

Revisión / Review

Evolution of the concept of drug-related problems: outcomes as the focus of the new paradigm

Evolución del concepto de problemas relacionados con medicamentos: resultados como el centro del nuevo paradigma

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Text in English

Texto en español

RESUMEN*

Objetivo: Revisar el concepto de problemas relacionados con medicamentos y problemas de la farmacoterapia y sus relaciones con otros conceptos, como los resultados negativos de la medicación.

Método: A través de una búsqueda en MEDLINE se identificaron los artículos primarios (1966 a 2005); las referencias citadas en esos artículos proporcionaron material adicional. Se revisaron los artículos recuperados y seleccionados.

Resultados: el término problemas relacionados (PRM) con los medicamentos ha sido ampliamente utilizado en la literatura, no siempre representando el mismo concepto. Bajo las diversas definiciones y clasificaciones de PRM se han mezclado proceso (causas) y efectos (resultados). Para denominar al mismo concepto indefinido, se han usado los términos problemas de la farmacoterapia, problemas de la medicación. La idea de problemas reales y potenciales fue creada para actuar preventivamente sobre el efecto de estos problemas. Este artículo sugiere el uso de términos biomédicos comúnmente aceptados, así como situar estos conceptos bajo paradigmas y modelos

reconocidos (concretamente, SPO y ECHO).

También se propone el uso del nombre de resultados clínicos negativos de la medicación.

Conclusiones: Cualquier resultado clínico negativo de la medicación puede ser asignado a una definición y una clasificación sencillas. Una herramienta sistemática de identificación ha demostrado ser efectiva para detectar todos y cada uno de los resultados clínicos negativos de la medicación de un paciente.

Palabras clave: Evaluación de resultados. Efectos adversos. Problemas relacionados con medicamentos. Errores de medicación.

ABSTRACT†

Objective: To review the concept of drug-related problems and drug therapy problems, and its relationship with other concepts, like medication negative outcomes.

Methods: Primary articles were identified through a MEDLINE search (1966 to September 2004); reference cites from the articles found provided additional resource material. Retrieved and selected papers were reviewed and relevant information was included.

Results: the term drug-related problem has been widely used in literature, not always representing a

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simple concept. Process (causes) and outcomes (effects) had been mixed under different DRP definitions and classifications. Drug therapy problems, medicine-related problems and medication related problems are other terms used to define the same unclear concept. The idea of actual and potential problems was created to act on preventing the effect of these problems. This paper suggests the use of commonly accepted biomedical terms, and put these concepts into recognized models and paradigms (namely, SPO and ECHO). Also the name of medication negative clinical outcomes is proposed.

Conclusions: Any medication negative clinical outcome can be assigned to a single definition and classification. A Systematic identification tool has been shown to be effective in detecting each and every one of the negative clinical outcomes in patient pharmacotherapy.

Keywords: Outcome Assessment; Adverse Effects; Drug-related Problems; Medication Errors.

(English)

SAFETY PROBLEMS

The advent of medicines has resulted in one of the most significant contributions to the increase in life expectancy in today's population. Over the past 50 years, average life expectancy at birth has increased from 46.5 years in 1950 to 65.2 years in 2002, reaching 78 years for women in developed countries.¹

The pharmaceutical industry produces safe, efficacious and good quality medicines. Sometimes, medicines produce undesirable effects. Focusing attention on the great tragedies, may lead us to forget the suffering that patients have to endure on a daily basis. The fact that a medicine does not present serious adverse reactions does not mean that harm or discomfort from its use will not occur. The concept of morbidity² is understood as "the proportion of patients with a particular disease during a given year per given unit of population". Drug-related morbidity should include, not only major adverse effects, but also any other undesirable effect occurring in patients.

Most studies that have analyzed this phenomenon have been carried out on the basis of emergency department visits or hospital admissions. These studies underestimate drug-related morbidity, because they ignore the adverse effects that do not lead to urgent medical consultation. These problems may produce treatment modifications by family physicians, due to the complaints of patients that do not turn to the hospital services for consultation. Frequently, these complaints may result in the prescription of more drugs.³ And in the best of the cases those problems cause, at least patient discomfort.

A great number of studies aimed at analyzing such adverse effects have been carried out. Lazarou et al.⁴ considered them to be between the fourth and

fifth cause of death, although their study had excluded errors in drug administration, non-compliance, overdoses, drug abuse and therapeutic failures. This study has been very contested, and has even been considered as invalid by other authors.⁵

EFFECTIVENESS PROBLEMS

Lack of safety of medicines is not the only possible problem with pharmacotherapy. Medicines may not achieve the outcomes for which they were prescribed. In pharmacotherapy the premise⁶ "above all, do no harm" should be cautiously considered. In pharmacotherapy, doing nothing can cause harm.⁷ Insufficient prescriptions^{8,9} or inappropriate prescriptions,¹⁰ or treatment non-compliance may well result in emergency department visits or hospital admissions.¹¹

DRUG-RELATED PROBLEMS

Drug-related problems and pharmaceutical care: what are they, do they matter, and what's next?¹² Although the term has been used for quite some time,¹³ it wasn't until 1990 when the first paper dealing with drug-related problems as a concept, first appeared.¹⁴ The use of this term brought with it a number of concept difficulties. On the one hand, the word "problem" had to be explained in this first article,¹⁴ stating that it was understood as meaning "a drug-related event amenable to detection, treatment or, more appropriately, prevention". On the other hand, the word 'drug' brings another two problems into consideration:

- It is not a word that is used throughout the whole world, because in Britain, the term 'medicine' is preferred.
- Furthermore, this is an ambiguous term, because it is used to refer to both medicines and abuse substances.

These particularities have resulted in the fact that this concept has not achieved uniform meaning in all the articles published. It is perhaps for this reason that a specific Medline Medical Subject Heading identifying this concept does not exist. Throughout the decade of the nineties, nearly 200 articles retrieved from secondary sources, using the terms drug-related problems (DRP), drug therapy problems (DTP), medicine-related problems (MRP), and medication-related problems (MTP) are to be found¹⁵ (table 1). One study even used these three terms as synonyms, DRP, DTP and MTP.¹⁶ Hepler used the terms drug-related problem, drug-treatment failure, and pharmacotherapeutic problem in one article.¹⁷

The original definition of drug-related problem¹⁴ was: "an undesirable patient experience that involves drug therapy and that actually or potentially interferes with a desired patient outcome". The use of words of scarce specific meaning, throughout a large part of the definitions, such as experience, event, or circumstance, has not contributed to clarify the concept.

Table 1. Articles published between 1990 - 1999 retrieved in secondary sources dealing with drug-related problems

	IPA	Medline	SCI	Embase
DRP	133	163	5	54
DTP	31	18	2	0
MTP	23	18	1	7
MRP	1	1	0	0

DRP= drug-related problem, DTP= drug-therapy problem, MTP= medication-related problem, MRP= medicine-related problem. IPA= International Pharmaceutical Abstracts, SCI= Science Citation Index.

Some authors think that all of these elements could be included in a wider concept of medication error.¹⁸ However, there are other causes associated with ineffectiveness or lack of safety, which should not be classified as errors. Other authors have proposed that the definition of medication error should be widened to include under use, overuse and misuse.¹⁹ Some have even gone as far as to consider all preventable adverse events as errors,²⁰ while others have preferred to maintain the two concepts as separate items.^{21,22} The comparison of the two terms may be confusing, because although most errors are preventable,²³ this is not true in all cases.²⁴ Furthermore, it is important to point out that not all errors affect patient's health status,²⁵ and at the same time, not all the negative outcomes were produced after a medication error. Medication errors should be understood as problems arising within the process of use of medicines, independently of their outcomes. The term morbidity is directly related to outcome, and not to medication errors (Figure 1). Consequently, the development of a theoretical approach is becoming essential.

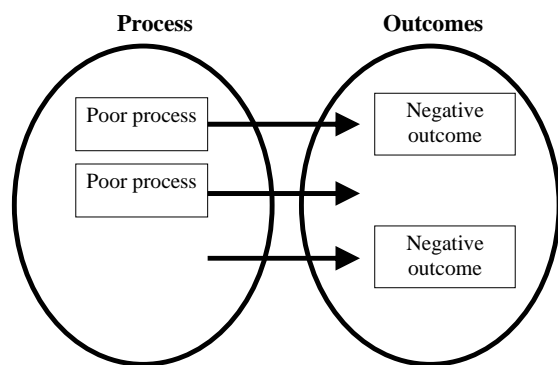


Figure 1. Relation between drug use process problems and medication negative clinical outcomes.

FROM PROCESS TO OUTCOMES

What are outcomes?²⁶ Although the SPO paradigm²⁷ (structure-process-outcomes) was created in 1966, Donabedian did not provide a real definition of outcomes²⁸ until 1978: "A change in patient health status resulting from health care service". According to this paradigm, health care quality assurance is multidimensional. Structure and process are important factors in the provision of high-quality care, but outcomes are the ultimate validators for determining the extent of the benefit or harm to the patient. This difference was clearly shown after demonstrating that differences in the use of resources in populations with similar health

status (process) did not lead to similar differences in outcomes.²⁹ Since that time, the lack of measurement of clinical outcomes has been considered as a weakness of a study,^{30,31} and the absence of improvement in outcomes has been the argument used against the necessity or convenience of pharmacist intervention.³²⁻³⁴ Perhaps, because technique alone will not make pharmacists professionals.^{35,36} These outcomes were divided into three categories in the ECHO model: economic, clinical and humanistic.³⁷

Another controversial point associated with outcomes, is the use of intermediate (surrogate) outcomes or end-point outcomes.³⁸ These criticisms are based on the fact that a positive intermediate outcome may not lead to a positive end-point outcome. As there are only two clinical end-point outcomes, that of death and cure, in clinical practice and in order to assess the evolution of the patient's condition, a proxy that can be measured is needed. To describe these intermediate outcomes and to verify that they correlate with end-point outcomes is researchers, and not practitioners, responsibility. However, the measurement of end-point outcomes should only be carried out in long term or epidemiological studies. The reason why some pharmacists' intervention studies have not been able to demonstrate significant differences in quality of life, may be due to the fact that this factor is a humanistic end-point outcome.³⁹

An open question has appeared in a recent publication:⁴⁰ "Must we [pharmacists] look at the patient's health problems when they are using drugs, or must we look at the problems of drug use within each patient?" Although the answer is probably not what authors had expected, it is clear: Yes, we should look at the patient's health problems when they are using drugs, because those are the outcomes of pharmacotherapy, and this is what is being called the "new paradigm", or new role of the pharmacist.⁴¹ The absence of a direct relationship between process elements and outcomes achieved makes this new paradigm necessary.⁴² A clear example of the absence of a relationship between the two is that of non-adherence. If, as seems obvious, non-adherence cannot be considered as a behavioral disorder,⁴³ we cannot accept that improving compliance is to be considered as a positive outcome (by the definition a positive change in patient's health status), but as an improvement in the process of use of medicines, which may or may not lead to a positive outcome.⁴⁴⁻⁴⁶ A similar situation has been occurring in relation to drug-interactions, which have been considered as DRPs in many definitions and classifications. However, other authors have considered drug interactions to be elements of process that generate a risk of appearing negative outcomes, but not outcomes by themselves.⁴⁷

This change in paradigm can probably be summarized in Robertsons⁴⁸ statement "... to show administrators the difference between pharmaceutical care and the old focus on 'the right drug to the right patient in the right dose at the right time'". The relationship between outcome and

pharmaceutical care was established beyond any doubt when Hepler stated that pharmaceutical care differs from prescribing improvement programs, because it attempts to manage drug therapy outcomes directly.¹⁷

The percentage of articles indexed in Medline that include in their titles or abstracts the word 'outcome' among those that include 'pharmacy' or 'pharmacist' has been increasing from less than 1% in the 1970s to almost 20% nowadays (figure 2). However, we should be aware of the fact that this term is not always used in accordance with its original definition.⁴⁹ In an eleven-year review of pharmacy literature published in 1986, most of the comments made under the heading 'outcomes' did not match the definition of health outcome.⁵⁰ In a 32-year review of pharmacy literature published in 1993, the term 'results' was used rather than the term 'outcomes'.⁵¹ Additionally, most of the studies also reported improved process indicators. More recently, in a systematic review on the impact of pharmacists providing a prescription review and monitoring service in ambulatory care, the authors divided outcomes into three categories: clinical and ADRs; quality of life, costs; and knowledge, compliance or satisfaction.⁵² Although in this last category the authors erroneously included 'knowledge' and 'compliance' as outcomes, most of the results that they identified in their review were in fact outcomes. A similar situation has occurred in other reviews.⁵³⁻⁵⁶ However compliance should not be considered as an outcome,²⁶ but rather as a treatment modifier,³⁷ or a process element.

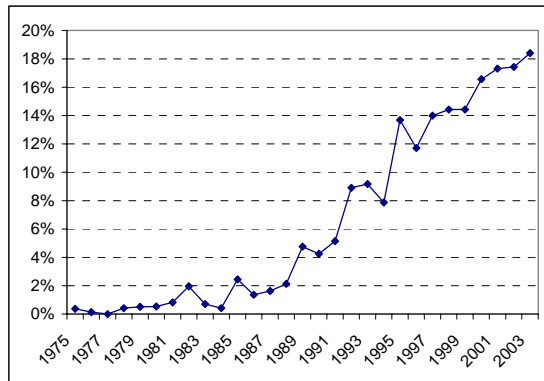


Figure 2. Percentage of articles using the word 'outcome' in their title or abstract from the total indexed in Medline that contain 'pharmacy or pharmacist' in title or abstract (publication date from 1975 to 2003)

A lot of work has been published on these 'events', usually without distinguishing between process and outcome indicators (Annex 1).^{14,57-150} In the analysis of patient oriented care provided by pharmacists, it is necessary to distinguish clearly between process and outcomes indicators.²⁷ So as to make such a distinction, it is necessary to assign a different indicator to each term definition. The following terms for outcome indicators have been used: drug-related problems,¹⁵¹ drug therapy problems,¹⁵² pharmacotherapy failures,¹⁵³ medicine-related problems.¹⁵⁴ Most of these terms

have also been used for process indicators or in classifications that do not make a distinction between them.

A consensus meeting in 1998, known as the Granada Consensus,¹⁵⁰ was held with the objective of creating a definition and a classification of negative clinical outcomes. After using Consensus statements different interpretations of the original definition appeared, consequently, it was necessary to hold a second consensus meeting in order to reach a definition¹⁵¹: "Drug Therapy Problems are health problems, understood as negative clinical outcomes, resulting from pharmacotherapy, that for different causes, either do not accomplish therapy objectives or produce undesirable effects". Furthermore, a classification of 6 items grouped into three categories, which complied with the necessary characteristics for a classification,¹¹⁷ was designed (table 2). The results of published research and practical work using this classification have been proven to be much more homogeneous.¹⁵⁵⁻¹⁶³ A comparative analysis was recently made, concluding the high reliability and ease of use of this tool.¹⁶⁴ However, this consensus has recently been criticized¹⁴⁶ on the basis that it does not provide a classification of causes, is not a hierarchical classification, and does not take potential DTP into consideration.

ACTUAL AND POTENTIAL OUTCOMES

Within a clinical entity, the concepts actual and potential are misleading. Term actual was understood as meaning the entity that had appeared in the patient, while the term potential referred to the situation in which the possibility that the entity could appear in the patient existed.¹⁴ This last concept corresponds to the definition of risk¹⁶⁵: "The probability that an event will occur. It encompasses a variety of measures of the probability of a generally unfavorable outcome".

Necessity	
	Untreated health problem
	Effects of an unnecessary drug
Effectiveness	
	Nonquantitative ineffectiveness
	Quantitative ineffectiveness
Safety	
	Nonquantitative unsafe
	Quantitative unsafe

In fact this confusion came about on trying to include different elements in clinical practice into the same classification: causes (process) and outcomes. Figure 3 shows a diagram, valid for all cognitive pharmacist services, in which the three possible scenarios can be distinguished.¹⁶⁶ Within the proactive scenario (prevention), the practitioner is capable of identifying the risk factors that may lead to a negative outcome. While within the reactive scenario (treatment), the practitioner identifies the actual negative outcome, and is able to try to determine its cause. Intervention may be

based on the attempt to eliminate the cause, or to symptomatically improve the actual outcome.

Consequently, once again, it seems reasonable to completely separate process and outcome.

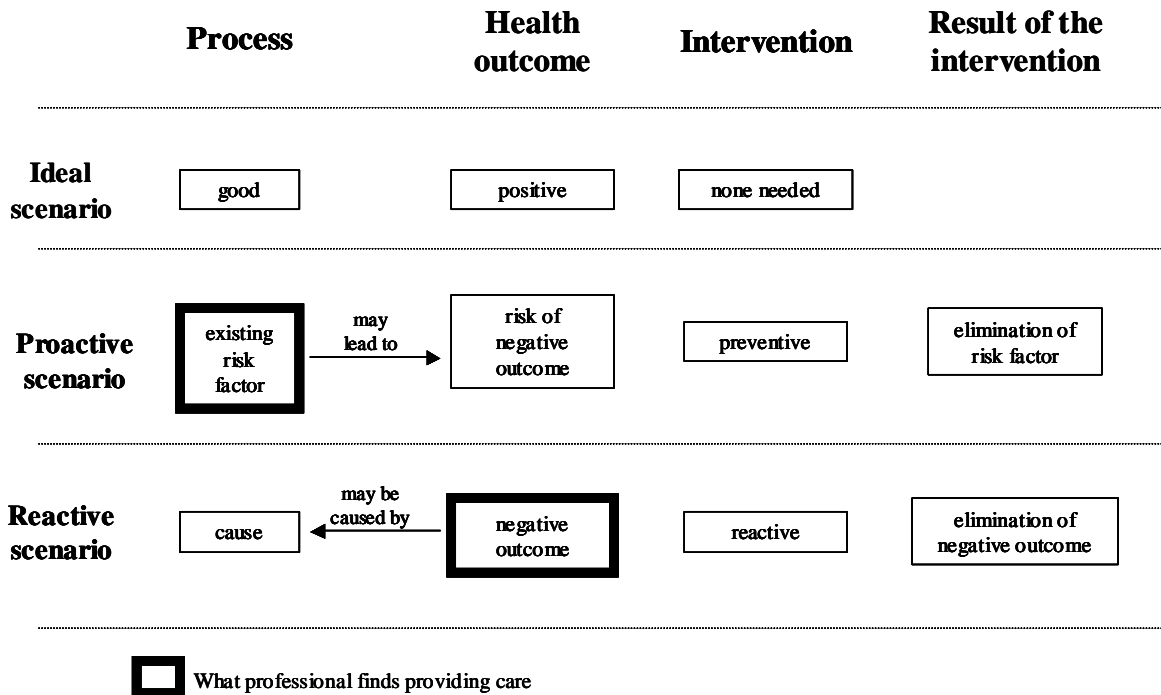


Figure 3. Different scenarios of care, and what a professional could find providing care¹⁶⁶

In order to classify these causes, it is primarily necessary to univocally identify the cause of each negative outcome, which is perhaps something that is not so easy. For example: A patient may have very high cholesterol levels, in spite of the fact that he has been prescribed a statin. In fact, he may not be complying with the treatment, because his erection problems may have worsened, and he had associated them with the use of this particular drug. The physician would try to avoid such a problem by prescribing sildenafil, but the patient would not be able to afford to pay for the new treatment, and would therefore prefer to simply abandon statin treatment. What in this case would be the cause of the ineffectiveness of the lipid lowering treatment? Low medicine intake? Non-compliance? Adverse drug reaction? Patient financial problems? A lack of coverage from his care plan? Few alternatives to treatment with statin? Or all of such possibilities? The correct answer is probably that all of such causes are responsible for the ineffectiveness of the statin treatment. This possible concurrence of more than one factor involved in each negative outcome has been recognized since the first studies on DRP were carried out.⁵⁸ This difficulty is common to all system analyses, and as an attempt to resolve it techniques such as root cause analysis (RCA)¹⁶⁷ have been used. RCA provides a structured and process-focused framework to approach sentinel event analysis. This procedure is excessively complex to be used in clinical practice, and is devoted to be used as a means to preventing recurrence, rather than a means to searching for an etiological treatment of the negative outcome.

The inability to determine a single cause of a negative outcome, rules out any consideration of a real classification of causes that complies with the whole appropriate conditions of a classification:¹¹⁷ that of being universal, univocal, and possessing mutually exclusive categories.

PREVENTABILITY

The discussion on actual and potential DRPs is in fact based on the necessity to prevent negative clinical outcomes. The clinical situation is not preventable due to the fact that a different situation, called 'potential', exists. The prevention of any clinical entity is based on the identification of risk factors.¹⁶⁸ Risk factors are indicators of process, which can predict a specific negative outcome. The failure to take into consideration the difference between process (risk factors) and outcomes (actual problems) may provide the reason for the absence of a uniform concept for drug-related problems. In accordance with the scenario in which the pharmacist is working, either proactive or reactive, he will identify in the patient either risk factors or actual problems, respectively (figure 3).¹⁶⁵

Determination of preventability of negative outcomes is not very clear. Some authors have established arbitrary criteria in their studies from which preventability has been assessed.¹⁶⁹⁻¹⁷²

Some authors have created indicators that attempt to determine the probability of negative outcomes occurring. Initially, attempts were made to identify patients who warranted pharmacist interventions,¹⁷³

as a means to working more efficiently and to justifying pharmacists' role into the care process.⁶⁶ The IMPROVE¹⁷⁴ researchers designed a similar approach in order to screen a large number of computerized patient records. Schumock¹⁷⁵ developed a list of criteria aimed at determining the preventability of ADRs, which has now been established as a standard approach. This list has recently been modified, in order to include all pharmacotherapy negative clinical outcomes.¹⁷⁶ Other authors have preferred to determine different levels of pharmacotherapy complexity,^{89,112,177} in order to predict the necessary effort required. Some studies have found these simple indicators to be of little reliability in comparison with expert assessment.¹⁷⁸

From drug utilization review practice, a complex indicator for determining inappropriate medication use in nursing home residents, Beers criteria,¹⁷⁹ was created, and was twice updated.^{180,181} It was designed to evaluate medication use in the absence of clinical information on diagnoses. This indicator is based on pharmacological criteria rather than outcome criteria. This drugs-to-avoid criteria identified no significant associations between use of these drugs and decline in functional status.^{182,183} In spite of those critics, some authors still defend it.¹⁸⁴

A more elaborate indicator is the Medication Appropriateness Index (MAI),¹⁸⁵ which has been used in various settings¹⁸⁶ for different types of patients.¹⁸⁷ Some authors have recognized MAI inadequacies for pharmaceutical care.^{188,189} The MAI is also an indicator of process, which is not directly related to patient outcomes, but it can be used for reducing complexity as a risk factor for negative outcomes.¹⁹⁰

Preventable drug-related morbidity indicators (PDRM) is a well structured system which establishes the relationship between patterns of care or management, representing process and potential expected outcomes through probability. In 2002, 52 indicators were described¹⁹¹ which have been subsequently validated in different settings^{192,193} and different countries.¹⁹⁴⁻¹⁹⁶ These PDRM indicators could substitute the concept of potential DRP, because they serve to quantify risk in a specific process.¹⁹⁷

SYSTEMATIC DETECTION TOOLS

The usefulness of systematic procedures to detect these problems has been demonstrated, comparing them to medication review traditional procedures.⁷⁶

Some algorithms have been designed, not as a means to identifying DRP type, but rather to determining whether or not a DRP exists.⁹⁴ Robertson created a system through which he intended, not only to identify problems in drug therapy, but also to suggest the course of action that should be taken.⁴⁸ However, this algorithm filled 10 journal pages, and was consequently of little use in practice.

After the first Granada Consensus¹⁵⁰ on drug-related problems, a simplified algorithm was created, in order to allow the identification and classification of a negative outcome to be placed into categories.¹⁹⁸ This algorithm has recently been updated,¹⁹⁹ in order to incorporate modifications arising from the Second Granada Consensus on drug therapy problems.¹⁵¹ Used on a specifically designed assessment form,²⁰⁰ it allows the patient's situation to be assessed including all the negative clinical outcomes that the patient is suffering from, or presents the risk of suffering from. Using the same classification, other authors considered alternatives to this algorithm.²⁰¹

CONCLUSIONS

The term drug-related problem and other similar terms have been used to describe a concept that is not particularly specific. For years, elements of process of use of drugs have been intermingled with health outcomes. In most cases, they have not been conceived within a previously formulated theoretical framework.

Merging practice with theoretical models and paradigms should help practitioners and researchers to work focused on the patient, being part of a multidisciplinary healthcare team. Thus, accepting common used biomedical terms can help to make communication easier. Structure, process and outcomes or causes and effects are commonly accepted terms that should be adopted in pharmacy practice and pharmaceutical care. There is a clear need to adopt a term which clearly identifies the negative outcomes associated with medication, and to distinguish them from any other process element.

(Español)

PROBLEMAS DE SEGURIDAD

La llegada de los medicamentos ha producido uno de las contribuciones más significativas en el incremento de la esperanza de vida de la población actual. En los pasados 50 años, la esperanza de vida al nacimiento ha aumentado de 46,5 años en 1950 a 65,2 años en 2002, alcanzando los 78 años en mujeres en los países desarrollados.¹

La industria farmacéutica produce medicamentos seguros, eficaces y de calidad. A veces los medicamentos producen efectos indeseables. Centrar la atención en las grandes tragedias, puede llevarnos a olvidar el sufrimiento que los pacientes soportan diariamente. El hecho de que un medicamento no presente efectos adversos graves no quiere decir que no aparezcan daños o molestias con su uso. El concepto de morbilidad² se entiende como "la proporción de pacientes con una enfermedad determinada durante un año por unidad de población". La morbilidad relacionada con medicamentos debería incluir, no solo los grandes efectos adversos, sino también cualquier

otro efecto indeseado que aparezca en los pacientes.

La mayoría de los estudios que han analizado este fenómeno han sido elaborados en servicios de urgencias o en ingresos hospitalarios. Estos estudios pueden subestimar la morbilidad relacionada con medicamentos, porque ignoran los efectos adversos que no llevan a consulta urgente al médico. Estos problemas pueden producir modificaciones del tratamiento por el médico de cabecera, debido a las quejas de los pacientes que no llegan a consulta de urgencias hospitalarias. Frecuentemente, estas quejas pueden conducir a la prescripción de más medicamentos.³ Y en el mejor de los casos estos problemas causan, cuanto menos, incomodidad en el paciente.

Un buen número de estudios tuvo como objetivo analizar estos efectos adversos. Lazarou y col.⁴ los consideraron la cuarta y quinta causa de muerte, aunque su estudio excluía los errores de administración, incumplimiento, sobredosificaciones, abuso y fracasos terapéuticos. Este estudio ha sido muy contestado, e incluso ha sido considerado inválido por otros autores.⁵

PROBLEMAS DE EFECTIVIDAD

La falta de seguridad de los medicamentos no es el único posible problema de la farmacoterapia. Los medicamentos pueden no alcanzar los objetivos terapéuticos para los que fueron prescritos. En farmacoterapia, la premisa⁶ "sobre todo, no hacer daño" debería ser considerada con cautela. En farmacoterapia, no hacer nada, puede causar daño.⁷ Las prescripciones insuficientes^{8,9} o inapropiadas,¹⁰ o el incumplimiento terapéutico pueden llevar a visitas a urgencias o a ingresos hospitalarios.¹¹

PROBLEMAS RELACIONADOS CON MEDICAMENTOS

Problemas relacionados con medicamentos y atención farmacéutica: que son, cuanto importan, y que es lo siguiente?¹² Aunque el término ha sido usado desde hace años,¹³ no fue hasta 1990 hasta que apareció el primer artículo que trató de los problemas relacionados con medicamentos conceptualmente.¹⁴ El uso de este término trajo numerosas dificultades conceptuales. Por un lado, la palabra 'problema' tuvo que ser explicada en aquel primer artículo,¹⁴ afirmando que se entendía que quería decir "un suceso relacionado con los medicamentos susceptible de detección, tratamiento o más adecuadamente, prevención". Por otro lado, la palabra *drug* trae a consideración dos problemas:

- No es una palabra que se use en todo el mundo (anglófilo), ya que los británicos prefieren *medicine*.
- Incluso, es un término ambiguo, porque se usa para referirse tanto a medicamentos como a sustancias de abuso.

Estas particularidades han provocado que de hecho este concepto no haya alcanzado un significado uniforme en todos los artículos que lo utilizan. Probablemente esta es la razón por la que no existe un *Medical Subject Heading* en Medline que identifique este concepto. Durante la década de 1990, se encontraron casi 200 artículos en las fuentes secundarias utilizaron los términos *drug-related problems* (DRP), *drug therapy problems* (DTP), *medicine-related problems* (MRP), and *medication-related problems* (MTP)¹⁵ (tabla 1). Incluso un estudio utilizaba los tres términos como sinónimos: DRP, DTP, y MTP.¹⁶ Hepler utilizó en un artículo los términos *drug-related problem*, *drug-treatment failure*, y *pharmaceutical problem*.¹⁷

La definición original de problemas relacionados con medicamentos¹⁴ fue: "una experiencia indeseable del paciente que involucra la farmacoterapia y que interfiere real o potencialmente con el resultado[‡] deseado en el paciente". El uso de palabras de escaso significado específico en la mayor parte de las definiciones, tales como experiencia, evento o circunstancia, no ha contribuido a clarificar este concepto.

Tabla 1. Artículos publicados entre 1990 - 1999 recuperados en fuentes secundarias que tratan sobre problemas relacionados con medicamentos.

	IPA	Medline	SCI	Embase
DRP	133	163	5	54
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MRP	1	1	0	0

DRP= drug-related problem, DTP= drug-therapy problem, MTP= medication-related problem, MRP= medicine-related problem. IPA= International Pharmaceutical Abstracts, SCI= Science Citation Index.

Algunos autores piensan que todos estos elementos podrían incluirse en un concepto más amplio de errores de medicación.¹⁸ Sin embargo, hay causas relacionadas con la ineffectividad o la falta de seguridad, que no pueden ser calificadas como errores. Algunos autores han propuesto que la definición de error de medicación debería ser ampliada para que incluyese la infrautilización, la sobre utilización y al mal uso.¹⁹ Algunos llegaron más allá hasta considerar todos los eventos adversos prevenibles como errores,²⁰ mientras que otros han preferido mantener los dos conceptos separadamente.^{21,22} La comparación puede ser confusa porque, aunque la mayoría de los errores son prevenibles,²³ esto no es cierto en todos los casos.²⁴ Incluso es importante señalar que no todos los errores afectan a la salud de los pacientes,²⁵ y que al mismo tiempo, no todos los resultados[‡] negativos se producen después de un error de medicación. Los errores de medicación deberían entenderse como problemas resultantes del uso de medicamentos, independientemente de sus resultados[‡]. El término 'morbilidad' está directamente relacionado con los resultados y no con los errores de medicación (figura 1). Consecuentemente, se hace imprescindible el desarrollo de un marco conceptual.

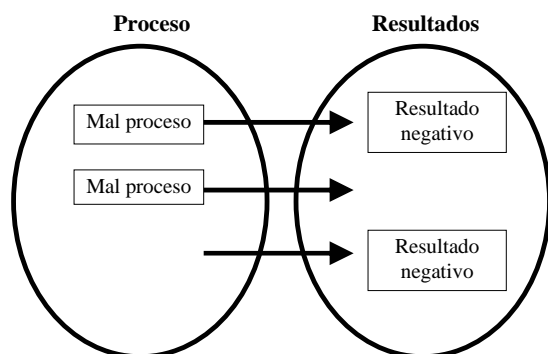


Figura 1. Relación entre proceso de uso de medicamentos y resultados[‡] negativos de la medicación.

DEL PROCESO A LOS RESULTADOS[‡]

Que son resultados?²⁶ Aunque el paradigma SPO²⁷ (*structure-process-outcomes*) [estructura, proceso y resultados] fue creado en 1966, no fue hasta 1978 que Donabedian produjo una definición real de resultado.²⁸ “cambio en el estado de salud del paciente consecuencia del servicio sanitario”. De acuerdo a este paradigma, la calidad de la atención sanitaria es multidimensional. La estructura y el proceso son factores importantes en la provisión de servicios de alta calidad, pero los resultados son los últimos validadores para determinar el grado de beneficio o daño para el paciente. Esta diferencia fue claramente expuesta al demostrar que diferencias en el uso de recursos (proceso) en poblaciones con similares estados de salud, no conducían a diferencias similares en resultados.²⁹ Desde entonces, no medir los resultados clínicos se ha considerado una debilidad del estudio,^{30,31} y la ausencia de mejoría en los resultados se ha usado como el argumento en contra de la necesidad o conveniencia de la intervención del farmacéutico.³²⁻³⁴ Quizás, porque la técnica sola no hará a los farmacéuticos más profesionales.^{35,36} Estos resultados[‡] se dividieron en tres categorías en el modelo ECHO: económicos, clínicos y humanísticos.³⁷

Otra controversia asociada a los resultados es el uso de resultados intermedios o resultados finales.³⁸ Esta crítica está basada en el hecho de que un resultado intermedio positivo puede no conducir a un resultado[‡] final positivo. Como solo existen dos resultados[‡] finales, la muerte o la curación, en la práctica clínica para evaluar el estado de un paciente se necesita un intermedio que pueda ser medido. Describir estos resultados intermedios y demostrar que se correlacionan con los resultados finales es responsabilidad de los investigadores, y no de los facultativos en ejercicio. Sin embargo, la medida de los resultados finales debería realizarse sólo en estudios epidemiológicos a largo plazo. La razón por la que algunos estudios no han podido demostrar diferencias significativas

[‡] NT: La palabra ‘resultado’ en español es polisémica. Las palabras ‘result’ y ‘outcome’ se traducen al español por resultado, aunque no tienen el mismo significado en inglés. El uso más frecuente de ‘resultado’ en este artículo se refiere a ‘outcome’.

en la calidad de vida puede deberse a que esta variable es un resultado final humanístico.³⁹

Recientemente ha aparecido en una publicación una pregunta abierta:⁴⁰ “Debemos [los farmacéuticos] mirar a los problemas de salud de los pacientes que utilizan medicamentos, o debemos mirar a los problemas de la utilización de esos medicamentos en cada paciente?” Aunque la respuesta no es la que probablemente esperaban los autores, esta clara: Sí, debemos mirar a los problemas de salud de los pacientes cuando utilizan medicamentos, porque esos son los resultados[‡] de la farmacoterapia, y esto es lo que se ha venido llamando “nuevo paradigma” o nuevo papel del farmacéutico.⁴¹ La ausencia de una relación directa entre elementos de proceso y resultados conseguidos hace necesario este nuevo paradigma.⁴² Un claro ejemplo de la ausencia de relación entre estos dos es el incumplimiento. Si, como parece obvio, el incumplimiento no puede ser considerado como una enfermedad,⁴³ no podemos aceptar que mejorar el cumplimiento sea un resultado[‡] positivo (por definición, un cambio en el estado de salud del paciente), sino una mejora en el proceso de uso de los medicamentos que puede o puede que no, conduzca a un resultado[‡] positivo.⁴⁴⁻⁴⁶ Una situación similar ocurre con las interacciones medicamentosas, que han sido consideradas PRM en muchas de las clasificaciones. Sin embargo otros autores han considerado las interacciones como elementos de proceso que producen riesgo de aparición de resultados[‡] negativos, y no como resultados[‡] en sí mismos.⁴⁷

Este cambio de paradigma puede resumirse en la afirmación de Robertson:⁴⁸ “...mostrar a los administradores la diferencia entre la atención farmacéutica y el viejo enfoque de el medicamento correcto al paciente correcto en la dosis y momento correctos”. La relación entre resultados[‡] y atención farmacéutica está establecida más allá de cualquier duda desde que Hepler afirmó que la atención farmacéutica difiere de los programas de mejora de la prescripción porque intenta gestionar directamente los resultados[‡] de la farmacoterapia.¹⁷

El porcentaje de artículos indexados en Medline que incluyen en sus títulos o *abstracts* la palabra ‘outcome’ entre los que incluyen las palabras ‘farmacia’ o ‘farmacéutico’, se ha incrementado desde menos del 1% en los años 1970 a casi el 20% en la actualidad (figura 2). Sin embargo, debemos ser conscientes de que este término no siempre se usa de acuerdo con su definición original.⁴⁹ En una revisión de 11 años de literatura farmacéutica, publicada en 1986, la mayoría de los comentarios hechos bajo el encabezamiento de ‘outcomes’, no encajaban en la definición de resultado en salud.⁵⁰ En otra revisión de 32 años de la literatura farmacéutica publicada en 1993, se utilizaba el término ‘results’ en lugar del de ‘outcomes’.⁵¹ Además, la mayoría de los estudios también comunicaban mejoras en indicadores de proceso. Más recientemente, en una revisión sistemática sobre el impacto del farmacéutico en la revisión de la medicación y seguimiento en atención

primaria, los autores dividieron los resultados[‡] en tres categorías: clínicos y RAM; calidad de vida y costes; y conocimiento, cumplimiento y satisfacción.⁵² Aunque en la última categoría los autores incluyen erróneamente 'conocimiento' y 'cumplimiento' como resultados[‡], la mayoría de los resultados que ellos identificaron son realmente resultados. Una situación parecida ha ocurrido en otras revisiones.⁵³⁻⁵⁶ Aunque el cumplimiento no debería incluirse como un resultado[‡],²⁶ sí como un modificador del tratamiento,³⁷ o un elemento de proceso.

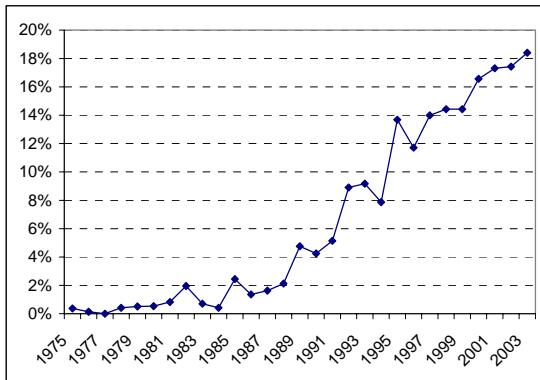


Figura 2. Porcentaje de artículos que usan la palabra 'outcome' en sus títulos o *abstract* respecto al total indexado en Medline que contiene 'pharmacy' o 'pharmacist' en título *abstract* (fecha de publicación desde 1975 a 2003)

Se ha publicado mucho sobre estos 'eventos' generalmente sin diferenciar entre indicadores de proceso y resultados[‡] (Anexo 1).^{14,57-150} En el análisis de la atención proporcionada por farmacéuticos y orientada al paciente es necesario distinguir claramente entre indicadores de proceso y de resultado.²⁷ Para hacer esta distinción, es necesario asignar un indicador diferente a cada definición. Se han utilizado los siguientes términos como indicadores de resultados[‡]: drug-related problems,¹⁵¹ drug therapy problems,¹⁵² pharmacotherapy failures,¹⁵³ medicine-related problems.¹⁵⁴ La mayoría de estos términos también había sido utilizado para indicadores de proceso o en clasificaciones que no hacían diferencia entre proceso y resultados.

En 1998 se celebró una reunión, conocida como el Consenso de Granada,¹⁵⁰ con el objetivo de crear una definición y una clasificación de los resultados clínicos negativos. Después de utilizar las declaraciones del Consenso, aparecieron diferentes interpretaciones de la definición original, por lo que fue necesario realizar un Segundo Consenso para alcanzar la definición.¹⁵¹ "problemas relacionados con medicamentos son problemas de salud, entendidos como resultados clínicos negativos, que producidos por diversas causas, o no alcanzan los resultados esperados o producen efectos indeseados". Además se diseñó una clasificación de seis elementos agrupados en tres categorías, que cumplía los requisitos necesarios para una clasificación¹¹⁷ (Tabla 2). Los resultados publicados y el trabajo en la práctica demostraron ser mucho más homogéneos.¹⁵⁵⁻¹⁶³ Recientemente se hizo un

análisis comparativo, concluyendo la alta fiabilidad y la facilidad de uso de esta herramienta.¹⁶⁴ Sin embargo, este Consenso ha sido recientemente criticado basándose en que no proporciona una clasificación jerárquica y no tiene en consideración los PRM potenciales.¹⁴⁶

Necesidad	
	Problema de salud no tratado
	Efecto de medicamento innecesario
Efectividad	
	Inefectividad no cuantitativa
	Inefectividad cuantitativa
Seguridad	
	Inseguridad no cuantitativa
	Inseguridad cuantitativa

RESULTADOS REALES Y POTENCIALES

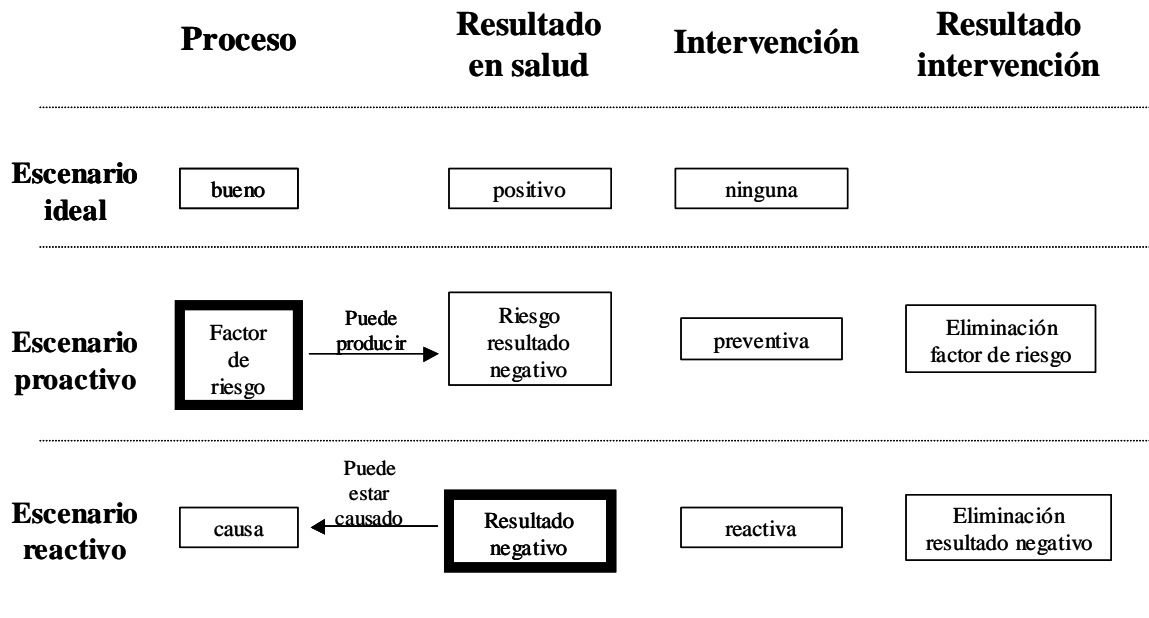
En una entidad clínica, los conceptos de real y potencial son engañosos. El término 'real' quería decir que la entidad había aparecido en el paciente, mientras que el término 'potencial' se refería a la situación en que existía la posibilidad de que la entidad apareciera en el paciente.¹⁴ Este último concepto se corresponde con la definición de riesgo.¹⁶⁵ "La probabilidad de que un evento ocurra. Incluye una variedad de medidas de la probabilidad de que un resultado, generalmente desfavorable, ocurra".

En realidad esta confusión aparece al intentar incluir diferentes elementos de la práctica clínica en la misma clasificación: causas (proceso) y resultados[‡]. La figura 3 muestra un diagrama, válido para todos los servicios cognitivos, en el que se distinguen los tres escenarios posibles.¹⁶⁶ En el escenario proactivo (prevención) el facultativo es capaz de identificar los factores de riesgo que pueden conducir a resultados[‡] negativos. Mientras en el escenario reactivo (tratamiento), el facultativo identifica resultados negativos reales, e intenta determinar su causa. La intervención puede basarse en eliminar la causa, o en mejorar el resultado real de modo sintomático. Consecuentemente, de nuevo parece razonable separar completamente el proceso y el resultado[‡].

Para clasificar estas causas, es necesario identificar unívocamente la causa de cada resultado negativo, lo que probablemente no es tan fácil. Por ejemplo, un paciente puede tener los niveles de colesterol elevados, a pesar de que tiene prescrita una estatina. En realidad no está cumpliendo el tratamiento debido a que sus problemas de erección han empeorado, y él lo asocia al uso de este medicamento. El médico intentaría evitar este problema prescribiendo sildenafil, pero el paciente no puede permitirse pagarlo, y prefiere abandonar la estatina. En este caso, ¿cuál sería la causa de la inefectividad del hipolipemiente? ¿Una escasa toma de medicamento? ¿el incumplimiento? ¿la ausencia de cobertura de su seguro? ¿las escasas alternativas al tratamiento con estatinas? O ¿todas las posibilidades anteriores?. La respuesta correcta

probablemente sea la de que todas ellas son causas de la ineffectividad del tratamiento con estatina. Esta posible concurrencia de más de un factor involucrado en cada resultado negativo ha sido reconocida desde los primeros estudios de PRM.⁵⁸ Esta dificultad es común a todos los análisis de sistemas, y se utilizan técnicas para resolverlo, como el análisis de causa raíz [root

cause analysis] (RCA).¹⁶⁷ El RCA proporciona un modelo estructurado y centrado en el proceso para aproximarse al análisis de situaciones centinela. Este proceso es excesivamente complejo para ser usado en la práctica clínica, y se ha desarrollado para evitar la recurrencia de una causa, mas como un medio de búsqueda de un tratamiento etiológico de un resultado negativo.




 Lo que el profesional encuentra en la atención al paciente

Figura 3. Diferentes escenarios de atención y lo que el profesional puede encontrar al prestar esa atención¹⁶⁶

estudios, con los que han determinado la preventabilidad.¹⁶⁹⁻¹⁷²

La imposibilidad de determinar una única causa para cada resultado negativo hace que no se pueda hablar de una verdadera clasificación de causas que cumpla con todas las condiciones de una clasificación: ser universal, unívoca, y que tenga categorías mutuamente excluyentes.¹¹⁷

Algunos han creado indicadores que intentan determinar la probabilidad de que aparezcan resultados negativos. Inicialmente se intentó determinar los pacientes que merecían la intervención del farmacéutico,¹⁷³ para trabajar de modo más eficiente y justificar el papel del farmacéutico en el proceso asistencial.⁶⁶ Los investigadores del IMPROVE diseñaron un sistema similar para cribar un gran número de historiales de pacientes informatizados.¹⁷⁴ Schmock diseñó una lista de criterios para determinar la preventabilidad de las RAM, que se ha convertido en un estándar.¹⁷⁵ Esta lista ha sido recientemente modificada para incluir todos los resultados negativos de la farmacoterapia.¹⁷⁶ Otros autores han preferido determinar los diferentes niveles de complejidad de la farmacoterapia, para predecir el esfuerzo necesario.^{89,112,177} Algunos estudios han encontrado que estos indicadores son poco fiables en comparación con el juicio de un experto.¹⁷⁸

PREVENTABILIDAD

La discusión sobre PRM reales y potenciales realmente esta basada en la necesidad de prevenir resultados clínicos negativos. Una situación clínica no es prevenible debido a que exista una situación diferente denominada 'potencial'. La prevención de cualquier entidad clínica esta basada en la identificación de los factores de riesgo.¹⁶⁸ Los factores de riesgo son indicadores de proceso, que pueden predecir un determinado resultado negativo. No tener en consideración la diferencia entre proceso (factores de riesgo) y resultado (problemas reales) puede ser la causa de la ausencia de un criterio uniforme sobre problemas relacionados con medicamentos. De acuerdo con el escenario en que trabaje el farmacéutico, ya sea proactivo o reactivo, identificará o los factores de riesgo o los problemas reales, respectivamente (figura 3).¹⁶⁵

A partir de la técnica de revisión de la medicación, se creó un indicador complejo para determinar la medicación inapropiada que se usaba en ancianos en residencias, el criterio Beers,¹⁷⁹ que se ha actualizado en dos ocasiones.^{180,181} Se diseñó para evaluar la medicación en ausencia de información clínica sobre los diagnósticos. Este indicador se basa más en criterios farmacológicos que en

La determinación de la preventabilidad de un resultado negativo no esta muy clara. Algunos autores han establecidos criterios arbitrarios en sus

criterios de resultados[†]. Este criterio de medicamentos-a-evitar identifica asociaciones no significativas entre uso de estos medicamentos y deterioro del estado funcional.^{182,183} A pesar de esto, algunos autores aún siguen defendiéndolo.¹⁸⁴

Un indicador más elaborado es el Índice de Propiedad de la Medicación (MAI),¹⁸⁵ que se ha utilizado en varios entornos¹⁸⁶ para varios tipos de pacientes.¹⁸⁷ Algunos autores han reconocido la inadecuación del MAI para la atención farmacéutica.^{188,189} El MAI es también un indicador de proceso que no está directamente relacionados con los resultados[†] en los pacientes, pero que puede utilizarse para reducir la complejidad como factor de riesgo de resultados negativos.¹⁹⁰

Los indicadores de morbilidad prevenible relacionada con medicamentos (PDRM) son un sistema bien estructurado que establece relaciones entre los modelos de atención y cuidados, que representan el proceso, y los resultados potenciales esperados por probabilidad. En 2002 se describieron 52 indicadores⁹¹ que han sido posteriormente validados en diferentes entornos,^{192,193} y diferentes países.^{194,195} Estos PDRM podrían sustituir al concepto de potencial en los PRM, porque sirven para cuantificar el riesgo en un proceso determinado.¹⁹⁷

HERRAMIENTAS SISTEMÁTICAS DE IDENTIFICACIÓN

La utilidad de los procedimientos sistemáticos de detección de estos problemas se ha demostrado comparándolos con procedimientos de revisión tradicional.⁷⁶

Se han diseñado algunos algoritmos, no para identificar el tipo de PRM sino para identificar si existe o n PRM.⁹⁴ Robertson creó un sistema a con el que intentaba, no solo identificar problemas de la farmacoterapia, sino también sugerir la acción que debería hacerse.⁴⁸ Sin embargo, este algoritmo

llenaba 10 páginas de revista, y por tanto era de escasa utilidad en la práctica.

Después del primer Consenso de Granada¹⁵⁰ sobre problemas relacionados con medicamentos, se creó un algoritmo simple que permite la identificación y clasificación de un resultado negativo.¹⁹⁸ Este algoritmo se ha actualizado recientemente¹⁹⁹ para incorporar las modificaciones del Segundo Consenso de Granada.¹⁵¹ Utilizado sobre un formulario específicamente diseñado,²⁰⁰ permite evaluar la situación del paciente identificando todos los resultados clínicos negativos que sufre el paciente o está en riesgo de sufrir. Utilizando la misma clasificación, otros autores han diseñado un algoritmo alternativo.²⁰¹

CONCLUSIONES

El término problemas relacionados con medicamentos y otros términos similares se han usado para describir un concepto que no es particularmente específico. Durante años, los elementos de proceso se han mezclado con los resultados en salud. En la mayoría de los casos no se han concebido con un marco teórico conceptual previo.

Unir la práctica con paradigmas y modelos teóricos podría ayudar a los facultativos e investigadores que forman parte de un equipo multidisciplinar. Aceptar términos comúnmente utilizados en biomedicina puede ayudar a que las comunicaciones sean más fáciles. Estructura, proceso y resultados[†] o causas y efectos son términos comúnmente aceptados y deberían ser adoptados en práctica farmacéutica y atención farmacéutica. Hay una necesidad patente de adoptar un término que identifique claramente a los resultados[†] negativos asociados al uso de medicamentos, y distinguirlos de otros elementos de proceso.

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Annex 1. Definitions, and process and outcomes elements used in studies mentioning drug-related problems, drug therapy problems, medicine-related problems, medication-related problems, or adverse drug events.				
Article	Name	Definition	Process	Outcomes
McKenney & Harrison ⁵⁷	DRP	-	<ul style="list-style-type: none"> • Drug interactions; erroneous drug use; inadequate therapy; 	<ul style="list-style-type: none"> • ADR; erroneous drug use; exacerbation of diseases because of patient's poor compliance
Frisk et al. ⁵⁸	DRP (DTP)	An undesirable drug effect or improper patient drug usage.	<ul style="list-style-type: none"> • Misuse or noncompliance; drug-diet interaction; detrimental patient treatment; inappropriateness of therapy 	<ul style="list-style-type: none"> • ADR; Therapeutic ineffectiveness
Morton & Bridges ⁵⁹	DRP (MTP)	-	<ul style="list-style-type: none"> • 	<ul style="list-style-type: none"> • Different signs and symptoms
Conner et al. ⁶⁰	DRP	-	<ul style="list-style-type: none"> • 	<ul style="list-style-type: none"> • Different signs and symptoms
Bergman & Wiholm ⁶¹	DRP	-	<ul style="list-style-type: none"> • 	<ul style="list-style-type: none"> • Symptoms resulting from excessive or adverse drug effects; failure to accomplish the intended purpose.
Miller ⁶²	DRP	-	<ul style="list-style-type: none"> • Poor compliance 	<ul style="list-style-type: none"> • Abnormal Lab. test results.
Erickson et al. ⁶³	DRP (DTP)	-	<ul style="list-style-type: none"> • 	<ul style="list-style-type: none"> • Different signs and symptoms
Strand, et al. ¹⁴ Briceland, et al. ⁶⁶ Briceland, et al. ⁷⁰ Kane, et al. ⁶⁸ Johnson & Bootman ⁷⁴ McDonough ⁷⁶ Chen & Shalansky ⁷⁷ Alderman ⁸⁰ Currie, et al. ⁸¹ Smith, et al. ⁸⁵ Bootman et al. ⁸⁷ Easton et al. ⁸⁸ Tafreshi et al. ⁹⁷ Setter et al. ¹⁰⁴ Ernst & Grizzle ¹⁰⁹ Patel & Zed ¹¹⁷ Manley & Carroll ¹²¹ Lassetter et al. ¹²⁷ Sellers et al. ¹²⁹ Triller et al. ¹³² Isetts et al. ¹³⁰ Easton-Carter et al. ¹³⁶ Bednall et al. ¹³⁸ Manley et al. ¹⁴⁰ Manley et al. ¹⁴³ Easton et al. ¹⁴⁷ Mamun et al. ¹⁴⁹	DRP	<p>An undesirable patient experience that involves drug therapy and that actually or potentially interferes with a desired patient outcome.</p> <p>Alderman⁸³ version: a DRP is said to exist when a patient experiences (or potentially could experience) an undesirable event of a medical, psychological or economic nature as a result of...</p>	<ul style="list-style-type: none"> • (Depending on the example, can be process or outcome): Medical condition without drug; medical condition with wrong drug; medical condition undertreated; toxicity; ADR; condition resulting from interaction; condition resulting from non-compliance; medical condition with wrong drug. 	
Brown ⁶⁴	Adverse outcomes	-	<ul style="list-style-type: none"> • 	<ul style="list-style-type: none"> • Avoidance or deterioration in signs or symptoms.

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Stewart et al. ⁶⁵	DRP	-	<ul style="list-style-type: none"> Duplication; inappropriate prescribing; interactions; complexity of drug regimens 	<ul style="list-style-type: none"> ADR
Lobas, et al. ⁶⁷	DTP	-	<ul style="list-style-type: none"> Serum drug concentration needed; too many drugs prescribed; too many doses; therapeutic duplication; better therapy in literature; patient noncompliance; Potential for ADE; drug concentration outside range; drug contraindication; potential for interaction 	<ul style="list-style-type: none"> Disease state not controlled; existing ADE; patient dissatisfaction; patient perceives signs and symptoms; abnormal lab.test; therapeutic failure; existing interaction
Mason & Colley ⁶⁹	Potential DTP	-	<ul style="list-style-type: none"> Complicated schedule; dosage adjustment; drug interaction; high cost; inappropriate indication; noncompliance; therapeutic duplication 	<ul style="list-style-type: none">
Rogers ⁷¹	Clinical intervention event	-	<ul style="list-style-type: none"> Incorrect strength or dose or drug; interaction; contraindicated drug; incomplete patient details. 	<ul style="list-style-type: none">
Kaplan, et al. ⁷² Kaplan, et al. ⁷³	DRP	-	<ul style="list-style-type: none"> Drug selection; drug regimen; interactions; compliance; self-care; miscellaneous 	<ul style="list-style-type: none"> ADR
Tomechko et al. ⁷⁵ Becker et al. ¹⁴⁸	DTP	Something unintended occurring with the drug therapy.	<ul style="list-style-type: none"> Unnecessary drug therapy; wrong drug; dosage too low; ADR; dosage too high; inappropriate compliance. Needs additional drug therapy. 	
Robertson, et al. ⁷⁸	Problems in drug therapy	-	<ul style="list-style-type: none"> Major significance recommendations; moderate significance recommendations; minor significance recommendations 	<ul style="list-style-type: none"> Cost avoidance.
Smith & Christensen ⁷⁹	DTP	-	<ul style="list-style-type: none"> Incorrect information; inappropriate drug; prescription clarification 	<ul style="list-style-type: none"> Clinical problem;
Cunningham et al. ⁸³	DRP	-	<ul style="list-style-type: none"> (Depending on the example, can be process or outcome): ADR; sub-therapeutic dose; failure to receive drug; untreated indication; inappropriate selection; overdose; drug without indication; duplication; interactions. 	
Reimold ⁸⁴	DRP	-	<ul style="list-style-type: none"> 	<ul style="list-style-type: none"> ADR
Grabe, et al. ⁸⁶	DRP	Refers to Strand et al. ¹⁵	<ul style="list-style-type: none"> Drug without indication; overdoes; subtherapeutic doses; failure to receive a drug; indication with a wrong drug; drug interactions; therapeutic duplication; other. 	<ul style="list-style-type: none"> Indication without a drug; ADR
Ahmed ⁸²	DRP	-	<ul style="list-style-type: none"> 	<ul style="list-style-type: none"> ADR; overdose
Gourley, et al. ⁸⁹ Solomon, et al. ⁹¹ Gourley, et al. ⁹³	Patient problems or needs	-	<ul style="list-style-type: none"> Patient knowledge; medication compliance; drug product selection; prescription order problems; regimen problems; risk of interaction 	<ul style="list-style-type: none"> Systolic blood pressure; dyspnea; symptoms interference with activities; ADR; patient satisfaction; quality of life; health resource use
Schmidt, et al. ⁹⁴	DRP	-	<ul style="list-style-type: none"> Inappropriate drug according to guidelines; no beneficial effect; formulation not appropriate; indication unclear; doses require adjustment; therapy follow-up required; drug interaction 	<ul style="list-style-type: none"> Obvious ADR;
Cipolle, et al. ⁹⁰ Ernst et al. ¹¹⁰ Ernst et al. ¹³⁷ Pretsch et al. ¹⁴⁵	DTP, DRP	Undesirable event experienced by the patient that involves or is suspected to involve drug therapy and that actually or potentially interferes with a desired patient outcome	<ul style="list-style-type: none"> (Depending on the example, can be process or outcome): Medical condition requiring new therapy; patient taking unnecessary therapy; medical condition with a wrong drug; medical condition with too little drug; medical condition with too much drug; ADR; medical condition by not taking the drug appropriately. 	

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Article	Name	Definition	Process	Outcomes
Lamsam & Kropff ⁹²	DRP		•	• Several signs or symptoms (hipokalemia, drowsiness, etc.)
Guemes, et al. ¹⁰¹	DRP		•	• ADR; toxicity; worsening condition after withdrawal; poor response to treatment.
Cerulli & Malone ⁹⁶	DRP	Event involving drug therapy that interferes with the achievement of an optimal patient outcome	• Drug interaction; inappropriate administration; drug without indication; improper selection; overdose; failure to receive drug; underdose; inadequate monitoring.	• ADE; untreated indication
Kassam et al. ⁹⁵ Kassam et al. ¹¹³ Volume et al. ¹¹⁴	DRP	Undesirable sign or symptom actually or potentially experienced by patients that is related to drug therapy	•	• Medical condition without drug; medical condition with wrong drug; medical condition undertreated; toxicity; ADR; condition resulting from interaction; condition resulting from non-compliance; medical condition with wrong drug.
Westerlund, et al. ¹⁰⁰ Westerlund, et al. ¹¹⁶ Westerlund, et al. ¹³¹	DRP	A circumstance of drug therapy that may interfere with a desired therapeutic objective	• Uncertainty about the indication for the drug; underuse of medication; overuse of medication; other dosage problems; interaction; contraindication; difficulty swallowing capsule; difficulty opening container; other practical problem; language deficiency	• Therapeutic failure; ADR
Briesacher, et al. ⁹⁸ Stuart, et al. ⁹⁹	Drug use review failures		• Dose; duration of therapy; duplicative therapy; drug-drug interactions; contraindications	•
Christensen, et al. ¹⁰⁶	DRP	Concerns with the drug prescribed relative to the patient or to other drugs in the regimen	• Duplication; interaction; complex drug utilization;	• Allergy; ADR
Blakey & Hixson-Wallace ¹⁰⁵	DRP		• Drug without indication; untreated indication; overdose; improper selection; duplication; laboratory monitoring necessary; subtherapeutic dosage; interaction; ADR	
Ellis et al. ¹⁰²	DRP		• Requires education; too much drug; taking a nonformulary drug; too little drug; taking not as prescribed; interaction; wrong drug; drug not indicated	• Needs a drug; ADR
Hanlon et al. ¹⁰³	DRP		•	• Therapeutic failure; ADR; adverse drug withdrawal effect
Follin & Kwong ¹⁰⁷	DRP		• Excessive dosages; subtherapeutic dosages; excessive time periods; absence of diagnoses; duplication; interaction; drug selection; monitoring; medication error	• Untreated indication; ADR;
Hohl et al. ¹¹¹	ADE, DRP, MRP	Any unfavorable medical event related to medication use or misuse.	•	• ADR, noxious effects caused by interactions; withdrawal reactions; adverse effects after errors or noncompliance

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Article	Name	Definition	Process	Outcomes
Van mil et al. ¹⁰⁸	DRP		<ul style="list-style-type: none"> Potential interaction; potential contraindication; intolerance; possible duplication; dosage incorrect; first-time dispensing; compliance alert; change daily use 	<ul style="list-style-type: none">
Alegre et al. ¹¹²	MRP		<ul style="list-style-type: none"> Lack of information; administration error; non-adherence; self-medication; non-indicated drug; interaction; duplication; polypharmacy; wrong route; inefficient prescription 	<ul style="list-style-type: none"> Manifested ineffectiveness; actual ADR
Schaefer ¹¹⁸	DRP	Being potentially harmful to the patient's health or which may prevent the patient from achieving the full therapeutic effect of the drug used"	<ul style="list-style-type: none"> Inappropriate drug choice; inappropriate drug use by the patient/compliance; inappropriate dosage; drug-drug interaction. 	<ul style="list-style-type: none"> ADR
Farris et al. ¹¹⁹	DRP		<ul style="list-style-type: none"> Adherence-underuse; suboptimal selection; needs therapy; Low dose, high dose; improper administration; interaction; unnecessary; adherence-overuse. 	<ul style="list-style-type: none"> ADR
Martin et al. ¹²⁰	DRP		<ul style="list-style-type: none"> 	<ul style="list-style-type: none"> ADR; therapeutic failure; toxicity
Audette et al. ¹²³	DRP		<ul style="list-style-type: none"> Drug without indication; lack of drug; drug not the safest or the most efficacious; duplication; contraindication; interaction; regimen in conflict; less costly drug available; inappropriate route, dosage form, dose, duration, interval or technique; lack of laboratory data; incorrect monitoring; unnecessary laboratory test; inadequate education. 	<ul style="list-style-type: none"> Suspected ADE; suspected ADR
Lee, et al. ¹²⁵	Medication misuse	-	<ul style="list-style-type: none"> Adjust dose or frequency; drug not indicated; drug interaction; duplication of therapy; duration of therapy; switch IV to PO. 	<ul style="list-style-type: none"> Cost avoidance; Improvement of medical problem; Drug allergy; Adverse drug event
Midlov et al. ¹²²	DRP		<ul style="list-style-type: none"> Improper drug choice; low dose; high dose; interaction; drug without symptom; dosage interval; drug intake with food; drug use without specification 	<ul style="list-style-type: none"> Not treated symptom; medical problems because of non-compliance; ADR; drug has not the intended effect
Mjorndal et al. ¹²⁴	DRP		<ul style="list-style-type: none"> 	<ul style="list-style-type: none"> ADR
Emmertson et al. ¹⁴⁴	MTP		<ul style="list-style-type: none"> Duplication; dose too high or too low; unnecessary therapy; incorrect drug, route or schedule; non-compliance; poor technique; interaction 	<ul style="list-style-type: none"> Need therapy; ADR
Zaidi et al. ¹²⁸	DRP		<ul style="list-style-type: none"> Unnecessary drug; renal adjustment; inappropriate dose; lack of monitoring; inappropriate route. 	<ul style="list-style-type: none">
Koh et al. ¹⁴²	DRP		<ul style="list-style-type: none"> Dose too high; dose too low; require synergistic therapy; noncompliance. 	<ul style="list-style-type: none"> Untreated condition; ADR
Gandhi et al. ¹³⁹	ADE	Injuries due to drugs, occur frequently among inpatients.	<ul style="list-style-type: none"> 	<ul style="list-style-type: none"> ADR

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Ruths et al. ¹³³	DRP		<ul style="list-style-type: none"> • Need additional drug; undertreatment; need test; need review; unnecessary drug; drug not indicated; drug more effective available; dosage too low; risk of ADR; interaction; dosage too high. 	<ul style="list-style-type: none"> •
Triller et al. ¹³²	DRP		<ul style="list-style-type: none"> • Inappropriate prescribing; noncompliance; interactions. 	<ul style="list-style-type: none"> • ADR
Guignard et al. ¹⁴¹	DRP Prescription-related problems		<ul style="list-style-type: none"> • Excessive dose; duplication; interaction. 	<ul style="list-style-type: none"> •
Carter et al. ¹³⁵	DRP		<ul style="list-style-type: none"> • Unnecessary medication; suboptimal medication; poor adherence; need additional medication 	<ul style="list-style-type: none"> • ADR
Gilbert et al. ¹²⁶	MTP		<ul style="list-style-type: none"> • Need additional test; unnecessary medicine; wrong medicine; too much medicine; too little medicine; hoarding of medicines; duplication; interactions; administration problems; need information; patient fearful; expired medicines; compliance problems 	<ul style="list-style-type: none"> • ADR; need additional medication or therapy;
PCNE v.4.0 ¹⁴⁶	DRP	An event or circumstance involving drug therapy that actually or potentially interferes with desired health outcomes.	<ul style="list-style-type: none"> • Drug choice problem; dosing problem; drug use/administration problem; interactions 	<ul style="list-style-type: none"> • ADR
Gordon et al. ¹⁵⁰	DRP	Any problem that impacts on the patients' ability to manage or take their medicines effectively.	<ul style="list-style-type: none"> • Interactions; non-compliance; cognitive, physical and sensory problems; problems with non-prescription medicines; drug prescribing problems; interface, monitoring and review problems; lack of information; problems with repeat prescriptions; GP surgery and pharmacy problems 	<ul style="list-style-type: none"> • ADR

ADE= Adverse drug event; DRP=Drug-related problem; DTP= Drug therapy Problem; MTP= Medication-related problem; MRP=Medicine-related problem.