−22%
	Double anti-aggregation ≥12 months	4,394	4,508	114	3%
Drugs advised against in geriatrics		82,252	79,187	−3,065	−4%
Combination of anticholinergic drugs		2,184	1,819	−365	−17%
Avoidable medication		26,986	23,907	−3,079	−11%
TOTAL NUMBER OF PROBLEMS DETECTED		243,780	227,856	−15,924	−7%
		YEAR 2018			
PROBLEM DETECTED BY SELF AUDIT		Apr 2018	Dec 2018	Variation	Percentage
Duplicate therapies		65,377	64,650	−727	−1%
AEMPS safety alerts		7,046	5,441	−1,605	−23%
Contraindications due to medical devices and/or clinical variables		45,175	46,469	1,294	3%
Treatment duration	Bisphosphonates ≥5 years	4,552	4,123	−429	−9%
	Double anti-aggregation ≥12 months	4,631	4,630	−1	0%
Drugs advised against in geriatrics		79,225	79,384	159	0%
Combination of anticholinergic drugs		1,854	1,736	−118	−6%
Avoidable medication		25,491	24,526	−965	−4%
TOTAL NUMBER OF PROBLEMS DETECTED		233,351	230,959	−2,392	−1%

*In the three years studied, April was taken as the baseline data because it is the time at which the definitions of the MRPs were updated according to the consensus of a group of experts, and it also is the month in which the incentive-based goals were proposed.

Upon the analysis of all clinical safety MRPs detected by Self Audit, overall resolutions of 9% (21,547), 7% (15,924), and 1% (2,392) were observed in 2016, 2017, and 2018, respectively. Subsequent analysis of the resolutions of the different MRPs throughout the whole study period (i.e., 2016–2018) showed an overall trend towards resolution, especially in the cases where AEMPS safety alerts were implemented, since this resulted in 49% resolution of the cases in 2016, 11% in 2017, and 23% in 2018.

The behaviours of the specific MRPs were then examined in further detail. More specifically, in April 2016, a total of 46,242 duplications were detected, while in December of the same year, such duplications had been reduced by 10% (i.e., to a total of 41,589). However, there was a significant increase in the absolute number of duplications detected in 2018 (65,377 in April and 64,650 in December), with a reduction of only 1% being achieved throughout the year. In addition, it was found that the MRPs related to drugs not recommended for use in geriatric patients exhibited reductions of 5% (4,755 cases) in 2016 and 4% in 2017 (3,065 cases), although no reduction was found in 2018. Furthermore, the MRP related to avoidable medications (including chondroprotectors and citicoline) showed a reduction of 3,651 cases in 2016 (−12%), 3,079 cases in 2017 (−11%), and 965 cases in 2018 (−4%).

Taking the last analysis point, namely that of December 2018, 34% of the 230,959 MRPs detected were due to the use of drugs not recommended for use in geriatric patients, while 28% were attributed to therapeutic duplications, and 20% were due to pathological contraindications. As a result, these three MRPs accounted for more than three-quarters of the overall MRPs detected at this point (i.e., 190,503 cases, 82.5%).

Analysis of clinically relevant MRPs linked to the PA safety indicator

In the period studied, 41,492 MRP cases were resolved in the Self Audit tool, of which 80% (33,148) were linked to the safety indicator. Upon examination of the 3 types of MRPs linked to this indicator, joint resolutions of 41% in 2016 (17,358), 20% in 2017 (7,655), and 21% in 2018 (8,135) were observed, as detailed detail in Figure 1. However, despite these promising percentages of resolution, the total number of these three MRPs increased from 24,720 in December 2016 to 31,501 in December 2018.

With reference to the specific MRPs, in the case of therapeutic duplications, the resolution of 5,413 cases in 2016, 4,892 cases in 2017, and 3,485 cases in 2018 was achieved. In addition, when considering the MRPs related to the AEMPS alert, 6,815 cases were resolved in 2016, which dropped to 2,160 cases in 2017, and 1,735 cases in 2018. Furthermore, for the MRP

related to polymedication, the corresponding reductions were 5,130 cases in 2016, 603 cases in 2017, and 2,915 cases in 2018.

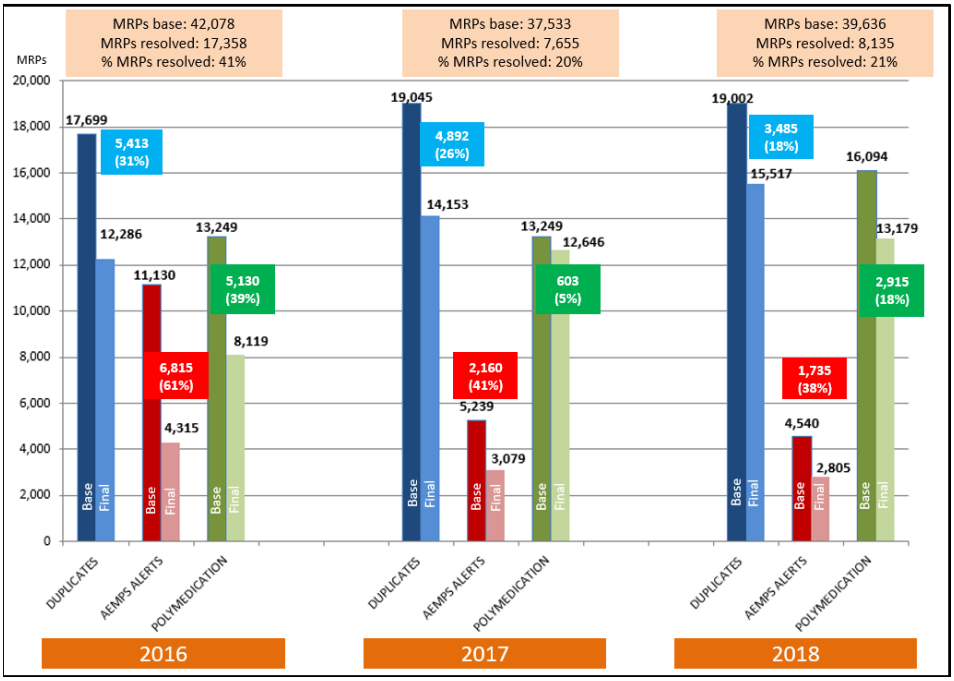

Fig. 1 Variation in the MRPs linked to the 2016–2018 incentive-based safety indicator.

The annual data for the safety indicator showed that at the time of the evaluation, there was a greater decrease in the number of MRPs, while after each evaluation point there was a rebound in the number of cases, as can be seen in Figure 2. The most pronounced rebound was observed after the December evaluation point, as will be discussed later.

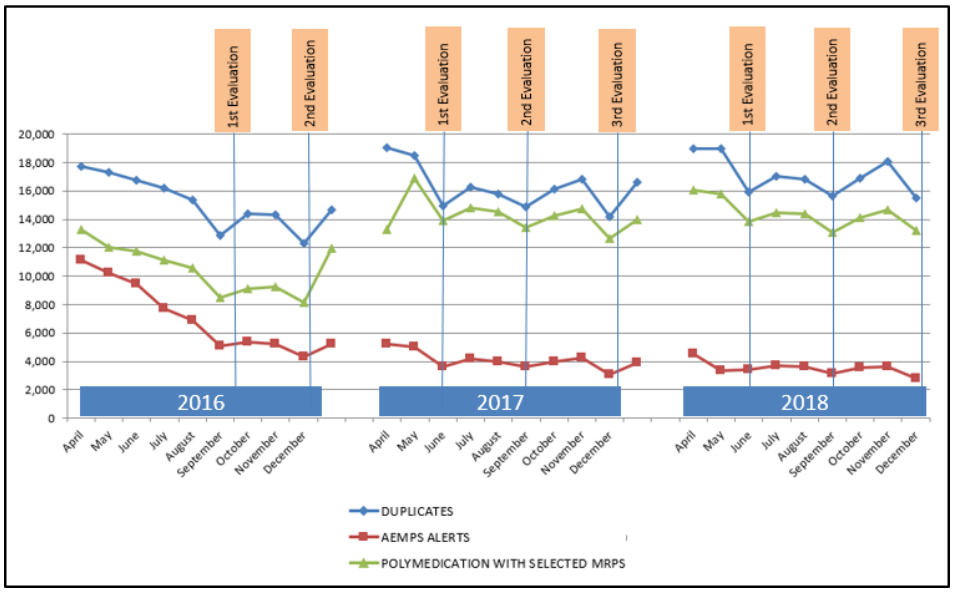

Fig. 2 Annual performance of the 2016–2018 incentive-based safety indicator.

Upon analysis of the detail relating to the AEMPS safety alerts (Table 3), it was observed that the Triple Whammy represented 89% (9,767/11,035) of the total alerts included in 2016, 80% (4,123/5,153) of those in 2017, and 73% (3,260/4,460) of those in 2018. Its reduction percentage ranged from 66% in 2016 to 43% in 2018.

Table 3. Evolution and reduction percentages by type of AEMPS safety alert

YEAR	2016				2017				2018			
AEMPS ALERT	Apr	Dec	Variation	Percentage	Apr	Dec	Variation	Percentage	Apr	Dec	Variation	Percentage
Triple whammy	9,767	3,356	−6,411	−66%	4,123	2,242	−1,881	−46%	3,260	1,850	−1,410	−76%
Coxibs	407	282	−125	−31%	349	240	−109	−31%	384	283	−101	−36%
Diclofenac	325	144	−181	−56%	189	109	−80	−42%	189	96	−93	−97%
Cilostazol	115	105	−10	−9%	107	82	−25	−23%	101	78	−23	−29%
Ivabradine	102	88	−14	−14%	87	73	−14	−16%	82	65	−17	−26%
Aceclofenac	82	60	−22	−27%	69	43	−26	−38%	51	28	−23	−82%
Agomelatine	74	62	−12	−16%	78	69	−9	−12%	81	63	−18	−29%
Escitalopram	55	51	−4	−7%	54	61	7	13%	60	45	−15	−33%
Citalopram	41	34	−7	−17%	48	47	−1	−2%	59	46	−13	−28%
Trimetazidine	40	27	−13	−33%	34	24	−10	−29%	34	26	−8	−31%
Raloxifene and Bazedoxifene	14	9	−5	−36%	10	7	−3	−30%	9	8	−1	−13%
Strontium ranelate	8	9	1	13%	3	0	−3	−100%	NA	NA	NA	NA
Aliskiren	5	4	−1	−20%	2	3	1	50%	3	2	−1	−50%
Canagliflozin	NA	NA	NA	NA	NA	NA	NA	NA	147	126	−21	−17%
TOTAL ALERTS	11	4	−7	−62%	5	3	−2	−42%	4,460	2,716	−1,744	−64%

*NA: Not applicable.

As indicated in Table 3, the reduction in the number of cases related to the AEMPS safety alert for diclofenac was 56% in 2016, while the reduction for acecloflenac was 27%. In 2017, the corresponding reductions for diclofenac and acecloflenac were 42 and 38%, respectively, and in 2018, they were 49 and 45%. Furthermore, the reductions in cases related to alerts for the coxibs were 31, 31, and 26% in 2016, 2017, and 2018, respectively, while the corresponding reductions for the cilostazol alert were 9% in 2016 but 23% in 2017 and 2018. The remainder of alerts represented few cases in absolute numbers.

Following analysis of the therapeutic duplications (Table 4), it was found that 70% fell into 10 pharmacological groups out of a total of 63. Of these 10 groups, the renin-angiotensin system inhibitors stood out particularly (2,828 detected in December 2016, and 1,939 detected in December 2018), along with non-steroidal anti-inflammatory drugs (2,084 and 1,969), long-acting benzodiazepines (1,796 and 1,854), and inhaled glucocorticoids (1,741 and 1,771). These four groups of drugs represented 68% of the duplicities detected in December 2016, and 48.5%

of those detected in December 2018. The groups that experienced an increase in detected duplications over the same period were the antidepressants (1,417 and 1,701 in December 2016 and December 2018, respectively), the urinary antispasmodics (1,219 and 2,020), and the thiazide diuretics (943 and 1,595). Thus, these three groups accounted for 29.1% of the duplications detected in December 2016, and 34% of those detected in December 2018.

Table 4. Top 10 prescribed duplicate groups in 2017 and 2018, including June–December variations**

DUPLICATE GROUP*	June 2017	Dec 2017	Variation	Percentage	June 2018	Dec 2018	Variation	Percentage
Renin-angiotensin system inhibitors	2,458	2,141	–317	–13%	2,107	1,939	–168	–9%
Anti-inflammatories	2,154	1,880	–274	–13%	2,203	1,969	–234	–12%
Long-acting benzodiazepines	2,032	1,911	–121	–6%	2,064	1,854	–210	–11%
Inhaled glucocorticoids	1,551	1,616	65	4%	1,583	1,771	188	11%
Alpha adrenergic antagonists	1,273	1,299	26	2%	1,337	1,346	9	1%
Gastric protectors	1,425	1,162	–263	–18%	1,364	1,276	–88	–7%
Other anti-depressants I	1,467	1,389	–78	–5%	1,562	1,702	140	8%
Urinary antispasmodic agents	1,655	1,547	–108	–7%	1,876	2,020	144	7%
Thiazide diuretics	964	823	–141	–15%	2,085	1,595	–490	–31%
Paracetamol (analgesic)	545	668	123	23%	523	570	47	8%

*For each duplicate group, all available active prescription data are shown, which coincide with the evaluation points.

**For technical reasons, the April data were not recorded at the level of detail required for the duplication group and so they have not been included in the table. The data were analysed in June and December, at which points they met the level of quality and detail required for analysis.

Through analysis of the 20 groups of therapeutic duplications with the highest number of cases, it was observed that in 2017, the groups that presented the greatest degrees of reduction in cases were the gastric protectors (−18%), the thiazide diuretics (−15%), and the metamizole-type analgesics (−14%, data not shown). In 2018, the groups exhibiting the greatest degrees of reduction were the sulfonamide diuretics (−75%), the thiazide diuretics (−24%), and the beta-blockers (−12%).

DISCUSSION

The prescription Self Audit system is a clinical management computer tool, aimed at increasing the quality of care by giving support to health professionals in the move towards the safe and effective prescription of drugs.

The main finding of this study was that Self Audit is positioned as a CDSS, which is widely used among the doctors of the Catalan PC system to help identify and resolve safety PRMs in a systematic manner, and leads to superior results for the MRPs linked to the incentive-based safety indicator developed for PC physicians. Therefore, we think that results could be improved by implementing awareness strategies and providing feedback to physicians. This should could be followed by more specific recommendations, which should be repeated and regularly inspected These hypothesis, of course, need to be verified.

In the period studied, 41,492 cases of potential safety problems that could affect patient health were resolved, of which 80% (33,148) were linked to the safety indicator. In general terms, the percentage of MRPs detected by Self Audit ranged between 2.2 and 2.4% of the active prescriptions in the ECW (>9 million) during the years studied. It should be noted there that the detection of an MRP depended on the defined clinical content, and in the case of Self Audit, this content was updated annually. As a result, data could not be compared between different years.

Although the number of MRPs resolved was significant, the percentage of MRPs resolved each year with respect to the number detected by Self Audit was low, namely less than 10%. In addition, the numbers of some MRPs increased over time, as in the case of therapeutic duplications (>60,000 cases pending resolution in 2018) and contraindications due to pathologies (>46,000 cases pending resolution in 2018). This result indicates that significant numbers of MRPs must still be solved, and so supports the need to design interventions that contribute to improving the prescribing attitude. Moreover, it will be necessary to analyse the reasons for these increases and/or low resolution levels, in addition to assessing the requirement to make the detections of some MRPs more specific, and/or to more clearly detail the therapeutic recommendations that are offered.

As pointed out in a previous study [9], Self Audit is common among PC physicians. However, during the study period examined herein, resolution of the different Self Audit MRPs was found to be heterogeneous and irregular. More specifically, some MRPs presented high percentages of resolution, such as those related to the AEMPS alerts. This was perhaps due to the fact that there is greater response from professionals when a safety alert is issued by a

regulatory body [13]. Although the use of AEMPS alerts resulted in a significant reduction in the number of cases in 2018, it should also be pointed out that part of this reduction was due to a change in the clinical content, wherein the warnings for citalopram and escitalopram became more specific (i.e., alerts were only issued if these drugs were prescribed together with other medications that prolong the QT interval), and so these medications generated fewer detections.

Several Self Audit MRPs also showed increases in the number of MRP in the period of study, and this could be attributed to various factors, that need to be validated. For example, the increase in therapeutic duplications over the years could be explained by the fact that new groups of drug duplications or new active ingredients marketed in different groups had been included.

Another MRP that attracted attention due to its negligible decrease, or even a certain increase, was the contraindication group. The results related to this MRP can be explained by considering that the content of this MRP changed substantially during the study period. More specifically, in 2017, the contents were expanded to include contraindications due to the altered values of some clinical variables (e.g., potassium and glomerular filtration), while in 2018, a global update of the contraindications took place, thereby resulting in increased detections of this MRP. However, the reasons behind their low resolution percentages require further investigation. It is possible that this could be attributed to a lack of specificity of the warning and/or recommendation, since different authors [14,15] have supported the fact that giving a clear and precise recommendation constitutes one of the success criteria of the CDSS. It is also a possibility that the recommendations provided in some cases suggest that a clinical follow-up should be carried out, and therefore do not result in the withdrawal of any medication. Under such circumstances it would be assumed that the MRP is not resolved, despite the fact that the recommendation is actually being followed.

In contrast, the MRP related to the drugs not recommended for use in geriatric patients exhibited a particularly low or no reduction during the years of study. In this case, there was no change in the clinical content; however, the low resolution percentage was attributed to this being an MRP of low clinical relevance, and the fact that the literature [16–18] does not consider that the use of these drugs are fully contraindicated in older patients, but instead it is simply recommended that they not be used. The same argument would serve to justify the low resolution of the MRP related to avoidable medications (i.e., chondroprotectors and citicoline). Thus, when doctors are faced with different MRPs, they prioritise those that are clinically more

relevant, or that can be solved more rapidly or with less effort [19]. Another explanation to consider for the low resolution percentages associated with these two MRPs is that they are not included in the safety indicator.

It is also known that healthcare practice generates multiple incidences of medication, which suggests that the total resolution of MRPs through the Self Audit tool was considerably higher than that indicated in the results of the study. This could be attributed to the resolution of some MRPs at the same time as new ones being created; this behavior is not reflected in the current study. It should also be noted that the patients with MRPs were not followed over time, but instead, the existing MRPs under active prescription were compared at two different times within a year. In addition, it must be taken into account that the world population is continually aging, and this is accompanied by a greater incidence of pathologies, and an increase in the use of medications [20–22]. Indeed, it has recently been reported that if recent health trends continue, Spain is on its way to becoming the leading country in terms of the highest life expectancy in 2040 (i.e., 85.8 years) [23]. As a result of such aging, the greater incidence of multiple associated pathologies results in an increased consumption of drugs, which favours the appearance of increasingly complex therapeutic regimens. This in turn is associated with a higher frequency of adverse effects, interactions, and hospital admissions, in addition to a poorer quality of life and a lack of treatment compliance [24].

In terms of the health impact, a reduction in the number of MRPs can be translated into the avoidance of adverse drug effects in patients, which are known to have a considerable impact on patient morbidity and mortality [3], in addition to increasing the average cost of care [5], increasing the number of visits to primary healthcare centres, and increasing hospital admissions [25].

Upon analysis of the MRPs linked to the safety indicator, it was observed that the resolution of these MRPs was significantly higher than that of the general Self Audit data. This could be explained by considering that the included MRPs are of greater clinical relevance, or that it is an economically incentivised indicator. Another key point is that the reduction in cases decreased year on year, both in terms of the absolute number and the percentage. One explanation for this could be that the composition of the indicator varied each year, and therefore the target population for intervention was different, and could have been smaller. Another hypothesis that was considered was that the baseline starting point improved over time, until it reached a point where further improvements were difficult to achieve.

The annual plots obtained for the evolution of the MRPs linked to the indicator clearly showed a decrease in cases at the time of evaluation. The highest degree of MRP resolution occurred at the end of December, and this was accounted for by considering that historically, this indicator had always been evaluated in a single evaluation point at the end of the year. Every January, a relevant increase in cases was observed, although the baseline point was not reached, and so it was assumed that the professionals were indeed acquiring a certain culture of safety, and that the MRPs generated during the daily healthcare practice were being solved. The results of our study therefore appear to be in line with a previous study, wherein the authors suggest that incentive-based systems could influence physicians, and ultimately lead to an improvement in healthcare provision [26,27]. However, in a Cochrane review by Scott et al. [28] regarding this point, it was concluded that there was insufficient evidence to indicate whether financial incentives had a positive impact on the quality of care in PC systems.

On the other hand, it is known that intervention strategies based on improving the prescription of drugs through audits and feedback to physicians have improved the quality of care, wherein such feedback includes information corresponding to their own patients, in addition to specific improvement recommendations; these strategies are repeated and supervised by other colleagues [11,12,29,30]. In this context, the ICS can highlight that this individualised feedback is standard practice for its pharmacists and PC pharmacologists [31,32]. However, the collected data show that there is significant room for improvement, as the number of MRPs that are pending resolution is considerable. It is therefore evident that it will be necessary to design specific intervention strategies to attain a change in the prescribing attitude. Such strategies could include the close monitoring of data at an individual level, training support, and continuous review of the clinical contents to ensure that they are specific and that they are accompanied by concrete therapeutic recommendations [33].

Furthermore, it does not go unnoticed that it is necessary to evolve and improve the Self Audit tool at a technological level to make it more user-friendly and intuitive, and to impart a greater degree of integration with the patient's medical records. Moreover, this tool should be provided with artificial intelligence elements that possess more agile algorithms for information interpretation, and to facilitate decision making.

Finally, it should be noted that one of the main limitations of this study is that there is no follow-up over time for patients with certain MRPs, thereby preventing us from knowing how many MRPs persist over time, how many are new MRPs, and how many MRPs return or reappear after a while. Indeed, such follow-ups would be beneficial to allow the consequences on the

patient's health to be evaluated. Likewise, continuous changes in the clinical contents also made it difficult to analyse the temporal evolution of each type of MRP.

CONCLUSIONS

The Self Audit clinical decision support system developed by the Institut Català de la Salut helps to systematically identify and resolve safety medication-related problems (MRPs) in a systematic manner, wherein superior results were obtained for the MRPs linked to a safety indicator that is included in the incentives of primary care physicians. However, it is noted that significant room for improvement exists in the prescribing attitude, and as a result, additional medical awareness strategies will be necessary, as well as improvements to the tool itself. Such improvements should be based at a technical level and should be aimed at increasing specificity in MRP detection and subsequent recommendations. Finally, we believe that in the context of clinical safety, the implementation HER tools similar to Self Audit could be a useful and beneficial healthcare strategy that could benefit patients from other healthcare systems worldwide.

LIST OF ABBREVIATIONS

AEMPS, Spanish Agency for Medicines and Health Products (Agencia Española del Medicamentos y Productos Sanitarios); CDSS, clinical decision support system; ECW, electronic clinical workstation; EHR, electronic health record; ICS, Institut Català de la Salut (Catalan Health Institute); MRP, medication-related problem; PC, primary care.

DECLARATIONS

Ethics approval and consent to participate

Not applicable.

This manuscript does not report studies involving human participants, human data or human tissue.

This manuscript does not report studies involving animals.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

Funding

The primary care component of this study was funded by the Institut Universitari d'Investigació en Atenció Primària (IDIAP Jordi Gol). Scholarship to complete a PhD thesis in primary care.

Authors' contributions

MAP extracted, analysed, and interpreted the data on the use of the Self Audit tool. She also wrote the majority of the manuscript. MO helped to interpret the data on the use of the Self Audit tool, in addition to giving support and making contributions to the writing of the manuscript. AF and ED reviewed the data analysis process, reviewed the various parts of the manuscript, and made the relevant contributions to give clarity and understanding to the study.

Acknowledgements

This study has been prepared within the framework of the Doctorate in Pharmacology at the Universitat Autònoma de Barcelona(UAB)

We would like to thank ICS Information Systems for supporting us during aquisition of the information required to conduct this study. We would also like to thank the Self Audit working group for helping to maintain a useful and up-to-date tool.

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TABLE LEGENDS

Table 1. Summary of the various AEMPS safety alert criteria

Table 2. Problems related to medications detected by Self Audit: April 2016–December 2018

Table 3. Evolution and reduction percentages by type of AEMPS safety alert

Table 4. Top 10 prescribed duplicate groups in 2017 and 2018, including June–December variations

FIGURE LEGENDS

Fig. 1 Variation in the MRPs linked to the 2016–2018 incentive-based safety indicator.

Fig. 2 Annual performance of the 2016–2018 incentive-based safety indicator.

DISCUSIÓN

Contribución del estudio derivado del análisis del PREFASEG y Self Audit

El análisis de los SADC actualmente operativos en la historia clínica informatizada de atención primaria en Cataluña (ECAP) proporciona una información detallada de sus resultados y de su evolución en un período de 3 años (2016 a 2018). Esta información, que no había sido publicada previamente con tanto detalle, es imprescindible para valorar su utilidad y para plantear posibles mejoras.

Fruto de este análisis, a partir de nuestro estudio, podemos confirmar que el PREFASEG y el Self Audit se posicionan claramente como SADC que contribuyen a mejorar la calidad, la seguridad y el coste-efectividad en el cuidado del paciente. Ambas herramientas actúan de manera complementaria sobre la prescripción, el PREFASEG ayuda a prevenir potenciales PRM de seguridad a los pacientes a partir de la generación de avisos on-line en el momento de dar de alta un nuevo tratamiento; mientras que el Self Audit actúa facilitando la identificación de los pacientes que por sus tratamientos y condiciones clínicas son susceptibles de padecer algún PRM. Así, el PREFASEG actúa evitando la generación del PRM y el Self Audit permite la identificación y resolución de potenciales PRM ya existentes en la HC del paciente. Las dos herramientas son manejadas diariamente por más de 6.400 médicos de familia de 288 equipos de AP de Cataluña. Su uso está muy consolidado en AP y cuentan con más de 12 años de experiencia. Se caracterizan por ser herramientas versátiles y dinámicas permitiendo adecuar las detecciones y los avisos de PRM según las necesidades de cada momento, añadiendo nuevos avisos o modificando los existentes.

Además de evidenciar la contribución del PREFASEG y Self Audit a la mejora de la seguridad clínica en el uso de medicamentos y a la salud de los pacientes, esta tesis también pone de manifiesto el enorme margen de mejora que hay sobre la prescripción de medicamentos. Esta constatación implica la necesidad de diseñar estrategias para concienciar al prescriptor sobre la importancia de la seguridad del paciente y hacer un acompañamiento individualizado al clínico. En este sentido, son diversos los autores que defienden que las estrategias de intervención de mejora de la prescripción de medicamentos basadas en la auditoria y retroalimentación a los médicos de la información correspondiente a sus propios pacientes, acompañada de recomendaciones de mejora específicas, reiteradas y supervisadas por otros compañeros, son capaces de mejorar la calidad de la misma[61 62 92 93]. En esta línea, el ICS puede destacar que esta

retroalimentación individualizada es uno de los métodos de trabajo habitual de sus farmacéuticos y farmacólogos de atención primaria[60 94].

Por otra parte, no cabe duda que nuestro estudio plantea de hecho un análisis de la relación entre sistema de inteligencia artificial (IA), el SADC, y los profesionales que la utilizan, los médicos de familia. Desde esta perspectiva cabe plantearse e investigar qué tipo de relación se establece entre clínicos e IA. ¿Deben los profesionales obedecer ciegamente a las recomendaciones de la IA? ¿En qué circunstancias puede haber conflictos entre la inteligencia humana, el conocimiento clínico y los algoritmos de toma de decisiones en los que se basa la IA? ¿Hasta qué punto se adaptan los algoritmos subyacentes en los SADC a la compleja realidad clínica que han de manejar los médicos de familia? Debemos ser conscientes que cualquier sistema de IA que, como los SADC analizados, pretendan ser útiles se enfrentan, actualmente, a un reto muy complejo y que seguramente estamos asistiendo a un nacimiento (aunque lleven activos desde 2008) de uno sistemas que tienen que madurar y mejorar con el tiempo y con futuros avances tecnológicos...

Sobre el análisis del uso del PREFASEG

Analizando el uso del PREFASEG se observó que un 28% de los avisos de seguridad generados, conllevaron una modificación de la prescripción (aceptación del aviso). En valor absoluto, entre 2016 y 2018, se aceptaron en global 1.222.159 recomendaciones que podrían evitar PRM a los pacientes. PREFASEG avisó de algún PRM de seguridad en 1 de cada 15 nuevas prescripciones. Los grados de aceptación de los avisos se podrían considerar relativamente altos comparándolos con otros estudios de avisos on-line de medidas preventivas, donde los porcentajes de aceptación que se reportaban eran del 12 al 14% [96]. Sin embargo, la variabilidad entre estudios es considerable, en una revisión de Cochrane 2009 sobre los efectos de los avisos/recordatorios on line, Shojania et al [44] encontró una mejora sólo del 4.2% . Otros estudios describían omisiones de recomendaciones entre un 49-96% de los casos [36]. En general, las revisiones sistemáticas posteriores [97] [92] concluyeron que los sistemas de avisos on-line tenían un efecto pequeño o moderado.

La respetable tasa de aceptación de los avisos de PREFASEG, podría explicarse por diversos motivos. Uno de ellos se podría atribuir a que la herramienta incorpora los requisitos de éxitos de los SADC descritos por diversos autores[37] [34]: está integrada en el flujo de trabajo de los

clínicos, el aviso salta automáticamente en el momento del encuentro asistencial con el paciente y en el entorno de su historia clínica y proporciona una recomendación terapéutica concreta en cada caso. Otro motivo sería que, el PREFASEG afronta diferentes tipos de avisos de seguridad considerando la situación clínica de cada paciente y los medicamentos que toma (contraindicaciones por patología o variable clínica, duplicidades, interacciones…), aborda avisos relacionados con la prescripción segura de medicación para diversas patologías (avisos relacionados con más de 60 grupos farmacológicos distintos). Pocos estudios publicados hasta ahora a nivel de AP analizan tanta diversidad de avisos para más de una situación[98 99], normalmente analizan una sola situación clínica[100 101 102 93]. Además, es un SADC implantado en ECAP desde el 2008, transcurso de tiempo que le ha permitido consolidarse como sistema de ayuda a la toma de decisiones en el ámbito de la seguridad clínica en el uso de medicamentos, e ir ganando la confianza de los médicos de familia.

Por otra parte, pese al número elevado de potenciales PRM evitados a los pacientes, debemos remarcar que tratándose de avisos de seguridad en el uso de medicamentos llamó la atención que en global se ignoraran más del 70% de los avisos generados por PREFASEG, 3.16 millones en los 3 años. Sin embargo hay que considerar que, en ocasiones, las recomendaciones que se daban desde PREFASEG no necesariamente implicaban un cambio (algunos avisos son precauciones y no contraindicaciones absolutas, como sucede con los fármacos desaconsejados en geriatría) o bien el cambio no quedaba registrado como tal (algunos avisos recomiendan una bajada de dosis o un seguimiento clínico de alguna variable y por tanto se continúa con la prescripción y, en consecuencia, el sistema no lo contabiliza como aceptado aunque se haya bajado la dosis o se haya pedido una analítica). Si estas modificaciones se hubiesen registrado, el grado de aceptación sería más elevado de lo que el sistema registró, ya que sólo se midió si se continuaba o no con la prescripción. También hay que considerar que no todos los avisos tenían el mismo grado de relevancia clínica, cada aviso iba acompañado de un icono naranja o rojo según la importancia de la recomendación, en línea con lo que defienden algunos autores[59].

A lo largo de los tres años de estudio, se observó un aumento progresivo en el número de avisos generados. Parte de ese aumento se puede relacionar con los nuevos contenidos que se fueron incluyendo y actualizando en PREFASEG. También se puede considerar la existencia de una relación directa entre el aumento del consumo de determinados fármacos, como las benzodiacepinas [103]y la probabilidad que se generaran más avisos de PRM con esos fármacos ya que su consumo va en aumento en la población. En paralelo, el grado de aceptación de los avisos

disminuyó en el tiempo y con mayor frecuencia los facultativos ignoraron los avisos. La disminución de la aceptación se podría atribuir a cierta fatiga de avisos por exceso, sin embargo, será necesario profundizar más en los motivos de descarte de los avisos, analizar por separado los avisos de relevancia alta y los de relevancia media-baja, así como analizar los casos donde la recomendación del aviso no implica cambiar de fármaco. También será esencial conocer la opinión de los profesionales que utilizan la herramienta. Según diversos autores, las principales razones por las que hay una baja aceptación por parte de los clínicos son la gran cantidad de alertas de baja relevancia que reciben y el contenido pobre de las mismas[46 47 51]. Así cuando los médicos se enfrentan a diversos avisos priorizan los que son clínicamente más relevantes o que se pueden resolver en menos tiempo o esfuerzo [84]. Para disminuir el riesgo de fatiga es necesario aumentar la especificidad de los avisos, dar la información de manera clara y no alterar el flujo de trabajo

Si analizamos de manera particular algunos avisos, podemos observar algunos hechos interesantes. En el caso de los avisos de duplicidades terapéuticas, alrededor de un 70% de los avisos de duplicidades fueron ignorados por los facultativos. Si miramos con detalle, resulta que los grupos que generaron más avisos de duplicidades fueron los medicamentos de uso más extendido en la población, como los analgésicos, los Antiinflamatorios no esteroideos (AINE), los protectores gástricos y los Inhibidores del Sistema Renina Anagiotensina (ISRA). De los tres primeros grupos hay que considerar que era habitual tener prescripciones autorizadas a demanda ‘si precisa’, lo que generaba avisos de duplicidades si se intentaba prescribir un medicamento del mismo grupo farmacológico. En el caso de los ISRA, es conocido que, frecuentemente se combinan presentaciones a diferentes dosis para conseguir dosis terapéuticas. Estos hechos podrían explicar en buena parte la elevada proporción de rechazo de este tipo de avisos.

Sin embargo, cuando consideramos los avisos relacionados con alertas de seguridad de la AEMPS nos resulta inesperado, preocupante y difícilmente explicable que tuvieran un bajo grado de aceptación (26%) teniendo en cuenta que se trata de alertas específicas de una agencia reguladora como la AEMPS.

Sobre el análisis del uso del Self Audit

Analizando el uso del Self Audit, en el período de los tres años estudiados, se resolvieron 41.492 casos de potenciales problemas de seguridad que podrían afectar a la salud de los pacientes, de los cuales el 80% (33.148) estaban vinculados al indicador de seguridad incentivado para los médicos de familia de AP. En términos generales, el porcentaje de PRM detectados por la herramienta respecto a las prescripciones activas en ECAP (más de 9 millones) osciló entre el 2,2% y el 2.4%. La detección de PRM estuvo vinculada a los contenidos clínicos definidos y en el caso de Self Audit la actualización de contenidos fue anual, lo que dificultó poder comparar datos entre años diferentes.

A pesar que el número de PRM resueltos no fue despreciable en números absolutos, el porcentaje de PRM resueltos cada año respecto a los PRM detectados por el Self Audit fue bajo, menos del 10%. Además, tal y como observamos en los resultados analizados, algunos PRM aumentaron en el tiempo, como es el caso de las duplicidades (más de 60.000 casos pendientes de resolver en 2018) y las contraindicaciones por patología (más de 46.000 casos pendientes de resolver en 2018). Ello puede poner de manifiesto que quedan muchos PRM por resolver y respalda la necesidad de analizar los motivos de esos aumentos y/o baja resolución, y valorando la necesidad de hacer más específicas las detecciones de algunos PRM y/o detallar mejor la recomendación terapéutica que se ofrece con el objetivo de diseñar intervenciones que contribuyan a mejorar la actitud prescriptora.

En el período de estudio la tasa de resolución de los distintos PRM de Self Audit fue heterogénea e irregular. Algunos PRM mostraron un elevado porcentaje de resolución como fueron los PRM de las alertas de la AEMPS, quizá porque hay mayor sensibilidad profesional cuando hay la emisión de una alerta de seguridad de un organismo regulador como AEMPS, o simplemente porque estaban vinculadas al indicador de seguridad incentivado que mide la reducción de PRM relacionados con duplicidades, con alertas de seguridad de la AEMPS y con polimedicación. Otros PRM como el de fármacos desaconsejados en geriatría, tuvo una reducción de casos muy baja o inexistente en los distintos años de estudio, hecho que atribuimos a que se trataban de avisos de baja relevancia ya que se consideraron recomendaciones y no contraindicaciones absolutas. No obstante, esta baja resolución genera especial preocupación en el entorno de un envejecimiento demográfico y de un aumento de la polimedicación en geriatría.

Al analizar los PRM vinculados al indicador de seguridad se observó que la resolución de estos PRM era mucho mayor comparada con los datos generales del Self Audit. Eso podría explicarse

porque los PRM incluidos son de mayor relevancia clínica o bien porque se trata de un indicador incentivado económicamente. Otro dato que se advirtió fue que la reducción de los casos fue menor de año en año, tanto en número absoluto como en porcentaje. Una de las explicaciones podía ser que la composición del indicador varió cada año y por tanto la población diana de intervención fue diferente y habría sido menor. Otra explicación alternativa que se consideró fue que cada vez el punto de partida basal era algo mejor y por tanto era más difícil mejorar.

Las gráficas anuales de evolución de los PRM vinculados al indicador dibujaron claramente un descenso de los casos en los momentos de evaluación. El mayor grado de resolución de PRM se dio a finales de diciembre, esto se explicaba porque históricamente siempre se había evaluado este indicador en un solo corte a finales de año. Cada enero se observó un aumento relevante de los casos, aunque no se llegó al punto basal, por lo que se asumió que los profesionales fueron adquiriendo cierta cultura de la seguridad y que se iban solucionando los PRM que se iban generando en la práctica asistencial diaria. Así, nuestro estudio podría estar alineado con los autores que sugieren que los sistemas de incentivación podrían influir a los médicos y comportar una mejora en prestación asistencial[89 90]. Sin embargo, en una revisión de la Cochrane de Scott A et al del 2011 sobre el tema se concluyó que no había evidencias suficientes a favor o en contra de que los incentivos financieros tuvieran un impacto positivo sobre la calidad de la atención en la AP [91].

Reflexionando sobre los resultados discretos de Self Audit, no hay que perder de vista que la práctica asistencial genera de por sí múltiples incidencias de medicación, lo que hace pensar que la resolución total de PRM a través del Self Audit fue considerablemente mayor a la que se ha mostrado en los resultados del estudio, ya que los PRM se han ido resolviendo a la vez que se han ido creando otros nuevos y ese comportamiento no se refleja en el estudio. No se siguieron en el tiempo los pacientes con PRM, sino que se compararon los PRM existentes en prescripción activa en dos momentos distintos dentro de un año. Además hay que tener en cuenta que cada vez más la población mundial va envejeciendo, ello se acompaña de mayor grado de patología y de un incremento en el uso de medicamento[23 85]. Según se ha publicado recientemente, España va camino de convertirse en el país con mayor esperanza de vida en 2040 (85,8 años) si continúan las tendencias de salud recientes [86]. La pluripatología asociada a este envejecimiento condiciona un consumo más elevado de fármacos, lo que está favoreciendo la aparición de regímenes terapéuticos cada vez más complejos, algo que se asocia a mayor frecuencia de

efectos adversos, interacciones, ingresos hospitalarios, peor calidad de vida y falta de cumplimiento [87].

Con los resultados presentados en este estudio, es innegable que PREFASEG y Self Audit son SADC que contribuyen a mejorar la seguridad clínica en el uso de medicamentos y evitan o resuelven potenciales PRM en pacientes. En términos de impacto sanitario la reducción de PRM se puede traducir en evitar efectos adversos a medicamentos de los pacientes, los que se sabe que tienen una considerable repercusión sobre la morbi-mortalidad de los pacientes[38], que incrementan además el coste medio de la actividad asistencial[39] y que aumentan tanto las visitas en atención primaria como los ingresos hospitalarios [88]. En esta línea, la Comisión Europea en uno de sus informes indicaba que entre el 3 y el 10% de las causas de ingresos hospitalarios entre 2012 y 2014 eran los efectos adversos a medicamentos (EAM) (2.5- 8.4 millones anuales), y que entre el 2.1 y el 6.5% de los pacientes hospitalizados experimentaron algún EAM (1.8- 5.5 millones anuales)[13]. También en un estudio clásico que analizaba las hospitalizaciones a causa de reacciones adversas, se observó que la mayor parte de las mismas se daban en ancianos y se debían a medicamentos de uso común con un perfil de seguridad bien conocido[104]. Teniendo en cuenta esta realidad, probablemente extrapolable a otros países, sería interesante analizar qué sucede con los pacientes en quienes se avisó de un posible PRM por PREFASEG o Self Audit y este no fue atendido o resuelto.

Sobre las limitaciones del estudio

Nuestro estudio no ha pretendido profundizar sobre la relación entre los médicos de familia y los SADC. Sin embargo, es importante destacar que sería deseable un más profundo de los datos de trazabilidad interna de las herramientas, con la finalidad de maximizar el grado de utilidad del PREFASEG y Self Audit para los clínicos, además de detectar áreas de mejora que permitan incrementar los resultados obtenidos. Es evidente que queda un amplio margen de mejora en cuanto a evitar generar potenciales PRM o a resolver los PRM existentes en las HC de los pacientes. El moderado porcentaje de aceptación de los avisos de PREFASEG y la mejorable resolución de potenciales PRM detectados por Self Audit, fomenta la necesidad de investigar en las causas que llevan al clínico a no seguir con las recomendaciones indicadas. Será necesario analizar por separado los avisos o detecciones de relevancia alta y

los de relevancia media-baja, así como analizar los casos donde la recomendación aportada no implica cambiar de fármaco. Un análisis a este nivel de detalle nos permitirá valorar los siguientes aspectos: eliminar alguno de los avisos o detecciones de baja relevancia que se generan y que se ignoran, especificar más los mensajes de orientaciones terapéuticas especificando alternativas terapéuticas claras. Como ya hemos mencionado anteriormente, son diversos los autores que defienden que las razones principales de una baja aceptación o resolución por parte de los clínicos son la gran cantidad de alertas de baja relevancia que reciben y el contenido pobre de las mismas[46 47 51]. Por lo tanto, para disminuir el riesgo de fatiga de los clínicos y mejorar los resultados derivados del uso de las herramientas es indispensable aumentar la especificidad de los avisos/detecciones, dar la información clara y concisa y evitar alterar el flujo de trabajo [95].

Otra de las limitaciones del estudio es que, puesto que no ha pretendido investigar la evolución temporal de los avisos en cada paciente, no podemos tener resultados relacionados con el seguimiento en el tiempo de los pacientes a los que se ha generado un PRM. Por el nivel de detalle de los datos disponibles, no ha sido posible conocer que pasa en el tiempo cuando se genera un nuevo PRM, la perduración del PRM en el tiempo, cuántos son PRM de nueva aparición y cuantos vuelven a reaparecer pasado un tiempo de su resolución. A nivel de impacto sanitario, sería de gran interés poder estudiar las consecuencias sobre la salud del paciente al cual se le generó o detectó un PRM.

Por otro lado, también será relevante y enriquecedor, conocer la valoración y el grado de aceptación y confianza de los clínicos con estos SADC. Como trabajo de futuro, se pretende realizar una encuesta de satisfacción a un grupo de prescriptores para valorar las herramientas a nivel de utilidad, a nivel de contenidos clínicos y a nivel tecnológico.

Nuestro estudio tampoco se propuso comparar los resultados obtenidos con los SADC entre diferentes niveles asistenciales como por ejemplo entre la atención primaria y los puntos de la atención hospitalaria en los que están disponibles (consultas externas, urgencias y altas). Así, a nivel de PREFASEG, ha sido imposible analizar el uso de la herramienta en la atención especializada debido a la falta de fiabilidad de los registros internos de la herramienta en la AE. Creemos que son atribuibles a que se genera un registro alterados de los datos en el momento que se sincronizan las prescripciones provenientes del repositorio de receta electrónicos de

Cataluña (SIRE). Será necesario investigar con los técnicos informáticos las causas de este mal registro de información e intentar buscar una solución.

Sobre las áreas de mejora futuras de PREFASEG y Self Audit

En cuanto a los contenidos clínicos, el desarrollo futuro de estos SADC pasa por incluir los medicamentos hospitalarios de dispensación ambulatoria (MHDA) y sus contraindicaciones; puesto que se trata de medicamentos que suelen ser de comercialización reciente, con escasa información sobre su seguridad por este motivo. Esta mejora es especialmente relevante en el caso de PREFASEG, que también se utiliza a nivel de la atención especializada.

Trabajar en la especificidad y la robustez de los avisos que generan estos SADC será indispensable para aumentar los resultados de usabilidad de las herramientas. Se tendrá que valorar eliminar alguno de los avisos o detecciones de baja relevancia que se generan y que se ignoran. Además, se deberá especificar las recomendaciones proporcionadas con los avisos y definir, en los casos que se requiera, alternativas terapéuticas claras, para facilitar la decisión clínica a los clínicos.

A nivel tecnológico, será imprescindible evolucionar la herramienta para hacerla más amigable e intuitiva, con mayor grado de integración en la historia clínica del paciente, además de dotarla de elementos de inteligencia artificial con algoritmos más ágiles para interpretar la información y facilitar la toma de decisiones[72]. La programación de estos SADC se inició en 2008 y ya ha quedado obsoleta. Actualmente existe tecnología mucho más evolucionada, más ágil y que presta especial atención al Look & Feel (aspectos visuales y de usabilidad) del programa.

Por otra parte, no hay que perder de vista que es indispensable incrementar la interoperabilidad entre sistemas informáticos. Actualmente aún existen muchas limitaciones en cuanto al intercambio de información clínica entre sistemas informáticos diferentes y entre diferentes niveles asistenciales. Utilizar una terminología común a todos los sistemas, como sería el SNOMED CT (Systematized Nomenclature of Medicine- Clinical Terms) ayudaría a la integración de información. Por ejemplo, en relación con el medicamento, utilizar la codificación SNOMED nos determinaría el principio activo, la dosis, la forma farmacéutica y las unidades del envase[74] [75] [76].

Para optimizar la generación de avisos/ detecciones a través del PREFASEG y SELF AUDIT, se podrían aplicar sistemas inteligentes para la gestión de la información clínica, como el procesamiento de lenguaje natural (PLN) que permitiría obtener e interactuar con la información registrada en formato texto en la HCE del paciente[77] [78].

CONCLUSIONES

CONCLUSIONES

1. PREFASEG y SELF AUDIT son dos sistemas de ayuda a la toma de decisiones integrados en la estación clínica de trabajo de atención primaria de Cataluña, orientados a mejorar la seguridad en el uso de medicamentos. El análisis detallado de sus resultados y evolución es indispensable tanto para valorar su utilidad y aceptación como para identificar aspectos de comunicación y formación continua de los profesionales.

2. El estudio de los resultados de PREFASEG entre 2016 y 2018 permitió constatar una aceptación moderada y heterogénea de los distintos avisos generados (4.4 millones avisos). La aceptación global de los avisos fue del 28%. Las interacciones farmacológicas, las duplicidades terapéuticas fueron los avisos con mayor detección, representando el 40% y el 30%, respectivamente. Las interacciones tuvieron un grado de aceptación del 25% y las duplicidades terapéuticas del 30%. Los avisos de antecedentes de sospecha de hipersensibilidades a medicamentosas obtuvieron el mayor grado de aceptación con un 35%.

3. El análisis de Selff Audit mostró una resolución de los potenciales problemas relacionados con la medicación inferior al 10%. Sin embargo, se ha observado que los resultados de resolución de estos PRM mejoran si están vinculados a un indicador de seguridad incluido en los incentivos de los médicos de atención primaria. Estudiando los 3 tipos de PRM de alta relevancia clínica vinculados al indicador de seguridad incentivado (duplicidades, alertas de seguridad de la AEMPS y de polimedicados con PRM específicos) se observó una resolución del 41% en 2016, del 21% en 2017 y del 20% en 2018.

4. Los grupos de medicamentos más implicados con los avisos y detecciones de PREFASEG y SELF AUDIT son los antiinflamatorios no esteroideos, las benzodiacepinas y los inhibidores del sistema renina-angiotensina, fármacos de amplio uso, susceptibles de provocar interacciones y que frecuentemente causan efectos adversos que motivan ingresos hospitalarios.

a. A nivel de PREFASEG, las duplicidades relacionadas con los antiinflamatorios no esteroideos (AINE), los analgésicos tipo paracetamol, los Inhibidores Sistema Renina Angiotensina (ISRA) y los protectores gástricos representaban el 42% del total avisos de duplicidades (1.4M).

b. A nivel de Self Audit, las duplicidades ISRA, AINE, Benzodiacepinas de vida larga y glucocorticoides inhalados representaban más del 50% de las duplicidades totales detectadas.

5. Los resultados de ambos estudios muestran que existe un amplio margen para la mejora de la actitud prescriptora y, quizás, de las mismas herramientas clínicas. Es necesario profundizar en los motivos por los que los prescriptores descartan los avisos o detecciones, así como valorar la posibilidad de reducir el número de avisos para evitar una fatiga por exceso de alertas. Además, es necesario aumentar la especificidad de los avisos y en algunos casos detallar mejor la recomendación terapéutica.

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ANEXO 1. Artículo publicado sobre PREFASEG

Pons-Mesquida et al.
BMC Medical Informatics and Decision Making (2021) 21:349
https://doi.org/10.1186/s12911-021-01710-8

BMC Medical Informatics and Decision Making

RESEARCH Open Access

Safer prescription of drugs: impact of the PREFASEG system to aid clinical decision-making in primary care in Catalonia

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Abstract

Background: In 2008, the Institut Català de la Salut (ICS, Catalan Health Institute) implemented a prescription decision support system in its electronic clinical workstation (ECW), which automatically generates online alerts for general practitioners when a possible medication-related problem (MRP) is detected. This tool is known as PREFASEG, and at the time of beginning a new treatment, it automatically assesses the suitability of the treatment for the individual patient. This analysis is based on ongoing treatments, demographic characteristics, existing pathologies, and patient biochemical variables. As a result of the assessment, therapeutic recommendations are provided. The objective of this study is to present the PREFASEG tool, analyse the main alerts that it generates, and determine the degree of alert acceptance.

Methods: A cross-sectional descriptive study was carried out to analyse the generation of MRP-related alerts detected by PREFASEG during 2016, 2017, and 2018 in primary care (PC) in Catalonia. The number of MRP alerts generated, the drugs involved, and the acceptance/rejection of the alerts were analysed. An alert was considered "accepted" when the medication that generated the alert was not prescribed, thereby following the recommendation given by the tool. The MRP alerts studied were therapeutic duplications, safety alerts issued by the Spanish Medicines Agency, and drugs not recommended for use in geriatrics. The prescriptions issued by 6411 ICS PC physicians who use the ECW and provide their services to 5.8 million Catalans through 288 PC teams were analysed.

Results: During the 3 years examined, 67.2 million new prescriptions were analysed, for which PREFASEG generated 4,379,866 alerts (1 for every 15 new treatments). A total of 1,222,159 alerts (28%) were accepted. Pharmacological interactions and therapeutic duplications were the most detected alerts, representing 40 and 30% of the total alerts, respectively. The main pharmacological groups involved in the safety alerts were nonsteroidal anti-inflammatory drugs and renin-angiotensin system inhibitors.

Conclusions: During the period analysed, 28% of the prescriptions wherein a toxicity-related PREFASEG alert was generated led to treatment modification, thereby helping to prevent the generation of potential safety MRPs. However, the tool should be further improved to increase alert acceptance and thereby improve patient safety.

Keywords: Clinical decision support system, Primary care, Clinical safety, Electronic prescription, Pharmacovigilance, Medicines use

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Background

According to a European Commission report, 3–10% of hospital admissions between 2012 and 2014 were caused by adverse drug events (ADEs), totalling 2.5–8.4 million

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cases annually. In addition, approximately 2.1–6.5% of hospitalised patients experienced an ADE, corresponding to 1.8–5.5 million annually [1]. Thus, since the late 1990s, patient safety has become a priority of health systems [2, 3], and several initiatives have identified the need for a new culture of safety in the health and policy environment [4–6]. To achieve this, and according to the definition of clinical safety, it is essential to define actions to avoid, prevent, and improve adverse effects or injuries from healthcare processes where possible, since it should be acknowledged that some adverse events are inherent in treatment, and cannot always be avoided or minimised.

In this context, the 1999 technical report 'To err is human' by the Institute of Medicine (OIM) highlighted the need to develop new information and communications technologies to reduce medical errors [2], and, beyond this, prescriptions which could increase the risk of developing adverse effects. Subsequent reports later affirmed that the electronic record of healthcare activity that is typical of an electronic health record (EHR), together with the integration of clinical decision support systems (CDSSs) into these EHRs, should contribute to guaranteeing quality in the healthcare system [7, 8] by helping to reduce preventable adverse effects.

In the scientific literature we find different definitions of a CDSS [9, 10]. According to Kawamoto et al. [11], a CDSS can be considered any electronic system designed to help clinical decision making, which takes into account the characteristics of the patient to generate a specific evaluation and provide a recommendation to be evaluated by the practicing clinician. The design and functionalities of these CDSSs can be very varied. Some authors consider that CDSSs aimed at the initial prescription phase may have the greatest impact on improving patient safety [12], while others discuss the fact that integration of a CDSS into the HER renders it possible to provide patient histories along with interactive signals that alert professionals to situations of risk for the patient [13]. As a result, the prescription process can be improved and the clinical safety of patients enhanced [12, 14, 15].

CDSSs have been found to bring multiple benefits to patient care [16–19], wherein it has been reported that they contribute to improving the dosage and selection of drugs, while also encouraging patients to take part in preventive activities, improving test results, decreasing morbidity, and improving the quality of care [20]. In contrast, the main risk of CDSSs is the alert fatigue experienced by physicians who are faced with a multitude of prompts and reminders on-screen, which can lead to important alerts being ignored [21, 22].

The Catalan Health Institute (ICS) is a public entity that provides health services to 80% of the population of Catalonia. In 2008, in line with promoting the clinical safety of the patient, it designed and integrated a CDSS into its primary care electronic clinical workstation (ECW) that made it possible to detect certain medication-related problems (MRPs) online. This CDSS, which is known as PREFASEG (PREscripción FArmacéutica SEGura, i.e., safe pharmaceutical prescription), is a computer tool that acts interactively to alert clinicians to any potential drug use-related problems during the process of deciding the most appropriate treatment for their patient.

To understand the means by which PREFASEG functions, we consider the prescription of a new drug to a specific patient. At the point at which the prescription is requested by the clinician, PREFASEG is activated and performs an assessment of the prescription to verify that it is safe for the patient, and that it does not pose a potential risk to their health. This evaluation is carried out based on the different MRPs detected by the tool, which include: (1) Drug interactions; (2) Therapeutic duplications; (3) Drugs advised against for use in geriatrics; (4) Contraindications with a safety alert published by the Spanish Agency for Medicines and Health Products (AEMPS, Agencia Española del Medicamentos y Productos Sanitarios); (5) Contraindications due to health problems and/or clinical variables; (6) Drugs that are known to be teratogens during pregnancy; (7) Anticholinergic drug combinations; (8) Patient history of hypersensitivity or suspected hypersensitivity reactions (suspected, not confirmed); and (9) Adverse drug events. To carry out this evaluation, a number of factors are taken into account, such as any active prescriptions that the patient already has on their record, other medical diagnoses or active health problems, the presence of any clinical variables with altered values, and the age and/or sex of the patient. In the event of a safety alert being generated following the above evaluation, the corresponding warnings are shown to the clinician (e.g., the risk to the patient and any therapeutic alternatives) so that he can decide whether to continue with the prescription or change the medication. These safety alerts are displayed in a simple manner on a single screen to permit their rapid consultation and understanding, as shown in Fig. 1, which presents an example relating to the prescription of a product that is not recommended for patients over 75 years of age. The information displayed includes the severity icon (two degrees, moderate or severe), the drug or active ingredient causing the alert, the cause of conflict (i.e., medication or active ingredient conflict, patient age, or pre-existing health problem), the risk to the patient, and any therapeutic alternatives. Each MRP alert is classified as either high (red indicator) or medium–low (orange indicator) clinical relevance, according to previously described recommendations [23].

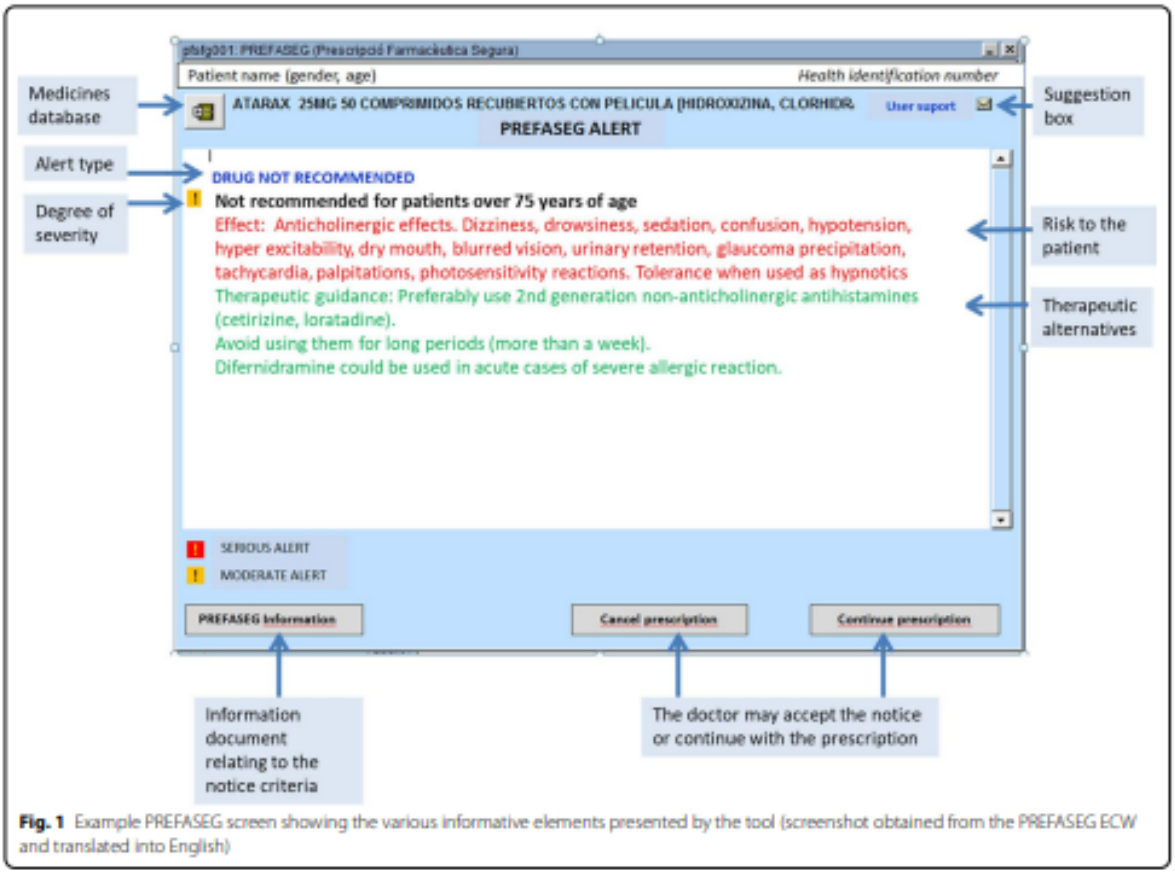

Fig. 1 Example PREFASEG screen showing the various informative elements presented by the tool (screenshot obtained from the PREFASEG ECW and translated into English)

It is also possible that more than one alert is generated by the tool, and in such a case, the clinician is informed of all warnings associated with the different potential safety issues, as can be seen in Fig. 2.

Each alert generated by PREFASEG is recorded as "audit data" along with the information related to whether it has been accepted or whether prescription of the product was continued. The evaluation of these data allows us to determine if certain types of alerts are accepted to a greater degree than others, thereby improving the clinical content definitions to adapt the tool to the healthcare reality. PREFASEG consists of a calculation core in the Oracle PL/SQL, in which the calculations that access the tables of clinical contents have been optimised, and in which there is a minimum visual interface for the communication of safety alerts. This interface was developed using Developer Forms, which is the same technology employed to produce the ECW. As a result, the look and feel of the alert screens are comparable to those of the original ECW, and so maximum integration is achieved.

The contents of the MRP alerts are defined and maintained as described by a multidisciplinary group of expert professionals from the ICS (i.e., primary care (PC) physicians, pharmacists, and clinical pharmacologists) according to previous literature [9, 24]. The MRP alerts are reviewed and updated each year according to the available scientific evidence, and as a result, the clinical content undergoes some changes from 1 year to the next. For example, references to the more current STOPP/START and Beers criteria were included in updates for drugs advised against for use in geriatrics. Importantly, the clinical content can be revised at any time, and are updated from a specific maintenance platform known as 'Know How.'

The purpose of this study is therefore to describe the principal characteristics of the PREFASEG tool, the main safety alerts generated by PREFASEG in the Catalan PC system, the degree of acceptance of these alerts by physicians, and the main pharmacological groups implicated in the alerts. Furthermore, three of the most frequent alerts are also described in greater detail.

Fig. 2 Example screen of the PREFASEG system with various included safety alerts and therapeutic recommendations (screenshot obtained from the PREFASEG ECW and translated into English)

Methods

A descriptive, cross-sectional study was designed, which began in January 2016 and continued until December 2018. This study was developed within the scope of the PC system of the ICS, which is the main entity that provides health services in Catalonia, and which covers a population of 5.8 million inhabitants of the different Catalan territories through a network of 288 PC teams and 8 hospitals. The ICS is a public company with a total of 42,374 professionals who provide services to 80% of the population of Catalonia.

Study sample

The sample studied consisted of all prescriptions issued by the 6411 ICS PC physicians who used the EHR during the study period.

Development of PREFASEG

In general terms, to provide the PREFASEG with clinical and pharmacological content, the following methodology was followed during its development:

1. Bibliographic search. Initially a bibliographic search was carried out in the PubMed database for the different MRPs addressed by PREFASEG, wherein national and international articles that were considered to be the most relevant and best adapted to our healthcare environment were reviewed. The safety alerts included in the ICS Clinical Practice Guidelines [25] were also considered.
2. Consensus with a group of experts. Following a literature review, the pharmacological groups to be included were selected and the messages to be presented to the prescribing physicians were defined. Each MRP alert was classified as high (red) or medium-low (orange) clinical relevance, as mentioned above [23]. The red alerts reflected situations of absolute contraindications, while the orange alerts were considered precautionary.
3. Adaptation of the clinical content to the table formats necessary for the PREFASEG computer program. The clinical content was transferred into a computer-readable language from various configuration tables presented in Excel, and for this purpose, it was necessary to code the active ingredients according to the Anatomical Therapeutic Chemical (ATC) classification. Similarly, the various health issues were coded according to the International Classification of Diseases ICD-10 system. To produce the clinical

contents, ATC groups or groups of health problems were built. Each alert type was then defined and configured using a combination of various attributes, as outlined in Table 1.

Variables and indicators

The main variable of the study was the number of MRP alerts generated by PREFASEG. Another of the variables studied was the number of accepted alerts. An alert was considered "accepted" when the medicine that generated the safety alert was not prescribed.

Some PREFASEG alerts are associated with recommendations for clinical follow-ups or dose reductions. Therefore, following these recommendations does not entail the withdrawal of the treatment that has generated the alert. Consequently, these alerts are not considered "accepted" alerts.

Description of the MRPs included in PREFASEG

The various MRPs that are defined in the PREFASEG system were outlined previously in the introduction (see also Table 1). Further details regarding these MRPs can be found in Additional file 1.

The global MRP alerts generated and accepted by PREFASEG were analysed. More specifically, the safety MRPs related to therapeutic duplications, medicines not recommended for use in geriatrics, and safety alerts from the AEMPS were examined in greater detail.

The contents of the MRP alerts were defined and maintained as described by a multidisciplinary group of expert professionals from the ICS according to previous literature [9, 24]. The MRP alerts were reviewed and updated each year according to the available scientific evidence, and as a result, the clinical content underwent some changes from 1 year to the next. Each MRP alert was classified as either high or medium–low clinical relevance, as described above [23].

The MRP alerts corresponding to "therapeutic duplications" detected patients with a non-beneficial prescription of two or more medicines based on the same active ingredient (alone or in combination) and/or with the same pharmacological action (further details can be found in Additional file 1). Duplications of more than 60 different pharmacological groups commonly used in PC were addressed. In each group, "clinically relevant duplications" and "dose adjustments duplications" (combinations sought with a therapeutic objective) were clearly differentiated. Depending on their relevance, alerts marked with different colours were generated, as indicated above.

During the study period, MRP alerts associated with "AEMPS safety alerts" reported contraindications for the "Triple Whammy," COXIBS, diclofenac, aceclofenac, cilostazol, ivabradine, agomelatine, escitalopram, citalopram, trimetazidine, raloxifene/bazedoxifene, strontium ranelate, aliskiren, and canagliflozin (further details can be found in Additional file 1). These alerts were considered to be highly relevant because they were absolute contraindications, in addition to having a specific safety alert originating from the AEMPS, and so they were indicated in red.

The MRP alerts corresponding to "medicines not recommended for use in geriatrics" detected patients $\geq$ 75 years of age who had been prescribed inappropriate medication that posed a more unfavourable risk–benefit profile due to their age (see Additional file 1). The selection of medications considered inappropriate for this age group was based on the Beers (2015) [26], EU-PIM (European Consensus) [27], STOPP/START

Table 1 Combinable attributes in the configuration of each PREFASEG notice

Type of alert	Combinable attributes in the PREFASEG message configuration
Interactions	ATC drug groups
Duplicate therapies	ATC drug groups
AEMPS safety alerts	Age
	ATC drug groups
	Grouping based on health problems
	Dose of the active ingredient that generates the warning
Advised against for use in geriatrics	Age
Contraindications due to health issues	ATC drug groups
Contraindications due to clinical variables	Grouping based on health problems
Teratogens in pregnancy	Labelling of clinical variables (e.g., glomerular filtration and potassium levels)
Combinations of anticholinergic drugs	ATC drug groups
Suspicions of hypersensitivity	ATC drug groups
Adverse drug reactions	ATC drug groups

[28], and PRISCUS [29] criteria (further details can be found in Additional file 1). These alerts were displayed on-screen as alerts of medium–low relevance (i.e., orange colour) since the literature indicates that they should be administered with caution.

Data collection and analysis

The analysed data were obtained from the ECW that stores the active prescriptions of all patients; however, data from specific patients were not analysed. The study was restricted to drugs prescribed and financed by the National Health System for use in the PC setting.

In January 2016, information began to be extracted regarding the different types of MRP alerts generated by PREFASEG, which were internally identified in the patient's EHR. Thus, the number of advisories for each MRP generated, the medicines involved in each alert, and the acceptance or rejection of the alert were recorded. Each month, the alerts generated by the system and accepted by the clinicians were accumulated in a computer repository. The data set was analysed annually through computerised extractions from the ECW databases. The alert traceability was stored and organised on computer servers according to the organisational structure of the ICS, i.e., with differentiation between the health territories in which the institution is organised.

A descriptive analysis was carried out of the generated and accepted alerts of the different MRPs from January 2016 to December 2018. Initially, the analysis was carried out on an annual basis because the clinical contents changed annually. These content changes occurred for a number of reasons, including the inclusion of new marketed drugs, modifications in the definitions of existing MRP alerts to render them more specific, and the inclusion of additional pharmacological groups. Despite these content changes, the data were accumulated, and a global analysis of the alerts generated and accepted during the 3-year study period was also carried out.

Results

General analysis of the MRP alerts generated by PREFASEG

During the period of study, 22.5, 22.3, and 22.4 million new prescriptions were issued in the ICS PC system in 2016, 2017, and 2018, respectively, while the number of alerts generated by PREFASEG were 1.17 million in 2016, 1.43 million in 2017, and 1.77 million in 2018. Thus, the percentage of MRP alerts generated by the tool with respect to the number of new prescriptions issued were 5% in 2016, 6% in 2017, and 8% in 2018.

The global acceptance of these alerts varied throughout the 3 years studied, ranging from 31% (362,732) in 2016 to 26% (457,976) in 2018 (see Table 2), which corresponds to 69–74% of the MRP alerts generated by PREFASEG during the years of study. Analysis of the accumulated number of alerts issued over the 3-year study period (i.e., 4.38 million alerts) gave a 28% degree of acceptance (i.e., 1.22 million accepted alerts).

When analysing the alerts generated from the different MRPs throughout the study period (2016–2018), it was observed that those related to drug interactions, therapeutic duplications, and drugs advised against for use in geriatrics were the most common. Taking the data collected over the 3 years, 39% (1,691,886) of the 4,379,866 million alerts generated were for drug interactions, 33% (1,436,721) were for therapeutic duplications, and 10% (441,920) were for the use of drugs advised against in geriatrics. Thus, these three types of MRP alerts accounted for more than three-quarters of the PREFASEG alerts (3,570,527; 82%). Of these, 27% were accepted and 73% were ignored. In addition, of the 34,063 alerts related to teratogens in pregnancy, 22,324 (66%) were ignored.

The types of alerts with the highest percentage of acceptance were those related to a history of suspected (unconfirmed) drug hypersensitivity, with 35% (89,279) of these alerts being accepted over the 3 years studied. Detailed analyses indicated that four non-steroidal anti-inflammatory drugs (NSAIDs, i.e., ibuprofen, naproxen, desketoprofen, and diclofenac) represented 45% (113,936) of the suspected hypersensitivity reactions reported by PREFASEG, with ibuprofen generating the highest number of alerts (61,026). In addition, during the study period, the number of suspected hypersensitivity reaction alerts for β-lactam antibiotics alone or in combination fell into the second largest group, with 39,622 alerts and an acceptance level of 63% (25,153).

In contrast, the alerts related to potential teratogenic compounds during pregnancy had a lower degree of acceptance (i.e., 34%, 11,739). It was observed that the active ingredients that generated the most alerts were ibuprofen (10,864) and acetylsalicylic acid (4336) out of a total of 34,063.

Overall, the alerts with the lowest degree of acceptance were those attributed to interactions between treatments, with 25% (423,884) of a total of 1,691,886 being accepted. More specifically, the interactions of NSAIDs with acetylsalicylic acid generated the greatest number of alerts, reaching 220,507 alerts with an acceptance level of 18% (40,227). Table 3 outlines the 10 main interactions at the active ingredient level, which represent 30% (506,082) of all alerts of this type.

Analysis of the PREFASEG alerts related to therapeutic duplication

In the 3 years studied, the four groups of duplications that generated the most alerts were the NSAIDs, paracetamol-type analgesics, renin-angiotensin system

Table 2 MRP alerts generated and accepted by PREFASEG between January 2016 and December 2018

PREFASEG	2016			2017			2018			Sum 2016–2018		
Type of MRP alert	Alerts generated	Alerts accepted	% Accepted alerts	Alerts generated	Alerts accepted	% Accepted alerts	Alerts generated	Alerts accepted	% Accepted alerts	Alerts generated	Alerts accepted	% Accepted alerts
Interactions	439,507	118,485	27	550,692	138,947	25	701,687	166,452	24	1,691,886	423,884	25
Duplicate therapies	426,506	141,371	33	463,418	136,097	29	546,797	148,943	27	1,436,721	426,411	30
Advised due to age (> 75 years)	108,974	32,345	30	144,807	41,740	29	188,139	50,299	27	441,920	124,384	28
AEMPS safety alerts	59,146	18,301	31	86,308	21,958	25	84,158	18,720	22	229,612	58,979	26
Contraindications due to health issues	35,164	13,771	39	67,452	21,330	32	105,749	28,390	27	208,365	63,491	30
Teratogens in pregnancy	11,721	4200	36	10,938	3830	35	11,404	3709	33	34,063	11,739	34
Combinations of anticholinergic drugs	1077	423	39	2619	863	33	3171	877	28	6867	2163	31
Suspicions of hypersensitivity	76,883	28,952	38	84,099	29,759	35	93,852	30,568	33	254,834	89,279	35
Adverse drug reactions	15,397	4884	32	23,712	6927	29	36,489	10,018	27	75,598	21,829	29
Totals	1,174,375	362,732	31	1,434,045	401,451	28	1,771,446	457,976	26	4,379,866	1,222,159	28

Table 3 Top 10 alerts related to drug interactions between January 2016 and December 2018

Original active ingredient	Conflicting active ingredient	Alerts generated	Acceptance (%)
Ibuprofen	Acetylsalicylic acid	97,847	19
Amlodipine	Simvastatin	85,358	24
Naproxen	Acetylsalicylic acid	64,913	16
Simvastatin	Amlodipine	59,453	26
Dexketoprofen	Acetylsalicylic acid	32,455	16
Acenocoumarol	Simvastatin	31,349	29
Simvastatin	Acenocoumarol	31,349	26
Tramadol and paracetamol	Citalopram	27,479	24
Tramadol and paracetamol	Sertraline	26,872	24
Diclofenac	Acetylsalicylic acid	25,292	24
Enoxaparin	Acetylsalicylic acid	23,715	16

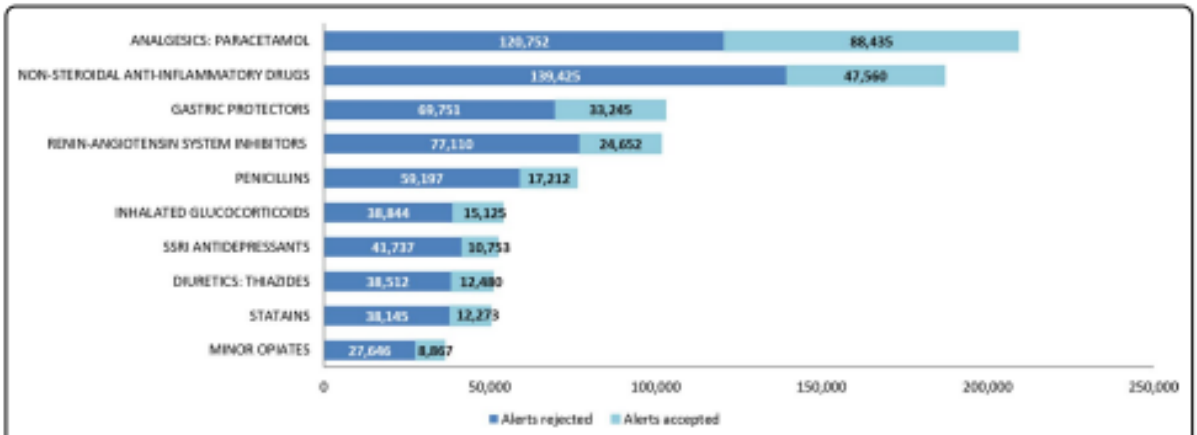

Fig. 3 Degrees of detection and acceptance of the main types of duplication from January 2016–2018

(RAS) inhibitors and gastric protectors (see Fig. 3). Out of a total of 65 groups, these 4 duplication groups represented 42% (600,930) of the total alerts generated (1,436,721). Duplications related to analgesics and gastric protectors had the highest levels of acceptance during the study period, reaching 42% (88,435) and 32% (33,245), respectively. In contrast, duplications related to the SSRI antidepressants and the RAS inhibitor antihypertensives had the lowest degrees of acceptance, i.e., 20% (10,753) and 21% (20,940), respectively.

Furthermore, the pairs of active ingredients with the greatest numbers of alerts generated for duplications during the 3 years studied were paracetamol–paracetamol, paracetamol–paracetamol with tramadol, omeprazole–omeprazole, ibuprofen–ibuprofen, and metamizole–metamizole. These 5 pairs represented 22% (317,390) of the duplications, of which 144,450 (46%) were accepted.

Moreover, the duplications related to antibiotics such as amoxicillin generated a considerable number of alerts, i.e., 76,409 over the 3 years studied, and their acceptance rate was relatively low at 23%. Upon the analysis of other groups of potentially dangerous duplications, such as those related to oral anticoagulants, it was observed that PREFASEG generated 14,903 alerts of duplications for this group, of which 42% (6314) were accepted, and the prescriptions were not continued.

Analysis of PREFASEG alerts related to AEMPS safety alerts

It was found that the number of alerts related to AEMPS safety alerts increased throughout the study period, i.e., from 59,146 in 2016 to 84,158 in 2018. This was accompanied by a reduction in the degree of acceptance of these alerts from 31% (18,301) to 22% (18,720), respectively.

Analysing the details of these AEMPS alerts (see Table 4), it was apparent that the Triple Whammy, which considered the concomitant therapy of NSAIDs, diuretics, and RAS inhibitors, generated the highest degree of alerts, representing 85% (195,987) of the total alerts. The

Table 4 Degree of detection and acceptance of the AEMPS safety alerts in 2016, 2017, and 2018

	2016			2017			2018		
AEMPS alert	**Alerts**	**Alerts accepted**	**% Accepted**	**Alerts**	**Alerts accepted**	**% Accepted**	**Alerts**	**Alerts accepted**	**% Accepted**
TRIPLE WHAMMY"	46,020	13,867	30	76,107	18,992	25	73,860	15,988	22
DICLOFENAC	7288	2588	36	5734	1774	31	5137	1511	29
COXIBS	3131	888	28	2535	616	24	2986	644	22
ACECLOFENAC	805	204	25	665	127	19	487	101	21
ESCITALOPRAM	645	204	32	270	95	35	305	72	24
CITALOPRAM	495	189	38	217	67	31	302	104	34
CILOSTAZOL	193	70	36	181	66	36	289	65	22
AGOMELATINE	133	54	41	175	54	31	249	72	29
IVABRADINE	130	51	39	153	56	37	200	48	24
CANAGLIFLOZIN	–	–	–	128	42	33	177	40	23
TRIMETAZIDINE	115	62	54	82	36	44	111	47	42
RALOXIFENE and BAZEDOXIFENE	106	64	60	23	11	48	30	20	67
STRONTIUM RENALATE	53	39	74	21	11	52	22	5	23
ALISKIREN	32	21	66	17	11	65	3	3	100
Total	59,146	18,301	31	86,308	21,958	25	84,158	18,720	22

*Triple Whammy: NSAIDs + RAS inhibitors + diuretics

degree of acceptance of this type of alert varied, ranging from 30% (13,867) in 2016 to 22% (15,988) in 2018, thereby indicating a decrease in acceptance over this 3-year period. Reviewing the main anti-inflammatory drugs that generated the Triple Whammy alerts, it was observed that in 65% of the cases, the NSAIDs involved were ibuprofen and naproxen.

As indicated in Table 4, the number of alerts generated by diclofenac decreased over time. More specifically, in 2016, diclofenac generated 7288 alerts, while by 2018 this number had reduced to 5137. However, the degree of acceptance also decreased from year to year, dropping from 36% (2588) in 2016 to 29% (1511) in 2018.

The alerts with the highest degree of acceptance were those related to strontium ranelate, raloxifene/bazedoxifene, and aliskiren; however the number of such alerts was low since these are drugs that are being gradually withdrawn from the market, or tend to be unused in daily practice.

Analysis of the PREFASEG alerts related to medicines not recommended for use in geriatrics between January 2016 and December 2018

The alerts generated by PREFASEG that were related to drugs advised against for use in geriatrics increased throughout the study period, i.e., from 108,974 in 2016 to 188,139 in 2018. However, a reduction in the degree of acceptance from 30% (32,345) to 27% (50,299), respectively, was also observed.

The two pharmacological groups that generated the highest number of alerts within this category were the benzodiazepines and the NSAIDs, representing 39% (172,574) and 21% (47,966) of a total of 441,920 alerts in the 3 years studied (see Table 5). More specifically, the alerts related to benzodiazepine usage in geriatrics increased by 55% during the study period, i.e., from 30,662 in 2016 to 68,974 in 2018. Alprazolam represented 44% (65,910) of the alerts generated for benzodiazepines in this group of patients (see Table 6), and overall, the benzodiazepine group showed an acceptance rate of 27% over the 3 years.

Within the NSAID alerts, it was observed that desketoprofen represented 48% (45,293) of the total alerts in this group, and this group showed one of the lowest levels of acceptance (i.e., 22%).

In general, analysis of the degrees of acceptance in this class of alerts shows a significant level of variation (see Table 5), and the pharmacological groups with the highest degree of acceptance (i.e., where no prescription was issued for the corresponding treatment) were the muscle relaxants (41%, 7521) and the peripheral vasodilators (39%, 6621).

Discussion

The main finding of this study was that the PREFASEG system appears to adopt the role of a CDSS that assists in preventing potential safety MRPs for patients by generating online alerts when starting a new treatment. During

Table 5 Pharmacological groups not recommended in the elderly that generated PREFASEG alerts from January 2016–December 2018

Not recommended pharmacological groups	Alerts generated	Total accepted	% Accepted
Benzodiazepines, hypnotics, and sedatives	172,574	47,966	27
Anti-inflammatory and anti-rheumatic (NSAIDs, COXIBS)	94,034	20,627	22
Antihypertensives	34,542	10,310	30
Digestive system (otilonium, metoclopramide, glibenclamide, chlorporpamide)	31,496	8945	28
Chronic obstructive pulmonary disease treatments (theophylline)	19,285	4758	25
Central action muscle relaxants (cyclobenzaprine)	18,170	7521	41
Tricyclic antidepressants and Fluoxetine	17,289	5654	33
Peripheral vasodilators (pentoxifilline, nicergoline, nafthydrofuril)	16,958	6621	39
Respiratory system (systemic antihistamines)	14,219	4917	35
Hormone therapy (megestrol)	10,776	2631	24
Urinary antispasmodics (oxybutynin)	7018	2495	36
Antithrombotics (cilostazol)	3270	1100	34
Beta-blockers (sotalol)	1105	392	35
Opioid and anti-migraine pain relievers	868	342	39
Antiparkinsonian drugs	316	105	33

the period studied, it was observed that 28% of the generated security alerts led to a modification of the prescription (i.e., acceptance of the alert). In absolute terms, between 2016 and 2018, a total of 1,222,159 recommendations were accepted globally, which likely led to the avoidance of numerous potential MRPs in patients. Overall, PREFASEG reported a safety MRP in 1 out of every 15 new prescriptions. The degrees of acceptance of the recommendations were relatively high when compared with a similar study into a different online preventive alert system, where the percentages of acceptance ranged from 12 to 14% [30]. However, the variability between studies was considerable; in a 2009 Cochrane review on the effects of online prompts/reminders, an improvement of only 4.2% was reported [18], while other studies described omissions of recommendations in between 49 and 96% of the cases [31]. In general, subsequent systematic reviews [32, 33] concluded that online notification systems had only a small or moderate effect.

Table 6 Top 10 alerts for drugs advised against for use in geriatrics between January 2016 and December 2018

Active ingredient responsible for the alert	Alerts generated	Acceptance (%)
Alprazolam	65,910	24
Dexketoprofen	45,293	24
Doxazosin	33,867	30
Clonazepam	23,887	35
Zolpidem	23,314	25
Pentoxifylline	20,395	31
Metoclopramide	19,098	28
Hydroxyzine	18,328	29
Etoricoxib	15,729	18
Potassium clorazepate	15,468	29

Our study presents a number of characteristics that could explain the relatively high acceptance rate of alerts. For example, the observed degree of acceptance could be accounted for by considering that the tool takes into account the success characteristics of CDSSs described by various authors previously [10, 34]. More specifically, it is integrated into the workflow of clinicians, it generates an alert automatically during the parent consultation and in the context of their medical history, and it provides a specific therapeutic recommendation in each case. In addition, PREFASEG produces different types of safety alerts based the clinical situation of each patient and any medication that they may be taking, and it gives alerts related to the safe prescription of medication for various pathologies. To date, few studies have analysed such a diversity of alerts simultaneously [35–37]. It should also be emphasised here that PREFASEG is a tool whose clinical contents are constantly being updated and that has been in use for more than 12 years, during which time it has exhibited a good degree of acceptance by a large number of medical professionals, since it is used by > 6400 PC physicians on a daily basis. Indeed, both ICS pharmacists and PC clinical pharmacologists promote the use of this tool.

Despite the high number of potential MRPs avoided in patients in Catalonia, it should be noted that in the case

of safety alerts relating to the use of medicines, it was striking that globally, > 70% of the alerts generated by PREFASEG were ignored, which amounts to 3.16 million over the 3-year study period. However, it must be considered that, on occasions, the recommendations given by PREFASEG did not necessarily imply a change, or the change was not recorded as such. In addition, some recommendations involved a dose reduction or a clinical follow-up of some variable, and therefore the prescription was continued. In such circumstances, the system did not count the recommendation as accepted, even if the dose was lowered or an analysis was requested. If these modifications had been registered, the degree of acceptance would be higher, as the presented acceptance values relate only to cases where the prescription was continued. It should also be considered that not all alerts had the same degree of clinical relevance, with alerts being accompanied by either an orange or a red icon, depending on the importance of the recommendation, as also described in a previous study [23].

Over the course of the 3 years studied, the number of generated alerts increased. This was partly related to the fact that new and updated content was introduced into the PREFASEG system on an annual basis. The existence of a direct relationship between the increased consumption of certain drugs (e.g., the benzodiazepines) was also considered, in addition to the probability that greater numbers of MRP alerts could be generated from such drugs due to their increased use among the population. At the same time, it should be noted that the degree of acceptance of the alerts tended to decrease over time, with practitioners gradually ignoring the recommendations. This decline in acceptance could be partly attributed to alert fatigue; however, it will be necessary to further investigate the reasons behind the rejection of alerts, in addition to separately analysing the high and medium–low relevance alerts, while also considering the cases where the recommendation does not suggest a change of drug. It will also be essential to collect the opinions of the professionals who use the PREFASEG tool. According to various reports, the main reasons for low acceptance by clinicians are the large number of low-relevance alerts they receive and their poor content [21, 22, 38]. To reduce the risk of fatigue, it is therefore necessary to increase the specificity of the alerts, provide clear and concise information, and not impact on the clinician's workflow.

In relation to the ignored alerts regarding suspicions of a history of hypersensitivity to certain drugs, it is known that general practitioners tend to register cases of hypersensitivity that are reported by patients, despite the fact that such hypersensitivity has not been confirmed, and in many cases, are not real [39–41]. To address this issue, a number of hospitals are now working on a project to delabel patients with a supposed hypersensitivity reported in their clinical history unless it is confirmed by the corresponding tests.

Another type of MRP that drew significant attention due to its severity was that of teratogenic drugs, for which 66% of the generated alerts were ignored. However, it must be considered that not all medicines act as teratogens in all trimesters of pregnancy, and PREFASEG is unable to distinguish between such cases. It is also possible that some alerts were generated for women who were no longer pregnant but who, by some registration error, maintained a pregnancy status in their health records.

Regarding the alerts related to therapeutic duplications, it was observed that approximately 70% of these alerts were ignored by clinicians. However, many such alerts were related to adjustment of the daily dose of treatment, and so it was necessary to combine presentations at different doses; this was common in the groups of antihypertensive RAS inhibitors and antidepressants, and in the replacement of amoxicillin with amoxicillin-clavulanate. In terms of the NSAIDs and paracetamol-type analgesics, it was observed that prescriptions were authorised for issuing on demand if necessary, which often generated alerts related to duplication if an attempt was made to prescribe a drug from the same pharmacological group. Another group of duplications that drew attention due to their association with a high risk of serious adverse effects that motivate hospital admissions were the oral anticoagulants [42]. During the 3-year study period, PREFASEG produced 14,903 alerts related to duplications in this group of drugs, which translated to an acceptance of 42% (6314), wherein the prescription was not continued.

In the case of the AEMPS safety alerts, an unexpected low degree of acceptance was recorded considering that these constituted specific alerts from a regulatory agency [43]. In fact, throughout the 3-year study period, the degree of acceptance of the AEMPS safety alerts decreased, and in 2018 they reflected the lowest percentage of acceptance (22%) of all alerts throughout that year. Among these notices, the Triple Whammy, which is associated with a significant increase in the risk of kidney failure [44], represented the largest number of alerts.

Upon examination of the alerts related to the use of drugs advised against in geriatrics, it was observed that the degree of acceptance ranged from 30% in 2016 to 27% in 2018. Despite the fact that this alert category is considered of low clinical relevance, wherein use of a specific drug may not be recommended in older patients but is not totally contraindicated, it produced similar or even superior acceptance results compared to the AEMPS safety alerts. It was therefore considered that this level of acceptance was due to physicians being somewhat

more sensitive to safety alerts related to elderly patients. However, we must not lose sight of the fact that > 70% of these alerts were discarded and the corresponding prescriptions was generated, which could lead to potential adverse reactions in patients. In this context, it is estimated that drug-associated adverse effects produce approximately 6.5% of hospital admissions, of which more than half of these could be prevented [45–48].

The pharmacological groups that generated the highest number of alerts in geriatric patients were the benzodiazepines and the NSAIDs, which are also widely used drugs throughout the population. The significant increase in the number of alerts for benzodiazepines (i.e., from 30,662 in 2016 to 68,974 in 2018) was particularly surprising, and these were mainly attributed to alprazolam. It is known that both an advanced age, which is linked to metabolic and pharmacokinetic changes, and the number of drug treatments that a patient is receiving, are two of the situations that increase the risk of adverse drug effects to the greatest extent [49–51]. In addition, it must be considered that the world population is constantly aging, which is accompanied by a greater degree of pathologies, and an increase in the use of pharmaceuticals [52–54].

Analysing the percentages of acceptance for alerts related to the use of drugs advised against in geriatrics, significant variation was observed between the different pharmacological groups. More specifically, muscle relaxants and peripheral vasodilators were the groups with the highest degrees of acceptance. According to a previous study, physicians tend to prioritise alerts that are more clinically relevant, or that can be resolved with the least amount of time or effort [55].

In a classic study looking at hospitalisations caused by adverse effects, it was found that the majority occurred in the elderly, and were due to commonly used drugs with well-known safety profiles [56]. Considering this point, which can likely be extrapolated to other countries, it would be interesting to analyse the situation of patients for whom PREFASEG detected a possible MRP that was not addressed.

In terms of limitations to the current study, it should be noted that the moderate percentage of alert acceptance highlights the need to investigate the causes that lead clinicians to discard such a high number of recommendations. Thus, to maximise the usefulness of PREFASEG and to avoid possible alert fatigue, it will be necessary to carry out a detailed review into the traceability data of the tool to eliminate low-relevance alerts that are generated but not accepted, and to highlight any alerts related to therapeutic orientations while providing one or more alternative active ingredients. The introduction of a block to prevent the continuation of a prescription associated with a severe MRP could also be considered.

On the other hand, essential future work should also focus on analysing the acceptance of MRP alerts based on their clinical relevance and the type of recommendation, which are key aspects to consider in the case of drug interactions. In addition, a satisfaction survey should be carried out to request feedback and suggestions from practitioners with regards to improving the PREFASEG system in terms of its clinical content and technological aspects.

The future development of PREFASEG also involves the inclusion of medicines that can only be prescribed in hospitals and their corresponding contraindications, which will allow the program to be extended to different levels of care. The technological evolution of the tool is also necessary to render it more specific when generating alerts. For example, this could be achieved using the terminology common to all SNOMED CT systems (Systematised Nomenclature of Medicine—Clinical Terms) that determine the active ingredient, the dose, the pharmaceutical form, and the number of packaging units [57–59]. To optimise the use of PREFASEG and improve the management of clinical information, intelligent systems such as natural language processing could be applied that would allow the clinician to obtain and interact with the information recorded in text format in the patient's clinical history [60, 61]. An improved follow-up and monitoring of the PREFASEG alerts would also be desirable, wherein details regarding the professional receiving the alert are registered and made visible, in addition to whether this alert is ignored, and the level of care of the corresponding professional.

In summary, PREFASEG appears to be a feasible and efficient strategy to improve some aspects of clinical safety related to the prescription of drugs, and as a result, in the health care received by patients.

Conclusions

Our study demonstrated that the PREFASEG (PREscripción FArmacéutica SEGura, i.e., safe pharmaceutical prescription) clinical decision support system contributes to the prevention of potential safety medicine-related problems in patients. In 28% of the cases in which the tool generated a safety alert, primary care physicians modified their prescriptions by some means. The main drug groups implicated in the PREFASEG alerts were the non-steroidal anti-inflammatory drugs, the benzodiazepines, and the renin-angiotensin system inhibitors; groups that frequently cause adverse effects and motivate hospital admissions.

In future, it will be necessary to study in detail the reasons behind the fact that > 70% of the generated alerts were ignored by physicians. In addition, the possibility of reducing the number of alerts should be assessed to

avoid alert fatigue. Moreover, it is evident that strategies must be designed to make the prescriber aware of the importance of patient safety, as well as to technologically improve the tool and render it more robust and specific.

Abbreviations

ADE: Adverse drug event; AEMPS: Spanish Agency for Medicines and Health Products (Agencia Española del Medicamentos y Productos Sanitarios); CDSS: Clinical decision support system; ECW: Electronic clinical workstation; EHR: Electronic health record; ICS: Institut Català de la Salut (Catalan Health Institute); MRP: Medication-related problem; NSAIDs: Non-steroidal anti-inflammatory drugs; PC: Primary care; PREFASEG: PREscripción FArmacéutica SEGura, i.e., safe pharmaceutical prescription; RAS: Renin-angiotensin system.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12911-021-01710-8.

Additional file 1. Annex Table 1. Description of the types of PREFASEG alerts; **Annex Table 2.** Groups of pharmacological duplications included in PREFASEG in 2018; **Annex Table 3.** Definitions of the AEMPS safety alerts included in PREFASEG in 2018; **Annex Table 4.** List of drugs not recommended for use in geriatrics in 2018.

Acknowledgements

This study has been prepared within the framework of the Doctorate in Pharmacology at the Universitat Autònoma de Barcelona (UAB). We would like to thank ICS Information Systems for supporting us during acquisition of the information required to conduct this study. We would also like to thank the PREFASEG working group for helping to maintain a useful and up-to-date tool.

Authors' contributions

MAP extracted, analysed, and interpreted the data on the use of the PREFASEG tool. She also wrote the majority of the manuscript. MO helped to interpret the data on the use of the PREFASEG tool, in addition to giving support and making contributions to the writing of the manuscript. AF and ED reviewed the data analysis process, reviewed the various parts of the manuscript, and made the relevant contributions to give clarity and understanding to the study. All authors read and approved the final manuscript.

Funding

The primary care component of this study was funded by the Institut Universitari d'Investigació en Atenció Primària (IDIAP Jordi Gol) Scholarship to complete a PhD thesis in primary care.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

Not applicable. This manuscript does not report studies involving human participants, human data or human tissue. This manuscript does not report studies involving animals.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Received: 13 July 2021 Accepted: 21 November 2021
Published online: 15 December 2021

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Publisher's Note

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ANEXO 2. Artículo publicado sobre Self Audit

Pons-Mesquida et al.
BMC Medical Informatics and Decision Making (2022) 22:70
https://doi.org/10.1186/s12911-022-01809-6

BMC Medical Informatics and Decision Making

RESEARCH Open Access

Impact of a system to assist in clinical decision-making in primary healthcare in Catalonia: prescription Self Audit

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Abstract

Background: In 2008, in the context of a complete computerisation of medical records, the Institut Català de la Salut (ICS, Catalan Health Institute) implemented a system in its electronic clinical workstation (ECW) to assist decision-making at the prescription level. This system is known as Self Audit, and it supports physicians in reviewing the medication of their patients. Self Audit provides lists of patients presenting medication-related problems (MRPs) that have potential for improvement, and provides therapeutic recommendations that are easy to apply from the system itself. The aim of this study was to analyse the main results derived from the use of Self Audit in primary care (PC) in Catalonia, and the effect of an incentive-based safety indicator on the results obtained.

Methods: A descriptive cross-sectional study was carried out to analyse variations in the MRPs detected by Self Audit during 2016, 2017, and 2018 in PC in Catalonia. The effect of a safety indicator on the results obtained was also studied. This safety indicator includes the most clinically relevant MRPs (i.e., therapeutic duplications, safety alerts from the Spanish Medicines Agency, and incidences of polymedication in patients over 65 years of age). Variation in the MRPs was measured using the differences between two evaluation points (initial and final). An MRP was considered resolved if the recommendation specified in the alert was followed. The prescriptions of 6411 PC doctors of the ICS who use the ECW and provide their services to 5.8 million Catalans through 288 PC teams were analysed.

Results: Analysis of the total safety-based MRPs detected by Self Audit gave overall resolutions from April to December of 9% (21,547) in 2016, 7% (15,924) in 2017, and 1% (2392) in 2018 out of the total number of MRPs recorded in April each year. Examination of the 3 types of MRPs with the highest clinical relevance that were linked to the safety indicator gave overall resolutions of 41% in 2016 (17,358), 20% in 2017 (7655), and 21% in 2018 (8135).

Conclusions: The ICS Self Audit tool assists in reducing the number of safety-based MRPs in a systematic manner, and yields superior results for the MRPs linked to a safety indicator included in the incentives of PC physicians.

Keywords: Decision support system, Primary care, Clinical safety, Electronic prescription

Background

In the past few decades, the development of new information and communication technologies in the field of healthcare has potentially contributed to improving the cost-effectiveness and quality of patient care. In this context, a range of technical reports from the American National Institute of Medicine have confirmed that an electronic record of healthcare activity, such as an electronic health record (EHR), together with the integration of clinical decision support systems (CDSSs) in such EHRs, constitute a guarantee of quality for the health system [1, 2]. According to several authors, CDSSs aimed at

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the prescription of medications have the greatest impact on improving patient safety [3]. Although a variety of different designs and functionalities exist, these systems have a common role in intelligently combining clinical knowledge and patient information, with the aims of ultimately improving the overall prescribing process. The possibility of integrating a CDSS into the EHR system has made it possible to provide medical histories with interactive signals that alert professionals to situations of risk for their patients [4], thereby helping to improve the prescription process and the overall clinical safety of patients [3, 5, 6]. Indeed, several Spanish studies have indicated that 50% of adverse events related to medication errors are avoidable [7, 8], and that the implementation of such technologies can help to reduce them.

With this background in mind, in 2008, the Institut Català de la Salut (ICS, Catalan Health Institute) integrated a combination of CDSSs into its electronic clinical workstation (ECW), namely PREFASEG, which generates online notifications when starting a treatment to prevent medication errors [9], and the Self Audit tool, which generates lists of patients presenting with active medication-related problems (MRPs). This study focuses on the Self Audit tool.

The Self Audit tool is a computerised system that is integrated into the EHR, and based on the combination of clinical with therapeutic data, it simplifies the search for patients with an MRP related to an ongoing medication, thereby facilitating changes and/or suspensions of treatment. In an agile and visual manner, it provides the professional with a list of patients with an MRP, such as a therapeutic duplication or a drug contraindicated by a previous or current pathology, thereby allowing the review and assessment of any possible change in treatment. The tool itself provides a therapeutic recommendation in each case and facilitates the management of changes and/or suspensions of treatment, without the need to leave the program. Thus, in this system, a number of aspects related to the review of a patient's medication are systematised based on an optional and individual self-evaluation exercise. Any changes carried out are recorded in the EHR.

The MRPs are defined by a group of expert professionals from the ICS. Each year, the clinical content of the MRPs is reviewed according to the scientific information available, and, for this reason, they may vary from year to year. Each MRP is classified as high or low clinical relevance, as recommended in the literature [10].

The Self Audit tool is activated voluntarily, wherein the practitioner can use the ECW to consult the lists of patients with an MRP in his assigned population. All primary care (PC) practitioners (i.e., 100% of practitioners) use this tool at some point over the course of a year. The practitioner can also check the schedule of visits for the day, which will indicate any patients who have an MRP, and allow the doctor to take advantage of the visit to review the medication. This system therefore does not alter the workflow during the consultation [11, 12], and allows the professional to decide when is the most appropriate time to review the MRP.

From 2008 to 2016, Self Audit evolved both at the technological level and at the level of its clinical content. Initially, the tool only allowed the detection of patients with certain therapeutic duplications and/or cases of polymedication (i.e., > 10 drugs). During this period, a number of new MRP detections were incorporated into the tool, and the detection specificity was improved overall. Thus, it was not until approximately 2014 that this tool was completed in its current Self Audit configuration. In addition, the process of obtaining data to monitor the use of the tool was expensive, taking a long time to validate and debug the data until the level of quality and detail required for analysis was obtained.

Linked to the Self Audit prescription system, an incentive-based safety indicator was designed in 2008, which selected some of the most clinically relevant MRPs, and was included in the "payment for objectives" program for ICS PC physicians (N.B. according to this program, objectives are linked to annual economic incentives up to approx. 6000 €). The aim of this indicator was to promote a culture of safety in the use of medicines, and also to encourage the use of the Self Audit tool.

The aims of this study are therefore to determine the main results derived from the use of Self Audit in the Catalan PC system, and to evaluate the effect of the safety indicator on the results obtained. A further aim of this article is to provide the international audience with details regarding a computer tool aimed at improving clinical safety, which has been widely managed in the Catalan PC system by 6411 users with more than 10 years of experience. This tool is of particular importance since it helps doctors to detect patients with potential MRPs, and as a result, any ongoing treatments related to these MRPs can be reviewed and modified to benefit the health of the patient. Self Audit is a versatile and dynamic tool that can be updated with new or modified warnings as desired. Due to the considered importance of this tool to provide improvements in healthcare practice, its implementation was essentially immediate for all PC teams and professionals. Physicians refer to Self Audit as a useful tool whose usability needs, nevertheless, to be assessed.

Methods

A descriptive, cross-sectional study was designed that began in April 2016 and continued until December 2018. This study was developed within the scope of the PC

system of the ICS, which is the main provider of health services in Catalonia, a region in the northeast of Spain, and covers a population of 5.8 million inhabitants over the different Catalan territories. Overall, it serves the population through a network of 288 PC teams and 8 hospitals. The ICS is a public company that has a total of 42,374 professionals, who provide services to 80% of the population of Catalonia. Since all PC doctors of the ICS employed the Self Audit tool during routine practice, no control group was available to establish a comparison. We therefore analysed the evolution of the results over time.

Study sample

The sample studied consisted of all the prescriptions of the 6411 ICS PC physicians (i.e., 100% of the physician staff) who used the EHRs during the study period.

Variables and indicators

The main variable was the number of resolved MRPs. An MRP was considered "resolved" when: (1) the drug or drugs causing the MRP had been dropped from the patient's active prescription, or (2) the diagnosis was registered as resolved.

The main types of safety MRPs detected by the Self Audit tool were analysed, wherein clinically relevant MRPs that had been linked to the incentive-based safety indicator were emphasised. This safety indicator included 3 MRPs: (1) Therapeutic duplications; (2) safety alerts from the Spanish Agency for Medicines and Health Products (AEMPS, Agencia Española de Medicamentos y Productos Sanitarios), and (3) polymedication in patients over 65 years of age with some specific MRPs, wherein polymedication is defined as the case where more than 10 medicines were prescribed in 2016 and 2017, and more than 8 medications were prescribed in 2018.

The MRP related to therapeutic duplication detected patients with a non-beneficial prescription of two or more drugs that exhibit the same active principle (alone or in combination) and/or the same pharmacological action. In addition, "clinically relevant duplications" and "duplications of dose adjustments" (i.e., combinations sought with a therapeutic objective) were clearly differentiated, and only those considered relevant were linked to the safety indicator.

During the study period, the AEMPS safety alerts included the following contraindications: The "Triple Whammy"; coxibs, diclofenac, and aceclofenac; cilostazol; ivabradine; escitalopram and citalopram; trimetazidine; raloxifene and bazedoxifene; strontium ranelate; aliskiren; and canagliflozin (see Table 1).

The MRP related to incidences of polymedication detected patients older than 65 years of age with 10 or more prescribed medications (in 2016 or 2017) and with some specific MRPs, such as double antiplatelet therapy for more than 12 months, a combination of anticholinergic drugs, or other avoidable medications. In 2018, the denominator changed, and polymedication was defined as a patient with 8 or more prescribed medications.

Data collection and analysis

The data were collected from the ECWs, where the active prescriptions of the patients are stored. The study was restricted to drugs prescribed and financed by the National Health System and employed in PC centres. The extraction of active prescription data was carried out automatically on a monthly basis, and identified the MRPs out of the prescritions of each physician detected by Self Audit.

Throughout the three years analysed (2016, 2017, and 2018), 6 points or cross-sections of information were studied. Within each year, the variations in the number of MRPs between the considered baseline data and the final data were calculated and thus the percentage variation was established. Data could not be compared between different years because the criteria that defined the detection of an MRP were different from year to year, and so such a comparison would not have been appropriate. For example, if a new pharmacological group was to be added to the "duplicate therapy" MRP in a particular year, or additional drugs were to be included in an existing duplication group, the number of MRPs related to duplicate therapies would increase.

The data obtained from the extractions carried out for the month of April were considered as the baseline data because this was the point at which the MRP detection criteria were defined and updated, and the incentive-based goals were proposed. The data obtained for the month of December were considered to be the final data since they correlated to the final month of the calendar year, and they coincided with the last evaluation point of the safety indicator. The difference between the baseline and the final data points reflected the number of resolved MRPs and the number of generated PRMs. The MRPs of individual patients were not followed over time.

The safety indicator averages the variation in the selection of the MRPs mentioned above. The effect of the incentive-based care indicator was therefore evaluated by the reduction in the number of MRPs at the PC level over a year, which was the time that the indicator remained unchanged, and which coincided with the validity of the management contract signed by the PC doctors.

To evaluate the indicator, the ability of the PC doctors to reach the goal established at the beginning of the year was measured for specific months, and was calculated from the baseline data. More specifically, the goal

Table 1 Summary of the various AEMPS safety alert criteria

Drug	Alert criteria
Citalopram	High doses:
	Above 40 mg/day
	Above 20 mg/day in patients > 65 years of age
	Above 20 mg/day in patients suffering from liver dysfunction
	Administered in combination with other drugs that also prolong the QT interval of the electrocardiogram
Escitalopram	High doses (> 10 mg/day in patients > 65 years of age)
	Administered in combination with other drugs that also prolong the QT interval of the electrocardiogram
Aliskiren	In patients with a diagnosis of diabetes mellitus II or undergoing treatment with antidiabetic drugs
	Jointly administered with ACE inhibitors
Cilostazol	In patients suffering from a health problem where its use is contraindicated, i.e., cerebral haemorrhage, severe ventricular arrhythmias, or heart failure
	Or, in concomitant treatment with:
	2 Antiplatelet agents
	Antiplatelet + oral anticoagulant
Trimetazidine	In patients with a diagnosis of extrapyramidal and movement disorders
Raloxifene or bazedoxifene	In patients suffering from any health problem where it is contraindicated, e.g., venous thromboembolism, uterine sac, endometrial cancer, or liver failure of any degree
COXIBS	In patients suffering from any health problem where it is contraindicated, e.g., ischemic heart disease, peripheral arterial disease, cerebrovascular disease, heart failure, or inflammatory bowel disease
Diclofenac or Aceclofenac	In patients suffering from any health problem where its use is contraindicated, e.g., ischemic heart disease, peripheral arterial disease, cerebrovascular disease, or heart failure
Agomelatine	In patients ≥ 75 years of age
Ivabradine	Co-administration with verapamil
"Triple Whammy" (NSAIDs + RAS inhibitors + diuretics)	In patients ≥ 75 years of age or undergoing treatment for diabetes
Canagliflozin	In patients suffering from a health problem in which it is necessary to be more careful due to an increased risk of amputation

for each physician corresponded to a specific number of MRPs less than that existing at the beginning of the year. In the years studied, there were 2 or 3 months of the year in which the extraction of information from the active prescription MRPs was evaluated, and the ability of the doctors to reach the goal was measured. In 2016, the evaluation was carried out in September and December, while in 2017 and 2018 the evaluations were carried out in June, September, and December.

Results

General analysis of the MRPs of the Self Audit tool

The data extractions corresponding to the months of December 2016, December 2017, and December 2018 showed that the ECW had registered 9.5, 9.6, and 9.7 million active prescriptions, respectively. In these months, 210,916 MRPs (December 2016), 227,856 MRPs (December 2017), and 230,959 MRPs (December 2018) were identified. Based on these data, it was observed that the percentage of MRPs studied with respect to the total number of active prescriptions represented 2.2% in 2016 and 2.4% in 2017 and 2018.

Upon analysis of the total clinical safety MRPs detected by Self Audit, an overall resolution of 9% (21,547) was observed in 2016, while resolutions of 7% (15,924) and 1% (2392) were found in 2017 and 2018, respectively (see Table 2).

Upon the analysis of all clinical safety MRPs detected by Self Audit, overall resolutions of 9% (21,547), 7% (15,924), and 1% (2392) were observed in 2016, 2017, and 2018, respectively. Subsequent analysis of the resolutions of the different MRPs throughout the whole study period (i.e., 2016–2018) showed an overall trend towards resolution, especially in the cases where AEMPS safety alerts were implemented, since this resulted in 49% resolution of the cases in 2016, 11% in 2017, and 23% in 2018.

The behaviours of the specific MRPs were then examined in further detail. More specifically, in April 2016, a total of 46,242 duplications were detected, while in December of the same year, such duplications had been reduced by 10% (i.e., to a total of 41,589). However, there was a significant increase in the absolute number of duplications detected in 2018 (65,377 in April and 64,650 in December), with a reduction of only 1% being

Table 2 Problems related to medications detected by Self Audit: April 2016–December 2018

Problem detected by Self Audit	Year 2016*			
	Apr 2016	Dec 2016	Variation	Percentage (%)
Duplicate therapies	46,242	41,589	−4653	−10
AEMPS safety alerts	13,521	6849	−6672	−49
Contraindications due to medical devices and/or clinical variables	37,359	37,421	62	0
Treatment duration				
Bisphosphonates ≥ 5 years	8246	7434	−812	−10%
Double anti-aggregation ≥ 12 months	4805	4332	−473	−10%
Drugs advised against in geriatrics	88,393	83,638	−4755	−5
Combination of anticholinergic drugs	2913	2320	−593	−20
Avoidable medication	30,984	27,333	−3651	−12
Total number of problems detected	232,463	210,916	−21,547	−9
Problem detected by Self Audit	**Year 2017**			
	Apr 2017	**Dec 2017**	**Variation**	**Percentage (%)**
Duplicate therapies	65,679	59,536	−6143	−9
AEMPS safety alerts	11,212	9935	−1277	−11
Contraindications due to medical devices and/or clinical variables	44,687	44,000	−687	−2
Treatment duration				
Bisphosphonates ≥ 5 years	6386	4964	−1422	−22%
Double anti-aggregation ≥ 12 months	4394	4508	114	3%
Drugs advised against in geriatrics	82,252	79,187	−3065	−4
Combination of anticholinergic drugs	2184	1819	−365	−17
Avoidable medication	26,986	23,907	−3079	−11
Total number of problems detected	243,780	227,856	−15,924	−7
Problem detected by Self Audit	**Year 2018**			
	Apr 2018	**Dec 2018**	**Variation**	**Percentage (%)**
Duplicate therapies	65,377	64,650	−727	−1
AEMPS safety alerts	7046	5441	−1605	−23
Contraindications due to medical devices and/or clinical variables	45,175	46,469	1294	3
Treatment duration				
Bisphosphonates ≥ 5 years	4552	4123	−429	−9%
Double anti-aggregation ≥ 12 months	4631	4630	−1	0%
Drugs advised against in geriatrics	79,225	79,384	159	0
Combination of anticholinergic drugs	1854	1736	−118	−6
Avoidable medication	25,491	24,526	−965	−4
Total number of problems detected	233,351	230,959	−2392	−1

*In the three years studied, April was taken as the baseline data because it is the time at which the definitions of the MRPs were updated according to the consensus of a group of experts, and it also is the month in which the incentive-based goals were proposed

achieved throughout the year. In addition, it was found that the MRPs related to drugs not recommended for use in geriatric patients exhibited reductions of 5% (4755 cases) in 2016 and 4% in 2017 (3065 cases), although no reduction was found in 2018. Furthermore, the MRP related to avoidable medications (including chondroprotectors and citicoline) showed a reduction of 3651 cases in 2016 (−12%), 3079 cases in 2017 (−11%), and 965 cases in 2018 (−4%).

Taking the last analysis point, namely that of December 2018, 34% of the 230,959 MRPs detected were due to the use of drugs not recommended for use in geriatric patients, while 28% were attributed to therapeutic duplications, and 20% were due to pathological

contraindications. As a result, these three MRPs accounted for more than three-quarters of the overall MRPs detected at this point (i.e., 190,503 cases, 82.5%).

Analysis of clinically relevant MRPs linked to the PA safety indicator

In the period studied, 41,492 MRP cases were resolved in the Self Audit tool, of which 80% (33,148) were linked to the safety indicator. Upon examination of the 3 types of MRPs linked to this indicator, joint resolutions of 41% in 2016 (17,358), 20% in 2017 (7655), and 21% in 2018 (8135) were observed, as detailed detail in Fig. 1. However, despite these promising percentages of resolution, the total number of these three MRPs increased from 24,720 in December 2016 to 31,501 in December 2018.

With reference to the specific MRPs, in the case of therapeutic duplications, the resolution of 5413 cases in 2016, 4892 cases in 2017, and 3485 cases in 2018 was achieved. In addition, when considering the MRPs related to the AEMPS alert, 6815 cases were resolved in 2016, which dropped to 2160 cases in 2017, and 1735 cases in 2018. Furthermore, for the MRP related to polymedication, the corresponding reductions were 5130 cases in 2016, 603 cases in 2017, and 2915 cases in 2018.

The annual data for the safety indicator showed that at the time of the evaluation, there was a greater decrease in the number of MRPs, while after each evaluation point there was a rebound in the number of cases, as can be seen in Fig. 2. The most pronounced rebound was observed after the December evaluation point, as will be discussed later.

Upon analysis of the detail relating to the AEMPS safety alerts (Table 3), it was observed that the Triple Whammy represented 89% (9767/11,035) of the total alerts included in 2016, 80% (4123/5153) of those in 2017, and 73% (3260/4460) of those in 2018. Its reduction percentage ranged from 66% in 2016 to 43% in 2018.

As indicated in Table 3, the reduction in the number of cases related to the AEMPS safety alert for diclofenac was 56% in 2016, while the reduction for acecloflenac was 27%. In 2017, the corresponding reductions for diclofenac and acecloflenac were 42 and 38%, respectively, and in

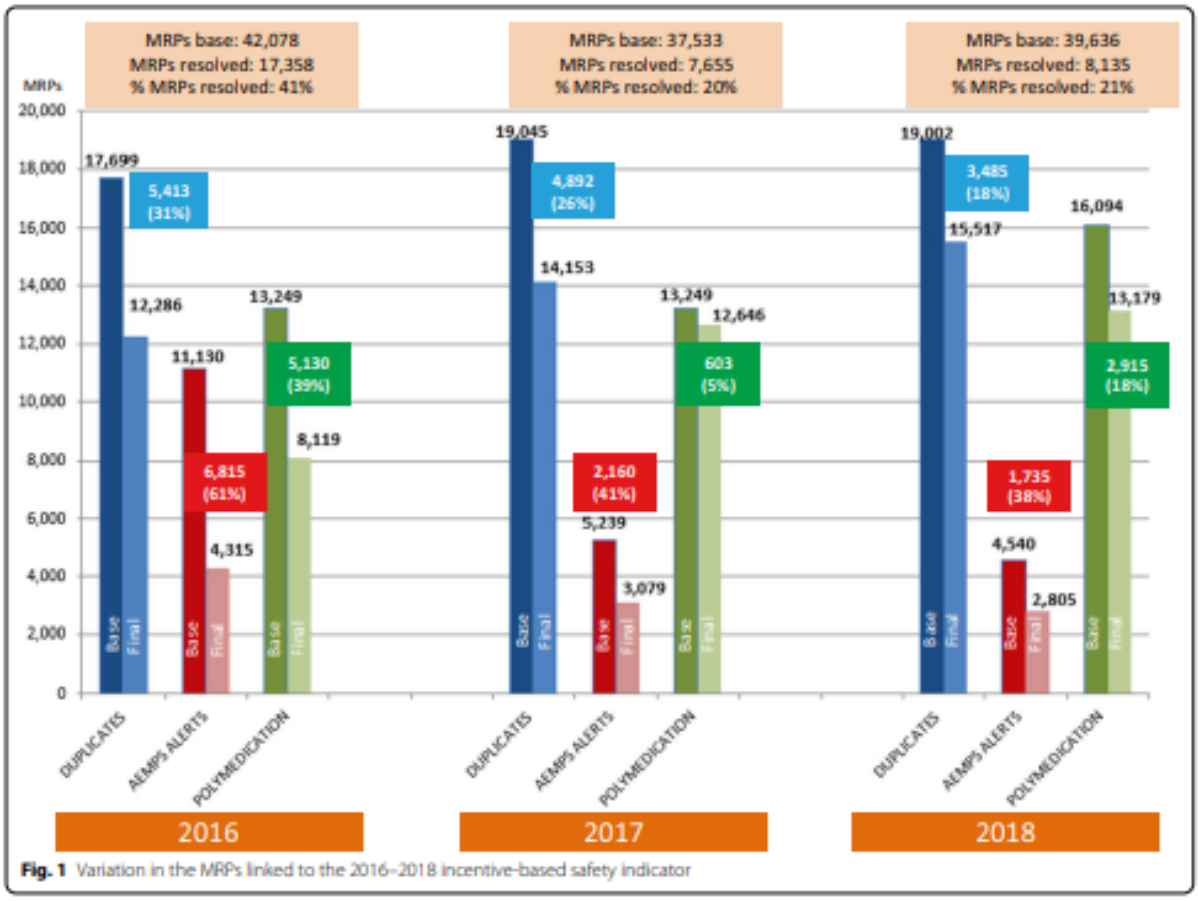

Fig. 1 Variation in the MRPs linked to the 2016–2018 incentive-based safety indicator

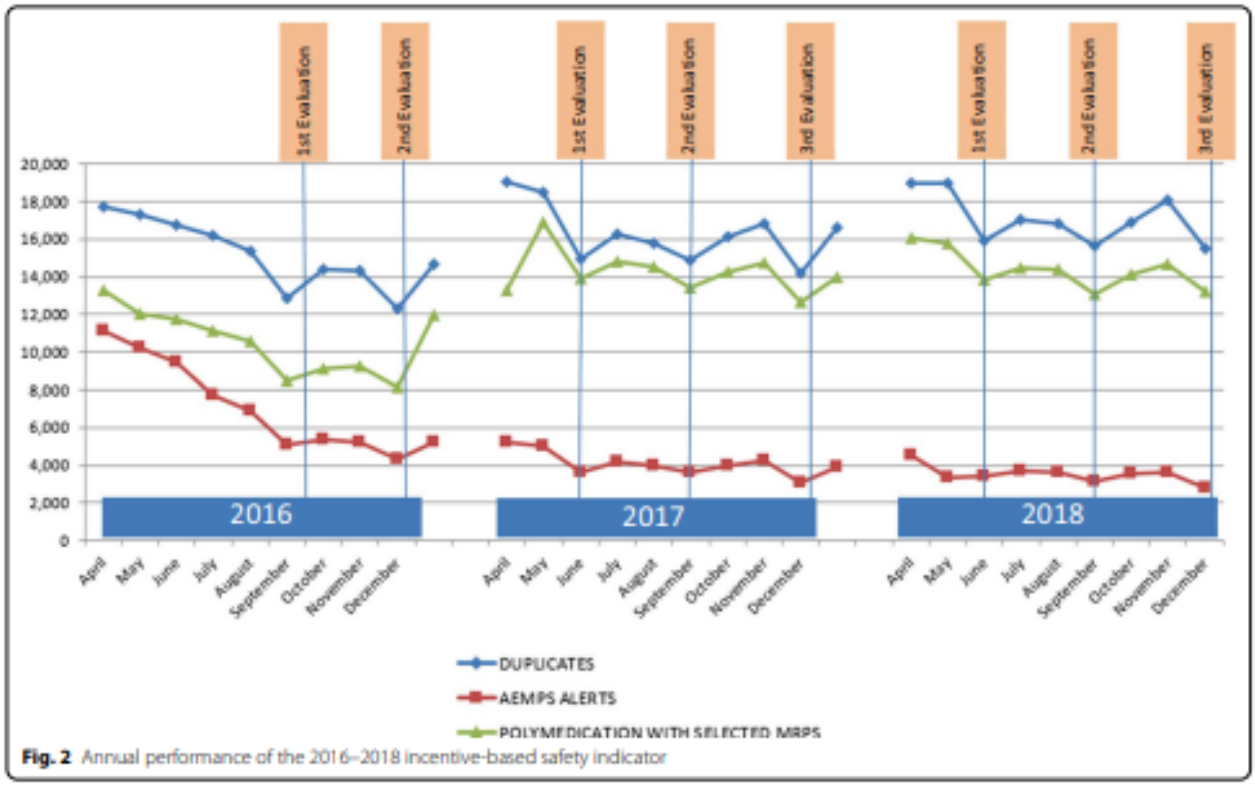

Fig. 2 Annual performance of the 2016–2018 incentive-based safety indicator

2018, they were 49 and 45%. Furthermore, the reductions in cases related to alerts for the coxibs were 31, 31, and 26% in 2016, 2017, and 2018, respectively, while the corresponding reductions for the cilostazol alert were 9% in 2016 but 23% in 2017 and 2018. The remainder of alerts represented few cases in absolute numbers.

Following analysis of the therapeutic duplications (Table 4), it was found that 70% fell into 10 pharmacological groups out of a total of 63. Of these 10 groups, the renin-angiotensin system inhibitors stood out particularly (2828 detected in December 2016, and 1939 detected in December 2018), along with non-steroidal anti-inflammatory drugs (2084 and 1969), long-acting benzodiazepines (1796 and 1854), and inhaled glucocorticoids (1741 and 1771). These four groups of drugs represented 68% of the duplicities detected in December 2016, and 48.5% of those detected in December 2018. The groups that experienced an increase in detected duplications over the same period were the antidepressants (1417 and 1701 in December 2016 and December 2018, respectively), the urinary antispasmodics (1219 and 2020), and the thiazide diuretics (943 and 1595). Thus, these three groups accounted for 29.1% of the duplications detected in December 2016, and 34% of those detected in December 2018.

Through analysis of the 20 groups of therapeutic duplications with the highest number of cases, it was observed that in 2017, the groups that presented the greatest degrees of reduction in cases were the gastric protectors (−18%), the thiazide diuretics (−15%), and the metamizole-type analgesics (−14%, data not shown). In 2018, the groups exhibiting the greatest degrees of reduction were the sulfonamide diuretics (−75%), the thiazide diuretics (−24%), and the beta-blockers (−12%).

Discussion

The prescription Self Audit system is a clinical management computer tool, aimed at increasing the quality of care by giving support to health professionals in the move towards the safe and effective prescription of drugs.

The main finding of this study was that Self Audit is positioned as a CDSS, which is widely used among the doctors of the Catalan PC system to help identify and resolve safety PRMs in a systematic manner, and leads to superior results for the MRPs linked to the incentive-based safety indicator developed for PC physicians. Therefore, we think that results could be improved by implementing awareness strategies and providing feedback to physicians. This should could be followed by more specific recommendations, which should be

Table 3 Evolution and reduction percentages by type of AEMPS safety alert

Year	2016				2017				2018			
AEMPS ALERT	Apr	Dec	Variation	Percentage (%)	Apr	Dec	Variation	Percentage (%)	Apr	Dec	Variation	Percentage (%)
Triple whammy	9767	3356	−6411	−66	4123	2242	−1881	−46	3260	1850	−1410	−76
Coxibs	407	282	−125	−31	349	240	−109	−31	384	283	−101	−36
Diclofenac	325	144	−181	−56	189	109	−80	−42	189	96	−93	−97
Cilostazol	115	105	−10	−9	107	82	−25	−23	101	78	−23	−29
Ivabradine	102	88	−14	−14	87	73	−14	−16	82	65	−17	−26
Acedoferac	82	60	−22	−27	69	43	−26	−38	51	28	−23	−82
Agomelatine	74	62	−12	−16	78	69	−9	−12	81	63	−18	−29
Escitalopram	55	51	−4	−7	54	61	7	13	60	45	−15	−33
Citalopram	41	34	−7	−17	48	47	−1	−2	59	46	−13	−28
Trimetazidine	40	27	−13	−33	34	24	−10	−29	34	26	−8	−31
Raloxifene and Bazedoxifene	14	9	−5	−36	10	7	−3	−30	9	8	−1	−13
Strontium ranelate	8	9	1	13	3	0	−3	−100	NA	NA	NA	NA
Aliskiren	5	4	−1	−20	2	3	1	50	3	2	−1	−50
Canagliflozin	NA	NA	NA	NA	NA	NA	NA	NA	147	126	−21	−17
TOTAL ALERTS	11	4	−7	−62	5	3	−2	−42	4460	2716	−1744	−64

NA: Not applicable

Table 4 Top 10 prescribed duplicate groups in 2017 and 2018, including June–December variations

Duplicate group*	June 2017	Dec 2017	Variation	Percentage (%)	June 2018	Dec 2018	Variation	Percentage (%)
Renin-angiotensin system inhibitors	2458	2141	−317	−13	2107	1939	−168	−9
Anti-inflammatories	2154	1880	−274	−13	2203	1969	−234	−12
Long-acting benzodiazepines	2032	1911	−121	−6	2064	1854	−210	−11
Inhaled glucocorticoids	1551	1616	65	4	1583	1771	188	11
Alpha adrenergic antagonists	1273	1299	26	2	1337	1346	9	1
Gastric protectors	1425	1162	−263	−18	1364	1276	−88	−7
Other anti-depressants I	1467	1389	−78	−5	1562	1702	140	8
Urinary antispasmodic agents	1655	1547	−108	−7	1876	2020	144	7
Thiazide diuretics	964	823	−141	−15	2085	1595	−490	−31
Paracetamol (analgesic)	545	668	123	23	523	570	47	8

For technical reasons, the April data were not recorded at the level of detail required for the duplication group and so they have not been included in the table. The data were analysed in June and December, at which points they met the level of quality and detail required for analysis

*For each duplicate group, all available active prescription data are shown, which coincide with the evaluation points

repeated and regularly inspected These hypothesis, of course, need to be verified.

In the period studied, 41,492 cases of potential safety problems that could affect patient health were resolved, of which 80% (33,148) were linked to the safety indicator. In general terms, the percentage of MRPs detected by Self Audit ranged between 2.2 and 2.4% of the active prescriptions in the ECW (>9 million) during the years studied. It should be noted there that the detection of an MRP depended on the defined clinical content, and in the case of Self Audit, this content was updated annually. As a result, data could not be compared between different years.

Although the number of MRPs resolved was significant, the percentage of MRPs resolved each year with respect to the number detected by Self Audit was low, namely less than 10%. In addition, the numbers of some MRPs increased over time, as in the case of therapeutic duplications (>60,000 cases pending resolution in 2018) and contraindications due to pathologies (>46,000 cases pending resolution in 2018). This result indicates that significant numbers of MRPs must still be solved, and so supports the need to design interventions that contribute to improving the prescribing attitude. Moreover, it will be necessary to analyse the reasons for these increases and/or low resolution levels, in addition to assessing the requirement to make the detections of some MRPs more specific, and/or to more clearly detail the therapeutic recommendations that are offered.

As pointed out in a previous study [9], Self Audit is common among PC physicians. However, during the study period examined herein, resolution of the different Self Audit MRPs was found to be heterogeneous and irregular. More specifically, some MRPs presented high percentages of resolution, such as those related to the AEMPS alerts. This was perhaps due to the fact that there is greater response from professionals when a safety alert is issued by a regulatory body [13]. Although the use of AEMPS alerts resulted in a significant reduction in the number of cases in 2018, it should also be pointed out that part of this reduction was due to a change in the clinical content, wherein the warnings for citalopram and escitalopram became more specific (i.e., alerts were only issued if these drugs were prescribed together with other medications that prolong the QT interval), and so these medications generated fewer detections.

Several Self Audit MRPs also showed increases in the number of MRP in the period of study, and this could be attributed to various factors, that need to be validated. For example, the increase in therapeutic duplications over the years could be explained by the fact that new groups of drug duplications or new active ingredients marketed in different groups had been included.

Another MRP that attracted attention due to its negligible decrease, or even a certain increase, was the contraindication group. The results related to this MRP can be explained by considering that the content of this MRP changed substantially during the study period. More specifically, in 2017, the contents were expanded to include contraindications due to the altered values of some clinical variables (e.g., potassium and glomerular filtration), while in 2018, a global update of the contraindications took place, thereby resulting in increased detections of this MRP. However, the reasons behind their low resolution percentages require further investigation. It is possible that this could be attributed to a lack of specificity of the warning and/or recommendation, since different authors [14, 15] have supported the fact that giving a clear and precise recommendation constitutes one of the success criteria of the CDSS. It is also a possibility that

the recommendations provided in some cases suggest that a clinical follow-up should be carried out, and therefore do not result in the withdrawal of any medication. Under such circumstances it would be assumed that the MRP is not resolved, despite the fact that the recommendation is actually being followed.

In contrast, the MRP related to the drugs not recommended for use in geriatric patients exhibited a particularly low or no reduction during the years of study. In this case, there was no change in the clinical content; however, the low resolution percentage was attributed to this being an MRP of low clinical relevance, and the fact that the literature [16–18] does not consider that the use of these drugs are fully contraindicated in older patients, but instead it is simply recommended that they not be used. The same argument would serve to justify the low resolution of the MRP related to avoidable medications (i.e., chondroprotectors and citicoline). Thus, when doctors are faced with different MRPs, they prioritise those that are clinically more relevant, or that can be solved more rapidly or with less effort [19]. Another explanation to consider for the low resolution percentages associated with these two MRPs is that they are not included in the safety indicator.

It is also known that healthcare practice generates multiple incidences of medication, which suggests that the total resolution of MRPs through the Self Audit tool was considerably higher than that indicated in the results of the study. This could be attributed to the resolution of some MRPs at the same time as new ones being created; this behavior is not reflected in the current study. It should also be noted that the patients with MRPs were not followed over time, but instead, the existing MRPs under active prescription were compared at two different times within a year. In addition, it must be taken into account that the world population is continually aging, and this is accompanied by a greater incidence of pathologies, and an increase in the use of medications [20–22]. Indeed, it has recently been reported that if recent health trends continue, Spain is on its way to becoming the leading country in terms of the highest life expectancy in 2040 (i.e., 85.8 years) [23]. As a result of such aging, the greater incidence of multiple associated pathologies results in an increased consumption of drugs, which favours the appearance of increasingly complex therapeutic regimens. This in turn is associated with a higher frequency of adverse effects, interactions, and hospital admissions, in addition to a poorer quality of life and a lack of treatment compliance [24].

In terms of the health impact, a reduction in the number of MRPs can be translated into the avoidance of adverse drug effects in patients, which are known to have a considerable impact on patient morbidity and mortality [3], in addition to increasing the average cost of care [5], increasing the number of visits to primary healthcare centres, and increasing hospital admissions [25].

Upon analysis of the MRPs linked to the safety indicator, it was observed that the resolution of these MRPs was significantly higher than that of the general Self Audit data. This could be explained by considering that the included MRPs are of greater clinical relevance, or that it is an economically incentivised indicator. Another key point is that the reduction in cases decreased year on year, both in terms of the absolute number and the percentage. One explanation for this could be that the composition of the indicator varied each year, and therefore the target population for intervention was different, and could have been smaller. Another hypothesis that was considered was that the baseline starting point improved over time, until it reached a point where further improvements were difficult to achieve.

The annual plots obtained for the evolution of the MRPs linked to the indicator clearly showed a decrease in cases at the time of evaluation. The highest degree of MRP resolution occurred at the end of December, and this was accounted for by considering that historically, this indicator had always been evaluated in a single evaluation point at the end of the year. Every January, a relevant increase in cases was observed, although the baseline point was not reached, and so it was assumed that the professionals were indeed acquiring a certain culture of safety, and that the MRPs generated during the daily healthcare practice were being solved. The results of our study therefore appear to be in line with a previous study, wherein the authors suggest that incentive-based systems could influence physicians, and ultimately lead to an improvement in healthcare provision [26, 27]. However, in a Cochrane review by Scott et al. [28] regarding this point, it was concluded that there was insufficient evidence to indicate whether financial incentives had a positive impact on the quality of care in PC systems.

On the other hand, it is known that intervention strategies based on improving the prescription of drugs through audits and feedback to physicians have improved the quality of care, wherein such feedback includes information corresponding to their own patients, in addition to specific improvement recommendations; these strategies are repeated and supervised by other colleagues [11, 12, 29, 30]. In this context, the ICS can highlight that this individualised feedback is standard practice for its pharmacists and PC pharmacologists [31, 32]. However, the collected data show that there is significant room for improvement, as the number of MRPs that are pending resolution is considerable. It is therefore evident that it will be necessary to design specific intervention strategies to attain a change in the prescribing attitude. Such

strategies could include the close monitoring of data at an individual level, training support, and continuous review of the clinical contents to ensure that they are specific and that they are accompanied by concrete therapeutic recommendations [33].

Furthermore, it does not go unnoticed that it is necessary to evolve and improve the Self Audit tool at a technological level to make it more user-friendly and intuitive, and to impart a greater degree of integration with the patient's medical records. Moreover, this tool should be provided with artificial intelligence elements that possess more agile algorithms for information interpretation, and to facilitate decision making.

Finally, it should be noted that one of the main limitations of this study is that there is no follow-up over time for patients with certain MRPs, thereby preventing us from knowing how many MRPs persist over time, how many are new MRPs, and how many MRPs return or reappear after a while. Indeed, such follow-ups would be beneficial to allow the consequences on the patient's health to be evaluated. Likewise, continuous changes in the clinical contents also made it difficult to analyse the temporal evolution of each type of MRP.

Conclusions

The Self Audit clinical decision support system developed by the Institut Català de la Salut helps to systematically identify and resolve safety medication-related problems (MRPs) in a systematic manner, wherein superior results were obtained for the MRPs linked to a safety indicator that is included in the incentives of primary care physicians. However, it is noted that significant room for improvement exists in the prescribing attitude, and as a result, additional medical awareness strategies will be necessary, as well as improvements to the tool itself. Such improvements should be based at a technical level and should be aimed at increasing specificity in MRP detection and subsequent recommendations. Finally, we believe that in the context of clinical safety, the implementation HER tools similar to Self Audit could be a useful and beneficial healthcare strategy that could benefit patients from other healthcare systems worldwide.

Abbreviations

AEMPS: Spanish Agency for Medicines and Health Products (Agencia Española del Medicamentos y Productos Sanitarios); CDSS: Clinical decision support system; ECW: Electronic clinical workstation; EHR: Electronic health record; ICS: Institut Català de la Salut (Catalan Health Institute); MRP: Medication-related problem; PC: Primary care.

Acknowledgements

This study has been prepared within the framework of the Doctorate in Pharmacology at the Universitat Autònoma de Barcelona (UAB). We would like to thank ICS Information Systems for supporting us during aquisition of the information required to conduct this study. We would also like to thank the Self Audit working group for helping to maintain a useful and up-to-date tool.

Authors' contributions

MAP extracted, analysed, and interpreted the data on the use of the Self Audit tool. She also wrote the majority of the manuscript. MO helped to interpret the data on the use of the Self Audit tool, in addition to giving support and making contributions to the writing of the manuscript. AF and ED reviewed the data analysis process, reviewed the various parts of the manuscript, and made the relevant contributions to give clarity and understanding to the study. All authors read and approved the final manuscript.

Funding

The primary care component of this study was funded by the Institut Universitari d'Investigació en Atenció Primària (IDIAP Jordi Gol). Scholarship to complete a PhD thesis in primary care.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

Not applicable. This manuscript does not report studies involving human participants, human data or human tissue. This manuscript does not report studies involving animals.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Received: 11 May 2021 Accepted: 25 February 2022
Published online: 19 March 2022

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