Independent Drug Information for Medicines Management

Laura Diego del Río

TESI DOCTORAL UPF / 2012

DIRECTOR DE LA TESI

Dr. Vicente Ortún, (Departament d'Economia i Empresa)

DEPARTAMENT DE CIÈNCIES EXPERIMENTALS I DE LA SALUT

UNIVERSITAT POMPEU FABRA

In loving memory of my father, whose disease inspired me to search for new effective drugs.

Acknowledgements

This PhD. Thesis is the result of four years of hard work. The real challenge has been to find the right equilibrium between this project, my professional activity as a drug information pharmacist and the exhausting but fascinating experience of becoming a mother of twins.

I am very grateful to my advisor, Professor Vicente Ortún, for helping me bridge my professional knowledge and my academic interests into a PhD. Thesis. He has always been very accessible and his encouragement and patience have been crucial in reaching this stage.

I will always be indebted to Professor Charles E. Daniels for having always blindly trusted me and for his unconditional support during my visit to the University of California, San Diego. In fact, we owe him much more than that. He provided me an enriching perspective, involved me in many projects and introduced me to a network of professionals, many of whom are now co-authors.

I also have to thank many of the people that I have found along my rather short professional life, many of whom have played a key role in my professional pathway During the year that I lived in Madrid, Pura Lledó gave me the best professional tip ever (I still stick to it!) and was a determinant factor in the reorientation of my professional career. I cannot forget Javier García del Pozo and Manolo Montero, at *Agencia Española de Medicamentos y Productos Sanitarios*, for being patient enough to teach me the basic principles of pharmaecopidemiology and of drug utilization studies.

Newly arrived to Barcelona, the members of the former *Unitat de Farmàcia de l'Institut Català de la Salut* provided me the outstanding opportunity to learn the insights of medicines management in primary care. In particular, I am especially grateful to Arantxa Catalán for having appointed me Secretary of the *Comitè d´Avaluació de Nous Medicaments* (CANM), this allowed me to learn about new drugs' in depth and helped me to settle on a topic for this PhD. Thesis. I have to thank all members of CANM, but in particular, Toni Guerrero, Rosa Madridejos, Rosa Morros, Àngels Pellicer and Cristina Vedia with whom I now have the

opportunity to work in other projects. I am very grateful to Eva Comín for providing me the opportunity to participate in the development of a (never ending) clinical guideline. I will always be indebted to Ester Amado. Her support, guidance and advice have been essential in many of the personal and professionals projects that I have started.

I would like to thank Josep Monterde for his insistence, encouragement, valuable ideas and final push to pursue this and many other academic projects. I have to thank Cristina Roure for, among many other things, providing me with the opportunity of becoming part of CedimCat. Laia Robert has made this project a lot easier for me. Her support has always been crucial in our daily routine, as well as during the last stage of the dissertation. Although she keeps denying it, I really hope I can return her the same favor in the near future. I am more than grateful to all members of Clinical Services Department at *Hospital Universitari Vall d'Hebron* for the warmest welcome ever, and in particular to Montse Ferré and Roser Prim for their unconditional support, advice, laughs and many of the good moments we have shared. I hope we eventually have a new chance to work together again.

I have to thank Oriol and Mònica for those late Thursday night dinners, Nick Monty for his fantastic editing and Inés and David for their permanent interest on the progresses I made as well as their support in every aspect of our daily life in Barcelona.

I am sure this PhD would not have been possible without the support of my family and in particular the support of Pedro. He encouraged me to start the PhD Program and helped me to find a way forward through many difficult situations. I am especially grateful for his extraordinary patience during the long reading-discussion nights. I owe an apology to Marta and Amaia, our 18 month old twins, for the time this PhD. Thesis has stolen from them. I promise I will eventually make up for it. I am grateful to my mother, Teresa, for transmitting to me, among many other things, her curiosity, energy and optimism, which have been essential to survive these four years. Among the many things I owe to the Rey-Biel family, the traditional breakfast-seminar on fixing healthcare has

definitely contributed to shape many of my opinions. In particular, I have to thank Javier, not only for being a never ending source of bibliographic references but also for the efforts he made in order to help me access data.

Abstract

On the 50th anniversary of the creation of the first medicines information center, this dissertation offers an insider perspective and provides several examples of independent drug information as a tool for medicines management. Chapter 1 reviews the origins, presents the challenges and proposes several strategic lines for current medicines information centers, done so from the perspective of public healthcare organizations. Chapter 2 assesses the place in therapy of methylnaltrexone a novel peripherally acting mu-opioid receptor antagonist licensed for opioid-induced constipation. Chapter 3 explores the current state of the art on novel opioid antagonists for opioid-induced bowel dysfunction including drugs currently in development and that are likely to be marketed in the future. Annex 1 compiles two editorials, the first on new drugs' policies and the second on how to maximize the impact of a pharmaceutical benefits scheme review. Annex 2 includes, for illustrative purposes, the front page of several drug information bulletins.

Resumen

En el marco del 50 aniversario de la creación del primer centro de información esta tesis ofrece una perspectiva contrastada de los mismos a la vez que muestra algunos ejemplos de información independiente como herramienta para la gestión de los medicamentos. El primer capítulo revisa los orígenes, presenta los retos actuales y propone las líneas estratégicas para los centros de información de medicamentos de la sanidad pública. El Capítulo 2 evalúa el lugar en la terapéutica de metilnaltrexona, un nuevo antagonista periférico de los receptores mu-opioides, en el manejo del estreñimiento inducido por opioides. El Capítulo 3 explora el estado del arte, incluyendo nuevas moléculas en desarrollo, de los nuevos antagonistas opioides para la disfunción intestinal inducida por opioides. El Anexo 1, recoge dos editoriales, la primera revisa la política de nuevos medicamentos y la segunda proponen algunos criterios para maximizar el impacto de la exclusión selectiva de medicamentos de la

financiación pública. El anexo 2, incluye, con fines ilustrativos, la carátula de varios boletines de información medicamentos.

Preface

This PhD. Thesis deals with several aspects related to the provision of independent drug information as a tool for medicines management, done so from the perspective of public healthcare organizations.

The work is structured in three chapters and two annexes. Chapter 1 reviews the origins, current challenges and perspectives of medicines information centers from an insider perspective. Chapters 2 and 3 present common independent medicines information tasks, such as the assessment of the place in therapy of a new drug, therapeutic group review and scanning of future technologies. Annex 1 compiles two editorials that reflect the current issues of concern in medicines management policies: namely new drugs and pharmaceutical benefits scheme review. Annex 2 gathers seven examples of independent drug information bulletins for illustrative purposes.

Chapter 1 reviews the origins, role, impact and current challenges that medicines information centers are facing. A key motivation for this study is the celebration in 2012 of the 50th anniversary of the creation of the first medicines information center. This chapter identifies areas for improvement and proposes several strategic lines to ensure medicines information centers continue to meet drug information needs. This paper is being considered for publication, following initial approval, for the *American Journal of Health-System Pharmacy.*

Chapter 2 provides a first-hand example of the type of work done at medicine information centers and, in particular, on independent evaluation of the therapeutic value of new drugs. This is a strategic instrument for medicines management within healthcare organizations as it helps to discriminate the value of new drugs over already existing therapies. This allows the implementation of strategies to moderate the rapid adoption of new drugs that offer no added value over already existing technologies. The chapter was published in 2009 in *Expert Review of Gastroenterology and Hepatology* as “Methylnaltrexone: a Novel Approach for the Management of Opioid-Induced Constipation in Patients with Advanced Illness”. It is a joint work with Atayee R, Helmons P, and von Gunten C. E. This paper assesses the place in therapy

and clinical impact of methylnaltrexone, the first of a new class of drugs called peripherally acting mu-opioid receptor antagonists. In clinical trials methylnaltrexone demonstrated to improve opioid-induced constipation in terminally ill cancer patients. Additionally, the article also explores the potential role in the management of opioid-induced constipation in non-cancer populations and for other common opioid-induced side effects such as nausea, vomiting or pruritus.

Although methylnaltrexone was the first of its class to be marketed, several pharmaceutical companies had in their pipeline opioid antagonists in different stages of clinical development for the management of a broader spectrum of symptoms defined as opioid-induced bowel dysfunction. In line with this, chapter 3 represents another example of one common independent medicines information activities; the review of new opioid antagonists and the scan of emerging technologies that are likely to be marketed where four agents under clinical development were identified. This task is essential for healthcare organizations in order to identify, anticipate and prepare for the impact which future medicines might have within their organizations. Chapter 3 was published in 2011 in *Expert Opinion on New Investigational Drugs* under the title "Novel Opioid Antagonists for Opioid-Induced Bowel Dysfunction". It is joint work with Atayee R, Helmons P, Hsiao G. and von Gunten C. E.

Annex 1 compiles two editorials published in *Atención Primaria* in 2011 and 2012. The first, "*Política de Nuevos Medicamentos: Calidad y Seguridad*", coauthored by Amado Guirado E. and Madridejos Mora M., reflects on the issues of concern, future perspectives and policies surrounding the marketing of new drugs focusing in the primary care setting. The editorial highlights that the most newly marketed drugs do not offer added therapeutic value over already existing technologies and that there are always uncertainties related to its safety profile. Furthermore, these new drugs are usually marketed at higher prices and are directly responsible of contributing to the permanent increase in pharmaceutical expenditure. The second editorial, "*Mejorar la Calidad Asistencial no Implica Financiar Públicamente Cualquier Medicamento*", coauthored by Amado Guirado E. and Ortún V., stresses the importance of

introducing cost-effectiveness elements to support decisions on the public funding of medicines. In the current context of a financial crisis and budgetary restrictions, the editorial presents several aspects to be taken into consideration when reviewing the pharmaceutical benefits scheme in order to maximize the economic impact without compromising healthcare quality.

Annex 2, compiles as illustration seven independent drug information bulletins where the efficacy, safety and place in therapy of the most relevant newly marketed drugs is evaluated.

Overall, this thesis provides an insider and comprehensive overview of independent medicines information. This include the origins, development, common tasks and the challenges current medicines information centers are facing; focusing on drug evaluation as a tool for medicines management with a special emphasis on new drugs.

Table of Contents

Pàg.

Chapter 1

The Role of Medicines Information Centers 50 Years Later: from Difficult Access to Value Drug Information

Laura Diego

To be submitted under request to the American Journal of Health-System Pharmacy

1. THE ROLE OF MEDICINES INFORMATION CENTERS 50 YEARS LATER: FROM DIFFICULT ACCESS TO VALUE DRUG INFORMATION

1.1 Introduction

Healthcare and pharmaceutical spending has grown significantly in recent decades. The increasing demand for healthcare technologies is one of the main challenges healthcare systems are experiencing and in a context of budgetary restrictions, countries are implementing policies to boost efficiency and provide better value healthcare.

Several reports from the Institute of Medicine have associated poor quality healthcare with deficiencies in access to data, information or available knowledge. Thus, the provision of relevant evidence-based independent drug information to both physicians and patients, can contribute to reducing the uncertainty inherent in clinical practice and to minimize some of the major drug related problems.

The first medicines information center (MIC) was created in 1962 in response to the ever increasing demand for drug information, with the aim of providing timely unbiased drug information and contribute to appropriate drug use. MIC are now well established and have shown to improve patient care and user satisfaction. Since their creation, their role has been transformed from facilitating the access to information, when it was not widely available, to becoming one of the few independent sources in an area saturated with easily accessible, and sometimes contradictory, resources. Nevertheless, contemporary MIC are experiencing challenges which are different to those of 50 years ago. Healthcare and society have experienced a profound change, but the development of information and communication technologies and the widespread access to healthcare information, have transformed definitively the scenario in which MIC provide their service. Thus, do MIC still do have a place

in healthcare organizations in this new context? We will argue in this article that the answer is clearly yes. Taking into consideration that patients' health problems are increasingly complex due to age and co-morbidities, that the available therapeutic options for a given condition are growing, that users can hardly discriminate among the abundance of information they can access, and even more importantly, that healthcare systems are in constant change in response to economic pressures and concerns about quality of care, the need for rigorous and independent drug information has probably never been greater. It is true, however, that MIC focus needs to shift from providing access to drug information to the provision of relevant, comprehensive information on drugs and pharmacotherapy, done so through the most appropriate dissemination strategy.

This paper covers a wide spectrum of aspects related to MIC and is organized in the following sections. Section 1.2 identifies several aspects that lead to an increasing demand for healthcare technologies contributing to the increase in healthcare costs. Section 1.3 focuses on how improving healthcare professionals' and patients' knowledge play an important part in healthcare quality. The origins and current situation of MIC, common activities and the available evidence (albeit scarce) on the economic and clinical impact of the services that MIC provide are reviewed in section 1.4. Finally, section 1.5 is the major contribution as it describes the main challenges contemporary MIC face, in particular, the fact that independent funding and adding value to the drug information process are key factors for MIC sustainability. In this section, five areas for improvement are identified and we propose five strategic lines of development. Section a) describes how MIC can still contribute to meet professionals' information needs. In order to do so, in section b) we argue that MIC should evolve from the provision of information to knowledge management services, taking advantage of the outstanding opportunities to improve dissemination and communication strategies provided by new information and communication technologies. Nevertheless, not all initiatives should be physician oriented; in fact, patients currently lack access to independent information on the benefits and risks of drug therapies. Thus, MIC not only have

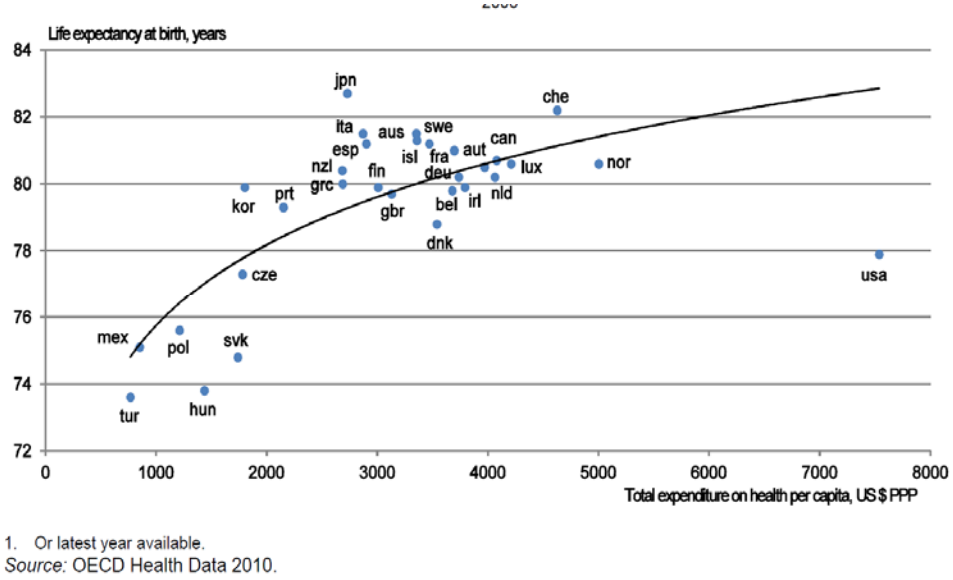
the opportunity, but also the responsibility, of leading independent medicines information for citizens and contribute to the development and dissemination of new tools to support shared decision making, such as decision aids or drug fact boxes as described in section c). In section d) we discuss how to improve efficiency and productivity in a context of budgetary restrictions. It is essential for MIC to promote those activities that increase coordination, encourage working in networks and the increased use of strategic partnerships in order to reduce duplicities, to introduce economies of scale and add value to the drug information process. Finally, in section e) we discuss that MIC have to ensure they improve the knowledge and skills of their personnel to meet the challenges of assessing the value of newer advanced therapies and support clinical decision making in personalized pharmacotherapy. Section 1.6 draws together the conclusions of this article.

1.2 Economic background

In OECD countries, healthcare spending per capita has increased by over 70% during the last decade, while total spending on healthcare absorbs on average over 9% of GDP, according to a recent OECD report. This has had an impact in healthier populations with significant longer life expectancy and lower mortality rate for certain diseases such as cancer. However, as shown in Figure 1 (OECD, 2010), higher healthcare spending does not necessarily correlate with better healthcare outcomes, with the US being an excellent example of this (OECD, 2010).

Taking a closer look to medicines, the pharmaceutical bill represents a significant proportion of total health spending, which in European countries is estimated to account for approximately 18% of total healthcare spending. Additionally, the average spending per capita on pharmaceuticals has risen by almost 50% in real terms over the last decade (OECD/Europe, 2010). Aside from drug prices, the rapid adoptions of costly new drugs (CBO, 2008; OECD/Europe, 2010) as well as inappropriate drug use (Willcox et al.,1994;

DTB, 2011; Johnell et al., 2007) are the main drivers of the increase in the pharmaceutical bill.



1. Or latest year available.
Source: OECD Health Data 2010.

Figure 1. Large differences in life expectancy and healthcare spending in OECD countries.

While the share of national income devoted to healthcare has continuously risen in past decades, the current global economic crisis has only heightened pressures and urgency to implement reforms and promote policies that boost efficiency to achieve better value healthcare. Many factors have contributed to the growth in healthcare expenditure. In any case, experts agree that the use of new medical services through technological advances, or what it has been coined as “increased capabilities of medicine”, is the main driver (CBO, 2008). In fact, one of the biggest challenges healthcare systems are experiencing is an increasing demand for healthcare technologies.

Part of the increase can be explained by population growth and longer life expectancy. In an ageing society, healthcare needs inevitably increase. However, its contribution is smaller than commonly perceived and the increasing demand for healthcare technologies is in part what health economists have defined as supplier-induced demand (CBO, 2008; Ahn et al., 2003; Fuentes Quintana et al., 1996; Mulley, 2009). This is demand in excess of

what would be chosen if a patient had available the same information and knowledge as the physician.

Variation and overutilization are commonly described consequences of supplier-induced demand. Variation was first described by Glover in the late 30´s who found a 10-fold variation rate of tonsillectomies in children among England and Wales that could not be explained by sociodemographic factors (Glover, 1938). Now we know that unwarranted variation in clinical practice occurs to a large extent due to uncertainty in decision making (Mulley, 2009). Differences in diagnosis and prescriptions among physicians can be generated by the inherent complexity of clinical practice or by the limited information on the effectiveness of procedures and therapeutic interventions (Wennberg et al., 1982; Mulley, 2009). Overutilization is also a consequence of supplier-induced demand. Roemer found higher hospitalization rates and longer length of hospital stays in those regions with higher bed supply per capita (Roemer et al., 1961). This correlation between capacity and utilization was coined in the statement "*when a bed is built, a bed is filled".* So when resources are available overutilization occurs, even when there is uncertainty of its benefit.

This intensive use of healthcare resources should not be underestimated as it can trigger a diagnostic-therapeutic cascade where factors, such as unnecessary tests or an unexpected result, can initiate a series of events (usually catalyzed by doctors or patients anxiety) which can precipitate a therapeutic intervention that may result in harming the patient (Mold, 1986).

1.3 What is the contribution of medicines information?

Several IOM reports have identified that health care systems´ most avoidable flaws are linked to poor quality or lack of access to data, information or available knowledge, thus impeding the delivery of high quality health care services (Detmer, 2003; IOM, 2000, 2001, 2007). Additionally, evidence shows that information contributes to reducing uncertainty (Djulbegovic, 2004). In fact, studies show that well designed information can affect patients' demand, for

example, on major elective surgery (O'Connor et al., 2003; Mulley, 2009). In line with this, a recent Cochrane review concludes that when patients are informed through decision aids, people improve their knowledge of the options, are more likely to choose more conservative treatment options and are helped to have more accurate expectations of possible benefits and harms (Stacey et al., 2011). Similarly, the provision of information to healthcare professionals in the form of clinical guidelines or protocols can contribute to *mask* the uncertainty inherent in many of the decisions that are taken daily in clinical practice (Mulley, 2009).

In this line, Muir Gray has stated that "by applying what we know from research, from experience and from the analysis of data, we can either minimize or prevent several major health care problems: errors, poor-quality health care, patients with negative experiences, variations in policy and practice, wasting of resources, overenthusiastic adoption of low-value interventions and failure to get new, high-value interventions into practice" (Muir Gray, 2006). Thus, the provision of drug information can contribute to reduce drug related problems. For example a recent study has linked the lack of access to a costless drug information resource like the British National Formulary, with higher incidence of medication errors (Dornan et al., 2009; Kendall et al., 2012). Additionally, answering clinical enquiries could contribute to reduce the incidence of adverse effects, inappropriate drug use or financial loss from drug wastage. However, the different types of interventions used to implement research findings in clinical practice, and their effectiveness for promoting behavioral change, fall beyond the scope of this paper.

The provision and advice of independent evidence based information on the benefits and risks of drug therapy to both healthcare professionals and patients, as well as information on the appropriate and efficient use of drugs is essential to move towards best practices and contribute to provide not only better quality, but better value healthcare.

1.4 Medicines information centers

a) Origins and development

During the early 60´s the thalidomide tragedy enhanced the debate on drug regulation that would establish the grounds for the development of the basic tools of contemporary medicines information. Thalidomide, the sedative prescribed for morning sickness to pregnant women during the late 50´s and early 60's, caused limb birth defects to more than 10.000 children worldwide. This public health tragedy was avoided in the US because although thalidomide was already marketed in over 20 other countries, the Federal Drug Administration (FDA) withheld the US drug approval and requested further efficacy studies. As a result, it gave time for the regulator to observe the negative side effects and deny the license to commercialize it.

In 1962 the Kefauver Harris amendment became law and changed regulation of new drug approvals. Manufacturers had now to prove to FDA that their drugs were not only safe, but also effective, before they reached the market. For the very first time, many companies had to put in place research and drug development programs, including the design and implementation of controlled clinical trials (Schifrin et al., 1977; Merrill, 1994). This offered drug information a comparative advantage over other healthcare areas such as diagnostics or surgery since the availability of clinical trials facilitated the information on the efficacy and safety of the drugs.

Traditionally pharmacists had always provided advice on drug use to healthcare professionals in a hospital setting. However, the increasing number and complexity of treatments available enhanced the demand of readily available and comprehensive drug information. This led to the creation of the first medicines information centre in 1962, by the designation of a specific area for drug information within the Pharmacy Department of the University of Kentucky Medical Centre (Parker, 1965). MIC can be defined as service units, under the direction of a qualified healthcare professional, committed to providing timely unbiased evidence based information to healthcare professionals and

patients/citizens. This information and advice about drugs and pharmacotherapy helps support decision making and improve drug use quality.

Following the creation of the first centre, the presence of MIC in the US was consolidated during the 60´s and during the 70's in Europe (Calder et al., 1981). However, new centers are still emerging in developing countries such as Uganda or India (Chauhan et al., 2009; Tumwikirize et al., 2011). Most MIC are established in teaching hospitals as this location offers certain advantages such as encouraging direct interaction with health professionals, responsiveness and opportunities for immediate action (UKMi, 2007). Others have been implemented at a regional or national level as part of the strategy designed to promote quality drug use (Leach et al., 1978).

Although MIC are now well established, there is neither published data nor an inventory of the number and characteristics of the centers available in each country. To our knowledge, information is limited to sporadic surveys in certain countries like the US or to institutional information in the case of countries with national health services. Rosenberg and colleagues suggest in the latest available survey that the number of US centers may be decreasing. In fact, the number of MIC has fluctuated notably, reaching its peak in 1986 with 127 centers and dropping to 75 in 2009. Authors suggest two possible reasons for the reduction in the number of centers. First, the fast development and adoption of information and communication technologies which has facilitated access to healthcare information. Second, changes in pharmacy practice and education (Rosenberg et al., 2009). However, access to healthcare information has also affected other countries with a strong tradition of National Health Services, such as the UK and Spain, where the number of centers remains essentially the same (Calder et al., 1981; Moya et al., 2010). This suggests that the sustainability of centers may be facilitated when they are part of the structure of a large national healthcare organization.

b) Role and impact

Although MIC activities can vary substantially depending on its structure and territorial organization, frequent activities carried out by MIC are summarized in Figure 2 (adapted from FIP).

Activities

Passive

- Answer drug and pharmacotherapy enquires

Active

- Drug evaluation
- Dissemination of drug information
- Advice on medicines and pharmacotherapy
- Education and training
- Research

Ancillary activities

- Pharmacovigilance
- Toxicology

Figure 2. Frequent MIC activities

Traditionally, MIC have supported clinical decision making through two information strategies that have conferred MIC a passive and active role. The passive role implies on waiting to receive a drug enquiry which is considered a fundamental part of MIC's activity. Answering enquires requires to clearly identify the clinical question, define a strategic search, critically appraise available information, synthesize the evidence and finally to contextualize it for specific patients or target population. Most queries can't be answered immediately and require a great amount of resources and time to synthesize the evidence making it a laborious and time consuming process. On the other hand,

the active role comprises multiple activities in which MIC are involved daily that are not specifically requested. These essentially involve drug assessment (especially of new drugs), dissemination of drug information (safety alerts, drug bulletins, emerging technologies), expert advice on drug related issues and education and training activities (Pla et al., 2002; FIP).

Most MIC provide general information on drugs and pharmacotherapy covering a wide spectrum of areas. However, some centers have had the opportunity to naturally specialize in certain fields as a result of enquires received or due to its proximity to a certain group of professionals or therapeutic centers (Calder et al., 1981). Some areas of drug information however, like toxicology and pharmacovigilance, require a high level of expertise and specific training; as a consequence, most countries usually have dedicated poisons or pharmacovigilance centers, operating as separate units from traditional centers.

A recurrent concern for MIC has been to quantify the clinical and economic impact of the service provided. Although several attempts were made in during the 90's, rigorous research on the service provided by drug information services is difficult to undertake, mainly because a part from the advice provided, there are many potential determinants for achieving the desired outcome. Thus, disentangling the effects of the intervention from the influence of contextual factors is extremely difficult when interpreting the results of individual studies on the impact of drug information.

Kozma et al divided outcomes in three categories and developed the economic, clinical and humanistic outcomes model (ECHO) to identify, collect, and use outcome data to assess the value of pharmaceutical treatment alternatives (Kozma et al., 1993). Although many of these outcomes are difficult to measure, in 1999 the European Society of Clinical Pharmacy Special Interest Group for Drug Information proposed the ECHO model for research in drug information by using a multicomponent model in order to facilitate research in the area. The ECHO model applied to drug information would consider economic (cost of advice, cost of treatments and benefits in life years gained or working days lost), clinical (treatment success or failure) and Humanistic (quality of life and

patient and career satisfaction) (Foppe van Mil, 1999; Hands et al., 2002). However, to our knowledge there are no published papers using this approach.

The absence of outcomes research does not mean MIC do not provide a useful service that cannot have a positive impact on quality drug use. There is modest evidence of its positive impact on users' satisfaction and patient care. Traditionally quality assurance of MIC has relied on users' feedback on the operational efficiency of the service and results show enquirers consider it a valuable service (Hands et al., 2002). Additionally, six published studies in US, UK and Canada report the therapeutic advice provided by MIC had a positive impact on patient care. Such results however, must be interpreted with caution, as possible patient outcomes have only been evaluated by an independent panel of experts in a limited number of studies (Adams, 1992; Bond et al., 1999; Cardoni et al., 1978; Melnyk et al., 2000; Najabat et al., 1999; Stubbington et al., 1998).

Evidence on the economic impact of drug information services is lacking. Only two studies have analyzed the costs associated to the answering enquires service (Kinky et al., 1999; Yousef 1994). In 1993, one study in Wales found the median time spent answering a query was 48,4 minutes with an average cost of £17,93 per enquiry (taking into consideration the pharmacist´s salary, time spent resolving queries, cost of information resources and the number of enquiries). Although costs and time spent per enquiry might not be representative of current practice, this is the only study that provides a scope of the cost to resolve enquiries (Hands et al., 2002; Yousef,1994). Alternatively, other authors have developed cost-avoidance models to determine the potential cost savings that could result from drug information enquires. (Hands, 2002; Kinky et al., 1999) In this study, an independent panel determined whether a drug related event may have occurred if the MIC had not been consulted and then rated it according to severity. Using a sensitivity analysis, annual potential cost savings in their centre ranged from $417.792 to $2.052.740 per year. The inherent difficulties in measuring the clinical impact of MIC have possibly limited research in this area. The impact of MIC activities goes far beyond quantifying the cost associated to answering enquires.

Therefore, a global consideration of all activities undertaken by MIC, which includes drug formulary development, evaluation of new drugs and education and training activities should be as well considered when evaluating their impact. Clearly, applying cost-benefit analysis to some of these areas is more complex than to others.

1.5 Contemporary challenges

Currently MIC face two big challenges: 1) overcoming budgetary restrictions and 2) providing value drug information.

Regarding funding, traditionally MIC have relied on healthcare organizations or health authorities as an independent source of funding that guaranteed their stability while, to some extent, preserved their impartiality. Recently, several organizations with a strong tradition and commitment to independent drug information such as the Therapeutics Initiative or the Drug and Therapeutics Bulletin, have experienced financial difficulties (Moynihan, 2008; DTB, 2012a). In such circumstances, relying on external organizations for funding might be tempting. Given that external sources naturally have their own agenda, funding from external organizations, especially from the pharmaceutical industry, should be avoided.

There exists strong and consistent evidence on the impact that the pharmaceutical industry has on prescribers' behavior and research (Lexching, 1993, 1997; Wasana et al., 2000; Jackson 2001; Katz et al., 2003; Prosser et al., 2003; Fugh-Berman et al., 2007; Prescrire, 2012). Moynihan described several examples of how interactions with the pharmaceutical industry correlate with doctor preferences for new drugs and a decrease in generic prescribing (Moynihan, 2003). Moreover, other studies show that industry sponsored research tends to draw conclusions which favor them, somehow jeopardizing evidenced based medicine. (Bero et al., 1992; Angell, 2000; Smith, 2003; Bekelman et al., 2003; Lexching et al., 2003; Liss, 2006). Under these premises, funding from external organizations should be avoided in order to

preserve MIC objectivity and independence from any potential commercial interests. An additional preoccupation factor that should be considered is the new challenges imposed by the wide availability of drug “information” and drug promotion activities in a deregulated space like the internet and other social media (Greene, 2010).

Regarding value drug information, 50 years after the creation of the first MIC, healthcare, society and more specifically information and communication technologies have experienced a profound change that has transformed the traditional scenario in which MIC used to operate. The creation of MIC responded to the need for organizing the increasing amount of medical information available; however over time this role has been transformed into more complex activities that require additional skills to manage and assess information in a more efficient manner (Pla, 2002). Moreover, the great amount of medical information published daily and the widespread access to internet has undoubtedly changed traditional access to healthcare information, with many sites offering free access to information that is not necessarily accurate and unbiased. Nevertheless, one should not see information and communication technologies as a menace, but as a potential new scenario in which new opportunities for MIC may develop.

Taking all this into consideration, and in the absence of reliable measures of patient and economic outcomes, policy makers may be tempted to reduce funding or even consider whether MIC are expendable. On the contrary, the need of evidenced-based, independent drug information has never been greater. In the actual healthcare scenario with an increasing demand for healthcare technologies and limited economic resources, systems need to implement strategies that provide value to pharmacotherapy and that is precisely the role MIC can take. Thus instead of being considered as a source of expenditure, in this context, drug information should be considered as a public good. This claim has also been recently made for clinical trials data (Rodwin et al., 2012). Drug information satisfies all the characteristics of a public good: once it exists, its use does not preclude its utilization by others, and there is not an effective way of excluding others from its benefit. The

problem exists with the provision and funding of such a public good. Who should invest the resources needed to maintain it? Up to what point should the information generated by one MIC, perhaps for a very specific target population, directly transferred to other regions which may not have paid for such information?

While the actual context provides MIC with a unique opportunity to contribute to the appropriate and efficient use of drug therapies, several areas for improvement have been identified, and possibly it is time to revisit the MIC model. We propose five strategic lines to work towards: meet medicines information needs, evolve to knowledge management services, lead drug information for patients, provide better value service and improve knowledge on the advances made in the personalized medicines area.

In the following subsections we describe what is in our opinion, the direction that MIC should take in the near future.

a) Meeting information needs

The literature describes that a number of questions arise during doctors' surgery visits and that they are most likely to be about treatment, particularly medicines (Osheroff et al., 1991; Ely et al., 1999). Some studies suggest that 80% of these questions remain unanswered either because answers are not actively pursued by doctors or because once pursued, answers can't be found. Although most of the questions can be resolved, it is often very time consuming (Ely et al., 2005). The most frequent reported obstacle for not finding an answer is lack of time. Other reasons have been suggested such as doubt that the answer to the question exists, the excessive time and effort required and the difficulty in navigating through the overwhelming body of existing literature (Ely et al., 2005; González-González et al., 2007).

One should take into account that today information can be found more efficiently than ever. The best example is literature searches, which have changed from a laborious process in the library that used to take several hours

or even days, to now the simple task of entering a combination of a few terms into MEDLINE and getting retrieval back, literally in seconds (Hartzband et al., 2010; Coleman et al., 2012). However, many healthcare professionals may feel the amount of information available is unapproachable. Since the mid 60's there has been an exponential growth in the number of papers published and as shown in Figure 3, in fact, the MEDLINE® database comprises more than twenty million citations. Nevertheless, experts consider that most of the existing evidence is irrelevant or unreliable and that the application of filters can help to reduce significantly 'background noise' and identify relevant and valid evidence (Haynes, 2004; Djulbegovic, 2004).

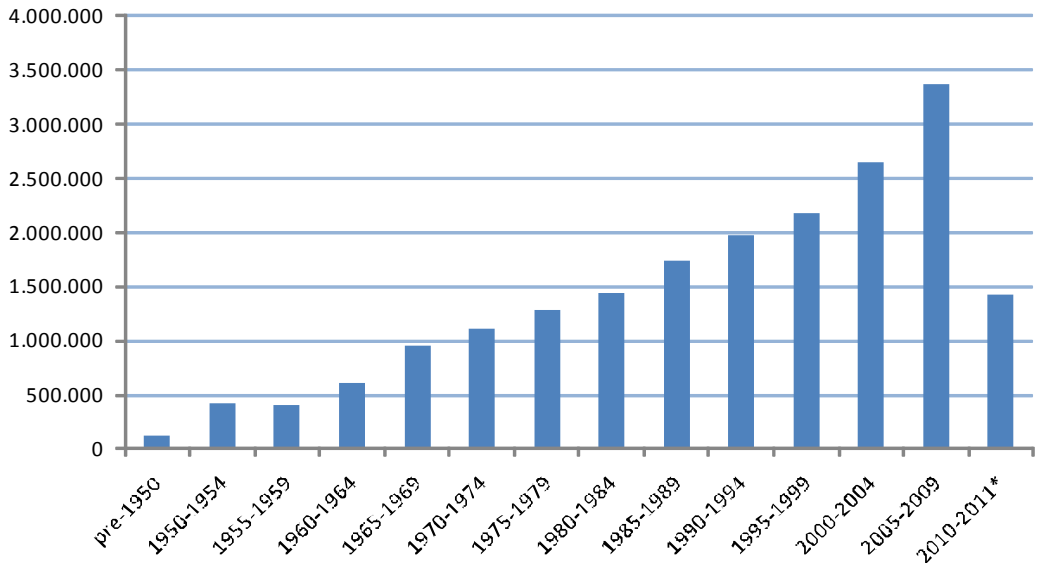


Figure 3. Number of citations published in MEDLINE®

It's worth noting that a paradox exists in that despite the amount of resources available and the facilities in the access to the information today, for various reasons, doctors still find it difficult to find the information they require and questions still remain unanswered. Of course there are many questions that now can be easily resolved, such as for example a dose adjustment in renal impairment, which can rapidly be consulted in the Summary of Products Characteristics. Others, such as *which patients are candidates to benefit from double antiplatelet therapy?* are much more complex and require a considerable

effort of synthesis. Part of the problem is precisely that enquires are often multidimensional, and professionals' informational needs are not just about medical knowledge, but seeking support, protocols, guidance or specific recommendations for a certain patient. This change in the type of questions has been reflected in enquiry patterns in US centers. Rosenberg and colleagues have observed that in the US, while in some centers the overall number of enquiries has reduced, there is a tendency towards more complex enquires that require additional time to be answered (Rosenberg et al., 2009).

MIC were created in a moment when the primary need was for drug information that was not easily accessible. The need today is for fast, clear, concise and comprehensive drug information based on evidence and best practices that has been digested from a great amount of information produced daily by researchers, pharmaceutical companies, regulatory agencies, health authorities and other institutions (Kendall et al., 2012). Thus, MIC should use their expertise in drug information to identify relevant and valid evidence, efficiently resolve clinical enquires and disseminate drug information at the right time in the most appropriate manner.

b) Evolving into knowledge management services

As previously described, the role of MIC has been transformed from organizing the increasing information available to more complex tasks. It is still necessary that the role of MIC evolves from the simple provision of information to knowledge management (KM) services. The concept of KM has been used in the business sector for decades, but it is only recently that the health care sector has begun to focus on the systematic management of knowledge, at least in part due to the ever growing amount of information managed. Kothari and colleagues define KM as a way of providing the right information, to the right person, at the right time, with the potential of attaining greater competitive advantage. Although KM uses different strategies including training sessions, communication technologies, processes mapping and communities of practice

among others, current KM practices in healthcare are basically limited to the use of information and communication technologies in the form of electronic libraries, and clinical guidelines. Nevertheless, it has been criticized that this provides a static approach, does not promote knowledge development or knowledge sharing and that tacit knowledge, that is the knowledge that is acquired through practice and experience, is underused (Kothari et al., 2011).

The application of information and communication technologies to drug information has a great potential and has had a major impact on the health sector and the provision of healthcare (Andreassen et al., 2007). On the one hand, it can contribute to enhance the collaboration and communication with other professionals. On the other hand, these technologies have become an essential support element of the daily clinical activity of prescribers. E-prescribing systems have enabled the integration of relevant medicines information to the point of drug prescription, contributing to improved safety, quality, efficiency and costs. (Coleman et al., 2012, e-Health Initiative 2004).

MIC have adapted to new technologies and developed Web Pages and tools to manage and disseminate the passive and active drug information they produce. In any case, web 2.0 technologies are still underused in this context and experiences are fundamentally limited to blogs. (Juárez Giménez et al., 2011) The Web 2.0 term refers to a second web generation based in communities and special services like social networks, blogs and wikis, which enhance collaboration, participation and exchange of information among users (Gené Badia et al., 2009.) In contrast to the World Wide Web, in web 2.0 the contents and management are handled by users, whereas in traditional websites users are limited to the passive viewing of content that was created for them. Web 2.0 technologies offer a number of user friendly and cost-efficient applications for the drug information specialist and knowledge-sharing among MIC. This can increase communication among healthcare professionals as well as the visibility of the center within the healthcare organization. (Juárez Giménez et al., 2011) In any case, although the potential application of these technologies is huge, the change in practice might be slower than expected. Recent studies have suggested that although physicians access the internet for immediate

information on a new drug, to access clinical guidelines or to use it as a diagnostic aid, they are still reluctant to engage social networks in clinical practice (Tang et al., 2006; Romano et al., 2012). MIC might be reluctant to implement these tools because of concerns on the openness, quality, volatility and immediateness of the information, as well as concerns on the resources required to continuously feed information. Perhaps the role of MIC should be to complement some of their activities as intermediaries in drug information to apomediaries, i.e., guiding users to activities or other relevant independent drug information available in the Web (Eysenbach, 2008).

The application of information and communication technologies has enabled physicians with a potent working tool that has become an important element for support of their daily clinical activity (Coleman et al., 2012). With regard to drugs, areas for improvement have clearly been recognized. A recent clinical safety study shows that 47% of patients´ safety problems identified in primary care were related to medicines and that 60% of these were avoidable (MSC, 2008). In fact, doctors today still find it hard to come up with reliable information that underpins everyday prescribing decision and information needs. In that regard, the increasing use of e-prescribing and e-dispensing systems offers new opportunities to link relevant drug information into these databases and improve safety, quality, and efficiency (e-Health Initiative, 2004). Clinical decision support systems (CDSS), offering drug information at the point of care, have demonstrated benefits such as avoiding prescription overdoses (Seidling et al., 2010). However the evidence on its clinical and economic outcomes and its effects on efficiency and workload remains scarce (Bright et al., 2012). Several attempts have been made to introduce classic CDSS like alerts, reminders or drug dose calculations. Currently, these systems are still not very sophisticated and there are concerns of over-alerting and slowing down the prescribing process (Kendall et al., 2012). Rahmner and colleagues have explored physicians' reported needs for knowledge databases at the point of drug prescription. According to this study, doctors would value the provision of integrated information on severe drug-drug interactions, adverse effects, allergies, drug doses related to age and renal function, recommended

alternative drugs and guidelines. Interestingly, physicians report that a registry using an image of the drug would facilitate the frequent and difficult task of identifying patients´ drug treatment when a patient can´t remember the drug they take and describe the form of the tablet or the container (Rahmner et al., 2011).

Taking all this into consideration, MIC should collaborate and promote the development and implementation of these new instruments in order to support clinical decision making at the point of prescription within healthcare organizations. In Catalonia, efforts have been made to integrate relevant drug information into e-prescribing systems. Several institutions have worked in the development and integration of interactive software to alert physicians when it detects a drug problem like a relevant clinical interaction, an allergy or an inappropriately prescribed drug in the elderly, which has been fairly well accepted among physicians (Catalán et al., 2011). Additionally, the integration of the regional MIC patient drug database has provided physicians with direct access to an image of the drug packaging which can facilitate patients´ drug identification during ambulatory doctor's visit and the elaboration of a personalized medication schedule.

c) Leading patient drug information

During the last decade the patient role in the healthcare system has experienced a profound change and there has been a paradigm shift from a doctor-patient paternalistic relationship to a partnership with shared care, shared decision making and shared responsibilities (Coulter, 1999). Shared decision making is a process in which clinicians and patients work together to decide about an intervention based on clinical evidence and patients informed preferences, which is appropriate for many type of healthcare decisions including whether to take a medication or not (Coulter, 2011; DTB, 2012b). Despite healthcare organizations promote partnership culture, the truth is that informed decisions can only be made with the combination of two inputs, facts

and values; that is, what are the available options and likely outcomes, and how much patients care about these outcomes and what are they able do in order to get it (Schwartz et al., 2011).

Additionally, the doctor-patient relationship has been characterized by informational asymmetries, as doctors have relevant information about the disease and treatment options, information that the patient lacks. Traditionally, patients' packages inserts have constituted citizens´ first source of written information on their drug treatment. However, most patients feel the information provided does not meet their needs due to poor legibility of written information, information that is not provided in the context of their illness and that there is often a lack of complementary information, for example on how the drug compares to other alternatives (Fuchs et al., 2006; Raynor et al., 2007; March Cerdá et al., 2010). In addition, easily accessible and accurate information is lacking, making it difficult to expect patients to make informed decisions about their treatment.

Today, the availability of healthcare information on the internet offers access to unlimited resources. The use of internet resources among citizens is without doubt increasing. A recent US survey suggests that one third of patients use social media for healthcare purposes (PwC, 2012). This should potentially bring the opportunity to reduce some of these informational gaps, complement the information provided by the doctor and promote patients autonomy to support decision making. (Bauschke, 2012; Hartzband et al., 2011; Romano et al., 2012). Nevertheless, although generic searches in Google have proved to be helpful to doctors for diagnosis, from the patients perspective this is more controversial (Tang et al., 2006). As we have discussed previously, the availability of more information does not necessarily mean more informed patients. The quality of drug information is variable and some patients lack the knowledge to fully discriminate among the sources. Although quality independent drug information exists, it can be difficult to find and there are concerns that easily accessed "information" might be masking direct commercial interests (Greene et al., 2010).

Europe is facing an additional challenge. Between 2001 and 2011, the pharmaceutical industry attempted to amend the European Union ban on 'direct to consumer advertising' (DTCA) of prescription drugs which has generated a great debate (Brooks et al., 2012). The effect of DTCA on both patients and doctors has been well studied in the only two countries, United States and New Zealand, where it is not banned. DTCA influences patient medicines demand, especially of new drugs, and affects doctors' prescribing behavior, but evidence of health benefits or improvements in underuse are lacking (Magrini et al., 2007). The debate surrounding this law amendment evolved from the initial strategy of eliminating the DTCA ban to a campaign on the provision first of "drug information" and now "health information". Beyond a semantic problem, it seems the continuous growth in internet and social media use is transforming traditional marketing strategies and thus it is likely that the next debate on "health information" could be held in the deregulated context of the World Wide Web (Brooks et al., 2012).

Traditionally MIC have mainly focused on providing service for healthcare professionals. In fact, the number of drug information centers exclusively devoted to patient information services is scarce, and to our knowledge may be just limited to the drug information center in Dresden (Goltz, 2012). Some centers may have found mixed formulas. Two regional centers in Spain, one in Catalonia and the other in the Basque Country, have opened drug information strategic lines for patients. Similarly some NHS centers in the UK collaborate directly with patient healthcare organizations in order to provide support to patient centered organizations (Cartwright, 2011).

Considering that regulatory agencies have failed to produce public, accurate, relevant drug information for patients and that both patients and organizations demand independent quality information to support decision making, MIC have the opportunity, but also the responsibility, to lead independent drug information for patients. This may be particularly true in Europe where changes in drug information for patients have recently been introduced and in the new scenario the role of regulatory bodies and health authorities cannot be limited to monitoring the "health information" that the pharmaceutical industry provides to

citizens (Font, 2011). While patients lack access to public accurate information on drug treatments, the role of MIC should be to direct citizens to quality drug information on the internet, to collaborate in the development of written information in traditional formats like leaflets tailored to individual illness or support the development and dissemination of new patients' decision tools to support shared decision making. In the partnership culture, information about the benefits and risks of the treatment and the development of tools for shared decision making is crucial for those patients seeking to make informed choices about their healthcare that take into account their personal values and preferences. Two interesting initiatives have been developed in this line, decision aids and drugs facts boxes. Decision aids describe the decision to be taken, the options available and the outcomes of this options based on the evidence (DTB, 2012b). A Cochrane review found that decision aids improve knowledge, help to have realistic expectations and enhance active participation in decision making (O'Connor et al., 2003). On the other hand, the drug facts box is standardized one page tables summarizing prescription drug benefits and risks specifically designed to highlight information from clinical trials that is usually missing in drug advertisements. Drug facts boxes are intuitive, are understood even by those with limited formal education and have demonstrated increase knowledge of prescription drug benefits and side-effects. (Schwartz et al., 2011).

The internet and social media offers a huge potential not only to improve access to drug information and instruments, but to tackle specific patient groups too. Although health professionals might still be reluctant to the introduction of social networks in clinical practice, joining virtual communities such as ¨PatientsLikeMe¨ is becoming an increasingly popular phenomenon among patients. Through virtual communities, patients can contact other patients with same chronic conditions and share experiences, lending support and promoting personal autonomy (Gené Badia et al., 2009). For example, after the publication in 2008 of a small study in Italy suggesting that lithium could slow the progression of amyotrophic lateral sclerosis, 149 members of "PatientsLikeMe" began taking the drug and started to use a new tool with a matching algorithm

to conduct a patient-lead observational study whose negative results were published in record time in Nature Biotechnology (Wicks et al., 2011).

d) Providing better value drug information

Some of the activities in the drug information processes tend to be replicated in different centers and, to a certain extent, information needs do not vary that much among MIC regardless of its territorial organization. We can use for example dabigatran, the new oral anticoagulant. When its second licensed indication for the prevention of systemic embolism for patients with non-valvular atrial fibrillation was approved, cardiologists, hematologists, biochemists, primary care physicians, pharmacists, policy makers, patients and citizens wanted to know whether it was worthwhile to switch patients on warfarin to dabigatran. They needed to know what benefits it offered, the risks that would have to be assumed and at what cost. In response, centers produced their own information, which meant that at least part of the information was inefficiently duplicated. Drug information processes are complex and very time consuming, thus, it should make us reflect on how we can reduce duplicities and inefficiencies in order to provide better value drug information service.

Some of the strategies that MIC can implement are: facilitate the coordination among centers in order to avoid duplicities, work in network to establish synergies and build strategic partnerships in order to maximize efforts while increasing efficiency and productivity. Additionally MIC are required to augment the coherence in their recommendations. A recent study by Puigventós and colleagues shows, for example, variability in the decisions taken on formulary additions by different Pharmacy and Therapeutics Committees in Spain, where in only 81% of the cases, the decisions taken coincided (Puigventós et al., 2011). Thus, collaboration and/or networking would be expected to not only contribute to provide a more efficient service and better value healthcare, but also to increase the concordance in many of the decisions about drug treatments taken among centers.

Network experiences have proved to be successful in various drug information areas. The United Kingdom was a pioneer in creating UKMi, an integrated network of local and regional of MIC providing an infrastructure of collective knowledge and skills that has consolidated UKMi as a reference in drug information (Calder et al., 1981; UKMi, 2007). The network is coordinated nationally whilst remaining locally based as it promotes responsiveness to local needs. There are similar network experiences at lower organizational levels. For example the regional Catalan MIC was conceived as a network of primary care and hospital based centers that were already active in the region. This enables centers to continue with their routine activities but at the same time work, share and stay in close contact with other centers that are geographically distant. These strategies are usually internet based, however, research show that there might be value in having a venue or space that encourages knowledge sharing (Kothari et al., 2011).

The introduction of economies of scale in the drug evaluation process has been implemented in new drug assessment committees as well as in drug information bulletins when the International Society of Drug Bulletins was constituted. (Aizpurua, 2007; Diego, 2009a). Working in networks offers undoubtedly the advantage of operational efficiency, standardization of processes, reduced variation in the decisions taken and cost reductions. On the other hand, taking advantage of economies of scale can potentially imply reducing the number of centers. It is worth noting that a drastic reduction in the number of centers may at the same time increase the impact of their reports, which would exploit the oligopoly power of the new structure. Under such circumstances, independence in published reports could be compromised and would require additional efforts from health authorities and regulators to preserve the quality, and more importantly, the impartiality of drug information provided. In any case, drug information networks require a solid structure that provides vision, sets standards and promotes integrity and cohesion, as these systems add complexity to an already complex process.

Although some of the activities carried by MIC may be duplicated, there are others that necessarily have to stay local. All in-house enquiries in a hospital

could hardly be resolved from and outside center. The resolution of enquires is considered a valuable service by users, yet is very time consuming and the work behind it is not fully exploited given that the answer is usually only addressed to the enquirer.

Nevertheless, with the development of new technologies MIC should find new pathways to share this information that may be valuable to others. It is generally the case that most enquires received in one centre are similar to those received in others. In order to reduce duplicities, or at least maximize efforts, MIC could collectively feed and share repository of clinical questions. Some enquires may be related to a specific patient or test results and might not benefit others. However, there are many enquires that can be considered of general interest like *what benefits offer newer oral hipoglycemiants over already existing ones?.* Aside from sharing enquires among drug information specialists, centers should increase the dissemination of general interest enquires. In that respect, UKMi for example publishes a selection of their clinical question through the New Electronic Library of Medicines in the Q&A section. In Catalonia, the regional MIC has an *on-line* application where enquires are received and replied privately. However, when considered appropriate, enquires can automatically be selected for publication in an open library and this information can be accessed by any healthcare professional. Another alternative is to publish regularly a selection of clinical questions in field journals. Although these initiatives might be useful, undoubtedly they can be more easily implemented in countries with national health services or within large organizations where centers work under the same policies.

Finally, centers will have to take into consideration the capabilities of the service to assume new responsibilities or tasks. It is essential to maximize efforts, with MIC likely to find advantages in establishing strategic partnership when developing drug information for specific areas. These alliances have for example been implemented in patients´ drug information or advice on drug resources for the implementation of CDSS (Cartwright, 2011).

e) Improving knowledge on personalized medicine

The concept of drug information was introduced with the creation of the first MIC. The establishment of centers helped consolidate the role of pharmacists as drug information specialist. (Francke, 1966) Traditionally, this figure has required a number of skills: advanced understanding of therapeutics, biostatistics, critical information appraisal and clinical experience which is essential for clinical interpretation of results. However, recent advances in medicine require drug information specialist to increase their current knowledge on advanced therapies in order to continue to meet healthcare professionals´ drug information needs in the personalized medicine era.

A recent report over viewing pharmaceutical sciences in 2020, forecasts that the blockbusters model for drug discovery and development is unlikely to be sustainable. In the future, the arsenal of new drugs is expected to be a large niche with agents tailored to individual needs and each associated to smaller sales, (Shah et al., 2010).

Additionally, the completion of the Human Genome and International HapMap Projects, have facilitated the tools to identify and obtain information on the biochemical bases that constitute individual response. This has generated an unprecedented change in the paradigm on how science affronts diseases. In this new approach the management of the disease is tailored to individual characteristics of the patient (Kennedy et al., 2011; Andreu, 2012). In Pharmacotherapy this implies taking drug therapy decisions according to the individual characteristics of the patient such as genotype, gene expression or molecular profile (Cavallari et al., 2010). Thus, personalized medicine will offer newer opportunities to improve pharmacotherapy.

Pharmacogenomics is one the areas of personalized medicine that is expected to have more impact in the near future. While clinical factors are poor predictors of drug response, the increase in our understanding on how variations in a single gene (phamacogenetics) or the whole genome (pharmacogenomic) can help us to predict drug response in a more accurate manner. We now know that mutations or polymorphisms can determine differences in drug metabolism,

drug distribution, disease-associated proteins and drug target proteins affecting the variability in patients´ drug response (Cavallari et al., 2010). In line with this, the general application of diagnostics test will provide more specific diagnosis, which will help reducing the incidence of adverse effects. Thus, pharmacogenomics provides a new personalized approach to improve pharmacotherapy through the identification of patient-specific predictors of drug response and toxicities, which will aid in therapeutic decision making.

Several drugs have already been approved which include pharmacogenomic information. Two recent examples are vemurafenib, licensed for patients with metastatic cancer with mutations associated to BRAF, or telaprevir and boceprevir which use has been restricted to individuals with genotype-1 VHC infection. Additionally, several advances have been made in the optimization of drug therapy related to metabolic characteristics of the patients, for example on how polymorphisms have a considerable impact on for example mercapturine toxicity or warfarin dose required to obtain optimal anticoagulation. In fact, some of this information is already being incorporated in routine clinical practice through drug labeling, clinical guidelines, protocols or algorithms.

Considering personalized pharmacotherapy is closer to becoming a reality, several organizations have stressed the importance of increasing pharmacist knowledge on the advances made in genomics. The American College of Clinical Pharmacy has highlighted four such particular areas: personalized medicine concepts and terminology with a focus on genomics, genomic applications in basic and applied pharmaceutical sciences, biotechnology and bioinformatics (Cavallari et al., 2010).

As drug information specialists, it is crucial that MIC personnel improve their general knowledge on genomics and in particular on pharmacogenetics, genetic testing and its clinical interpretation, in order to continue to meet healthcare professionals' and patients' information needs and support decision making in the personalized pharmacotherapy era.

1. 6 Conclusion

The widespread availability of internet, especially now with high-speed internet and mobile devices, has facilitated the access to health information. In a context of increasing budgetary restrictions and in the absence of patient and economic outcome data on MIC activities, policy makers may be tempted to reduce funding or even consider that MIC services are expendable. On the contrary, the need for independent, relevant drug information has never been greater.

Despite the wide availability of information, physicians and other healthcare professionals still have drug information needs. Similarly, patients require access to a reliable source of information on the benefits and risks of drug treatments in order to make informed decisions. Nevertheless, it is true that information needs in today's context are clearly different to those when the first MIC was created 50 years ago and thus, the classic MIC model might need to be revised.

In particular, five areas for improvement have been identified. First, in order to continue meeting information needs centers have to provide concise and relevant drug information digested from the overwhelming amount of research and information published daily. Secondly, MIC should take a step forward and evolve from the simple provision of drug information to knowledge management services, i.e., use information and communication technologies to improve not only drug information dissemination, but to enhance communication among professionals and patients as well as knowledge sharing. Third, MIC have the opportunity, and responsibility, of leading independent patient information. Currently, accessible independent drug information to support shared decisions making is lacking. Thus, it is crucial that MIC facilitate access to quality information on the internet and provide information on the benefits and risks of drug therapy. They must collaborate in the development and promote the dissemination of newer drug information instruments to support decision making, such as decision aids or drug facts boxes. Fourth, MIC must provide a better value drug information service. This will imply promoting coordination, facilitating networks and establishing strategic partnerships with other relevant

institutions. The introduction of economies of scale to the drug information process can reduce duplicities, increase efficiency and productivity and moreover reduce variation in the recommendations provided. Finally, drug information specialists will need to increase their knowledge of the advances made in the area of personalized medicine in order to provide valuable support for decision making in the personalized pharmacotherapy era.

Finally, despite the inherent difficulties in quantifying monetary savings, it is crucial to understand that better informed healthcare professionals and patients alike make better informed therapeutic decisions. Thus, 50 years on, there is still potential to continue developing medicines information centers to manage medicines effectively and contribute to healthcare sustainability.

Chapter 2

Methylnaltrexone: a Novel Approach for the Management of Opioid-Induced Constipation in Patients with Advanced Illness.

Laura Diego
Rabia Atayee
Pieter Helmons
Charles von Gunten

Expert Rev Gastroenterol Hepatol. 2009;3(5):473-85.

Diego L, Atayee R, Helmons P, von Gunten CF. Methylnaltrexone: a novel approach for the management of opioid-induced constipation in patients with advanced illness. Expert Rev Gastroenterol Hepatol. 2009; 3(5):473-85.

Chapter 3

Novel Opioid Antagonists for Opioid-Induced Bowel Dysfunction.

Laura Diego
Rabia Atayee
Pieter Helmons
Grace Hsiao
Charles von Gunten

Expert Opin Investig Drugs. 2011; 20(8):1047-56

Diego L, Atayee R, Helmons P, Hsiao G, von Gunten CF. Novel opioid antagonists for opioid-induced bowel dysfunction. Expert Opin Investig Drugs. 2011; 20(8):1047-56

BIBLIOGRAPHY

Adolor Corporation. Press Release: (ADLR) to stop development of bowel dysfunction drug. 18 December **2008**.

Adolor Corporation. Press release: Adolor Corporation initiates clinical testing in opiod bowel dysfunction program. 12 December **2009**.

Adolor Corporation. Press release: Adolor Corporation initiates phase 2 OIC study of ADL5945. 19 October **2010**.

Adams P. Evaluation of Welsh Drug Information Services. PhD Thesis, University of Wales **1992**.

Ahn N, Alonso Meseguer J, Herce San Miguel JA. Gasto sanitario y envejecimiento de la población española. **2003**. Documento de Trabajo n7.Madrid: Fundación BBVA.

Aizpurua I. Spanish Bulletins work together: ISDB Newsletter July **2007**.

Andreassen HK, Bujnowska-Fedak MM, Chronaki CE, Dumitru RC, Pudule I, Santana S, et al. European citizens' use of E-health services: a study of seven countries. BMC Public Health. **2007**; 7: 53.

Andreu T. La medicina personalizada: Una nueva forma de entender la medicina. CedimCat. **2012**. In Press.

Angell M. Is academic medicine for sale? N Engl J Med. **2000**; 324(20): 1516-8.

Aparasu R, McCoy RA, Weber C, Mair D, Parasuraman TV. Opioid-induced emesis among hospitalized nonsurgical patients: effect on pain and quality of life. J Pain Symptom Manage. **1999**; 18(4): 280-8.

Bauschke R. Regulatory agencies, pharmaceutical information and the Internet: a European perspective. Health Policy. **2012**; 104(1): 12-8.

Becker G, Blum HE. Novel opioid antagonists for opioid-induced bowel dysfunction and postoperative ileus. Lancet. **2009**; 373(9670): 1198-206.

Bekelman J, Li Y, Gross C. Scope and impact of financial conflicts of interest in biomedical research. JAMA. **2003**; 289(4): 454-65.

Bell TJ, Panchal SJ, Miaskowski C, Bolge SC, Milanova T, Williamson R. The prevalence, severity, and impact of opioid-induced bowel dysfunction: results of a US and European Patient Survey (PROBE 1). Pain Med. **2009**; 10:35-42.

Berde C, Nurko S. Opioid side effects - mechanism-based therapy. N Engl J Med. **2008**; 358: 2400-2.

Bero L, Galbraith A, Rennie, D. The publication of sponsored symposiums in medical journals. N Engl J Med. **1992**; 327(16): 1135-40.

BNF. British National Formulary (57th Edition). British Medical Association and Royal Pharmaceutical Society of Great Britain, London, UK: Pharmaceutical Press; **2009**.

Bond CA, Raehl CL, Franke T. Clinical pharmacy services and hospital mortality rates. Pharmacotherapy. **1999**; 19(5): 556-64.

BPS. British Pain Society. Opioids for persistent pain: good practice. London: The British Pain society; **2010**.

Bright TJ, Wong A, Dhurjati R, Bristow E, Bastian L, Coeytaux RR, et al. Effect of clinical decision-support systems: a systematic review. Ann Intern Med. **2012**; 157(1): 29-43.

Brooks E, Geyer R. From DTCA-PD to patient information to health information: the complex politics and semantics of EU health policy. J Eval Clin Pract. **2012**; In Press.

Calder G, Davies JS, McNulty H, Smith JC. Drug information network in the United Kingdom National Health Service. Am J Hosp Pharm. **1981**; 38(5): 663-6.

Campora E, Merlini L, Pace M, Bruzzone M, Luzzani M, Gottlieb A, et al. The incidence of narcotic-induced emesis. J Pain Symptom Manage. **1991**; 6(7): 428-30.

Cardoni AA, Thompson TJ. Impact of drug information services on patient care. Am J Hosp Pharm. **1978**; 35(10): 1233-7.

Cartwright R. Providing medicines information for patients & public. II Jornada de Colaboración de Centros de Información de Medicamentos. Barcelona; **2011**.

Catalan A, Borrell F, Amado E, Baena JM, Bendaham G, Galvan L et al. Prescripció farmacèutica segura (PREFASEG). Annals de Medicina. **2011**; 94(1): 2-3.

Cavallari LH, Overholser BR, Anderson D, Boyce E, Buie L, Formea CM et al. Recommended Basic Science Foundation Necessary to Prepare Pharmacists to Manage Personalized Pharmacotherapy. Pharmacotherapy. **2010**; 30(6): 228e–235e.

CBO. Congressional Budget Office. Technological change and the growth of healthcare spending. The Congress of the United States; **2008**. Pub. No. 2764.

Chauhan NS, Firdous , Raveendra R, Geetha J , Gopalakrishna B, Karki R. Drug Information Centre (DIC)-An Indian Scenario. Indian Pharm Pract. **2009**; 1(2): 21-27.

Cherny N, Ripamonti C, Pereira J, Davis C, Fallon M, McQuay H, et al. Strategies to manage the adverse effects of oral morphine: an evidence-based report. J Clin Oncol. **2001**; 19: 2542-54.

Cherny NI. The pharmacological management of cancer pain. Eur J Cancer. **2001**; 37 Suppl 7: S265-78.

Choi YS, Billings JA. Opioid antagonists: a review of their role in palliative care, focusing on use in opioid-related constipation. J Pain Symptom Manage. 2002; 24(1): 71-90.

ClinicalTrials.gov. Available from: www. Clinicaltrials.gov.

Coleman JJ, McDowell SE. The potential of the internet. Br J Clin Pharmacol. **2012**; 73(6): 953-8.

Collett BJ. Opioid tolerance: the clinical perspective. Br J Anaesth. **1998**; 81(1):58-68.

Coombe R, Schaefer M. National PBM Drug Monograph: Alvimopan (Entereg). **2009**. Available from: www.pbm.va.gov [Last accessed: 25 January 2011]

Coulter A. Paternalism or partnership? Patients have grown up-and there's no going back. BMJ. **1999**; 319(7212): 719-20.

Coulter A, Collins A. Making shared decision-making a reality: no decision about me, without me. **2011.** Available from: http://www.kingsfund.org.uk/publications/nhs_decisionmaking.html. [Last accessed: 18 August 2012].

Delaney CP, Weese JL, Hyman NH, Bauer J, Techner L, Gabriel K, et al. Phase III trial of alvimopan, a novel, peripherally acting, mu opioid antagonist, for postoperative ileus after major abdominal surgery. Dis Colon Rectum. **2005**; 48: 1114-25.

Delaney CP, Wolff BG, Viscusi ER, Senagore AJ, Fort JG, Du W, et al. Alvimopan, for postoperative ileus following bowel resection: a pooled analysis of phase III studies. Ann Surg. **2007**; 245: 355-63.

Detmer DE. Building the national health information infrastructure for personal health, health care services, public health, and research. BMC Med Inform Decis Mak. **2003**; 3:1.

De Schepper HU, Cremonini F, Park MI, Camilleri M. Opioids and the gut: pharmacology and current clinical experience. Neurogastroenterol Motil. **2004**; 16(4): 383-94.

Diego L, Catalán A, Amado E. "New Drug Assessment Network". Health Policy Monitor, March **2009 (a)**. Available at: http://www.hpm.org/survey/es/a13/3. [Last accessed: 24 August 2012]

Diego L, Atayee R, Helmons P, Von Gunten CF. Methylnaltrexone: a novel approach for the management of opioid-induced constipation in patients with advanced illness. Expert Rev Gastroenterol Hepatol. **2009 (b)**; 3: 473-85.

Djulbegovic B. Lifting the fog of uncertainty from the practice of medicine. BMJ. **2004**; 329(7480): 1419 -1420.

Dornan T, Ashcroft D, Heathfield H, Lewis P, Miles J, Taylor D, et al. An in depth investigation into causes of prescribing errors by foundation trainees in relation to their medical education. EQUIP study. December **2009**. Available at http://www.gmc-uk.org/about/research/research_commissioned_4.asp. [Last accesed: 11 June 2012]

DTB. Drug and Therapeutics Bulletin. Targinact - opioid pain relief without constipation? Drug Ther Bull. **2010**; 48: 138-41.

DTB. Drug and Therapeutics Bulletin. PPIs: too much of a good thing? Drug Ther Bull. **2011**; 49(5): 49.

DTB. Drug and Therapeutics Bulletin. The future of independent drug bulletins. **2012 (a)**; 50(6): 61.

DTB. Drugs and Therapeutics Bulletin. An introduction to patient decision aids. Drug Ther Bull. **2012 (b)**; 50(8): 90-2.

Duerden M, Weil A, Yu D, Schulman MS, Tzanis E, Manley A, et al. Subcutaneous methylnaltrexone improves bowel movement frequency and quality in patients with chronic non-malignant pain and opioid induced constipation. Journal of Pain. **2010 (a)**; 11(4): S46.

Duerden M, Weil A, Yu D, Schulman S, Tzanis E, Zhang, et al. Subcutaneous methylnaltrexone for the treatment of opioid-induced constipation in patient with chronic non-malignant pain: safety results in patients treated for 12 weeks. Journal of Pain. **2010 (b)**; 11(4): S50.

e-Health Initiative. Electronic Prescribing: Toward Maximum Value and Rapid Adoption, Washington, DC. April **2004**.

Ely JW, Osheroff JA, Ebell MH, Bergus GR, Levy BT, Chambliss ML, et al. Analysis of questions asked by family doctors regarding patient care. BMJ. **1999**; 319:358-61.

Ely JW, Osheroff JA, Chambliss ML, Ebell MH, Rosenbaum ME. Answering physicians' clinical questions: obstacles and potential solutions. J Am Med Inform Assoc. **2005**;12(2):217-24.

EMA. The European Medicines Agency Assessment report for Relistor. **2008**. Available from: www.emea.europa.eu/humandocs/PDFs/EPAR/relistor/H-870-en6.pdf. [Last accessed: 25 January 2009].

Eysenbach G. Medicine 2.0: Social Networking, Collaboration, Participation, Apomediation and Openness. J Med Internet Res**. 2008**; 10(3):e22.

FDA REMS. FDA-approved Risk Evaluation and Mitigation Strategies (REMS). Available from: www.fda.gov/cder/drug/DrugSafety/REMS.htm. [Last accessed: 25 March 2009]

FIP. International Pharmaceutical Federation. Requirements for drug information centers. Available at: http://www.fip.org/files/fip/PI/RequirementsforDrugInformationCentres.pdf. [Last accessed: 12 August 2012]

Francke DE. The role of the pharmacist as a drug information specialist. Am J Hosp Pharm. **1966**; 23(2): 49.

Font M. Publicidad de Medicamentos Directa al Consumidor: Situación Actual en Europa. In: II Jornada de Colaboración de Centros de Información de Medicamentos. Barcelona; **2011**.

Foppe van Mil. Assessing the impact of drug information on hospital and community care. In European Society of Clinical Pharmacy Special Interest Group for Drug Information - mini symposium during ACCP-ESCP Conference. Orlando;**1999**.

Foss JF, Bass AS, Goldberg LI. Dose-related antagonism of the emetic effect of morphine by methylnaltrexone in dogs. J Clin Pharmacol. **1993**; 33: 747-51.

Foss JF, O'Connor MF, Yuan CS, Murphy M, Moss J, Roizen MF. Safety and tolerance of methylnaltrexone in healthy humans: a randomized, placebo-controlled, intravenous, ascending-dose, pharmacokinetic study. J Clin Pharmacol. **1997**; 37(1): 25-30.

Foss JF, Yuan CS, Roizen MF, Goldberg LI. Prevention of apomorphine - or cisplatin-induced emesis in the dog by a combination of methylnaltrexone and morphine. Cancer Chemother Pharmacol. **1998**; 42: 287-91.

Fuchs J, Hippius M, Schaefer M. Analysis of German package inserts. Int J Clin Pharmacol Ther. **2006**; 44(1): 8-13.

Fuentes Quintana E, Barea Tejeiro J. El déficit público de la democracia española. Papeles de Economía Española **1996**; 68: 86-191.

Fugh-Berman A, Ahari S. Following the script: how drug reps make friends and influence doctors. PLoS Med. **2007**; 4(4):e150.

Gale S, Croasdell G. 28th Annual JPMorgan Healthcare Conference-Exelixis and Nektar Therapeutics. I Drugs. **2010**; 13: 139-41.

Galligan JJ, Vanner S. Basic and clinical pharmacology of new motility promoting agents. Neurogastroenterol Motil. **2005**;17(5):643-53.

Gené Badia J, Grau I Sánchez E, Bernardo M. Forumclínic: the virtual community for chronic patients. Journal of Health Innovation and Integrated Care. **2009**; 1: 1.

Glare P, Lickiss JN. Unrecognized constipation in patients with advanced cancer: a recipe for therapeutic disaster. J Pain Symptom Manage. **1992**; 7(6): 369-71.

Glaxo SmithKline and Adolor. Press release: GlaxoSmithKline and Adolor report top line results from Phase 3 studies of Alvimopan (Entereg/Entrareg®). 5 September **2006.**

Glaxo SmithKline and Adolor. Press release: GSK and Adolor announce preliminary results from Phase 3 Safety study of Alvimopan (Entereg/Entrareg). 9 April **2007**.

Glover JA. The incidence of tonsillectomy in children. Proc R Soc Med. **1938**; 31(10): 1219-36.

Goltz L, Kirk W. The independent drug information service, Dresden, Germany in its 10th anniversary year. Int J Clin Pharmacol Ther. **2012**; 50(8): 618-19.

González-González AI, Dawes M, Sánchez-Mateos J, Riesgo-Fuertes R, Escortell-Mayor E, et al. Information needs and information-seeking behavior of primary care physicians. Ann Fam Med. **2007**; 5(4): 345-52.

Greene JA, Kesselheim AS. Pharmaceutical marketing and the new social media. N Engl J Med **2010**; 363(22): 2087-2089.

Hands D, Stephen M, Brown D. A systematic review of the clinical and economic impact of drug information services on patient outcome. Pharm World Sci. **2002**; 24(4): 132-8.

Hartzband P, Groopman J. Untangling the Web - Patients, doctors and the internet. N Engl J Med. **2010**; 362: 1063-6.

Haynes B. Bridging the gap between the Cochrane Collaboration and clinical practice. Plenary presentation. 12th Cochrane Colloquium, Ottawa, **2004**.

Herndon CM, Jackson KC, Hallin PA. Management of opioid-induced gastrointestinal effects in patients receiving palliative care. Pharmacotherapy. **2002**; 22: 240-50.

Herzog TJ, Coleman RL, Guerrieri JP Jr, Gabriel K, Du W, Techner L, et al. A double-blind, randomized, placebo-controlled phase III study of the safety of alvimopan in patients who undergo simple total abdominal hysterectomy. Am J Obstet Gynecol. **2006**; 195: 445-53.

Ho WZ, Guo CJ, Yuan CS, Douglas SD, Moss J. Methylnaltrexone antagonizes opioid-mediated enhancement of HIV infection of human blood mononuclear phagocytes. J Pharmacol Exp Ther. **2003**; 307(3): 1158-62.

Holzer P. Opioid receptors in the gastrointestinal tract. Regul Pept. **2009**; 155: 11-17.

Holzer P. Opioid antagonists for prevention and treatment of opioid-induced gastrointestinal effects. Curr Opin Anaesthesiol. **2010**; 23:616-22.

IOM. Institute of Medicine. To Err Is Human: Building a Safer Health System Washington, D.C., National Academy Press; **2000**.

IOM. Institute of Medicine. Crossing the Quality Chasm: A New Health System for the 21st Century Washington, D.C., National Academy Press; **2001**.

IOM. Institute of Medicine. Committee on Identifying and Preventing Medication Errors. Quality Chasm Series. Preventing Medication Errors. Washington, DC: Institute of Medicine, National Academies Press; **2007**.

Jackson T. Are you being duped ? BMJ. **2001**; 322: 1312.

Johanson JF, Morton D, Geenen J, Ueno R. Multicenter, 4-week, double-blind, randomized, placebo-controlled trial of lubiprostone, a locally-acting type-2 chloride channel activator, in patients with chronic constipation. Am J Gastroenterol. **2008**; 103(1): 170-7.

Johnell K, Fastbom J, Rosén M, Leimanis A. Inappropriate drug use in the elderly: a nationwide register-based study. Ann Pharmacother. **2007**; 41(7): 1243-8.

Juárez Giménez JC, Puyal González C, Valdivia Vadella C, Palacio Lacambra ME, Vidal Otero J, Cerqueira Dapena MJ. Application of the Technology Web 2.0 in a Drug Information Centre. Farmacia Hospitalaria. 2011; 35(6): 315.e1–315.e5.

Katz D, Caplan A, Merz J. All gifts large and small: toward and understanding of the ethics of pharmaceutical industry gift giving. Am J Bioethics The American Journal of Bioethics. **2003**; 3(3): 39-46.

Kendall M, Enright D. Provision of medicines information: the example of the British National Formulary. Br J Clin Pharmacol. **2012**; 73(6): 934-8.

Kennedy MJ, Phan H, Benavides S, Potts A, Sorensen S. The role of the pediatric pharmacist in personalized medicine and clinical pharmacogenomics for children: pediatric pharmacogenomics working group. J Pediatr Pharmacol Ther. **2011**; 16(2): 118-22.

Kinky DE, Erush SC, Laskin MS, Gibson GA. Economic impact of a drug information service. Ann Pharmacother. **1999**; 33(1): 11-6.

Kothari A, Hovanec N, Hastie R, Sibbald S. Lessons from the business sector for successful knowledge management in health care: a systematic review. BMC Health Serv Res. **2011**; 11:173.

Kozma CM, Reeder CE, Schulz RM. Economic, clinical, and humanistic outcomes: a planning model for pharmacoeconomic research. Clin Ther. **1993**; 15(6): 1121-32.

Kraft MD. Methylnaltrexone, a new peripherally acting mu-opioid receptor antagonist being evaluated for the treatment of postoperative ileus. Expert Opin Investig Drugs. **2008**; 17: 1365-77.

Kromer W. Endogenous and exogenous opioids in the control of gastrointestinal motility and secretion. Pharmacol Rev. **1988**; 40(2): 121-62.

Leach FN. The regional drug information service: a factor in health care? BMJ. **1978**; 1(6115): 766-8.

Lexchin J. Interactions between physicians and the pharmaceutical industry: what does the literature say? CMAJ. **1993**; 149(10): 1401-7.

Lexchin J. What information do physicians receive from pharmaceutical representatives? Can Fam Physician. **1997**; 43: 941-5.

Lexchin J, Bero LA, Djulbegovic B, Clark O. Pharmaceutical industry sponsorship and research outcome and quality: systematic review. BMJ. **2003**; 326(7400): 1167-70.

Liss H. Publication bias in the pulmonary/allergy literature: effect of pharmaceutical company sponsorship. Isr Med Assoc J. **2006**; 8(7): 451-4.

Liu M, Wittbrodt E. Low-dose oral naloxone reverses opioid-induced constipation and analgesia. J Pain Symptom Manage. **2002**; 23: 48-53.

Longstreth GF, Thompson WG, Chey WD, Houghton LA, Mearin F, Spiller RC. Functional bowel disorders. Gastroenterology. **2006**; 130(5): 1480-91.

Lowenstein O, Leyendecker P, Hopp M, Schutter U, Rogers PD, Uhl R, et al. Combined prolonged-release oxycodone and naloxone improves bowel function in patients receiving opioids for moderate-to-severe non-malignant chronic pain: a randomised controlled trial. Expert Opin Pharmacother. **2009;** 10: 531-43.

Magrini N, Font M. Direct to consumer advertising in Europe. BMJ. **2007**; 335(7619): 526.

March Cerdá JC, Prieto Rodríguez MA, Ruiz Azarola A, Simón Lorda P, Barrio Cantalejo I, Danet A. Quality improvement of health information included in drug information leaflets. Patient and health professional expectations. Aten Primaria. **2010**; 42(1): 22-7.

McNicol ED, Boyce D, Schumann R, Carr DB. Mu-opioid antagonists for opioid-induced bowel dysfunction. Cochrane Database Syst Rev. **2008**; (2): CD006332.

Mehendale SR, Yuan CS. Opioid-induced gastrointestinal dysfunction. Dig Dis. **2006**; 24(1-2): 105-12.

Meissner W, Leyendecker P, Mueller-Lissner S, Nadstawek J, Hopp M, Ruckes C, et al. A randomised controlled trial with prolonged-release oral oxycodone and naloxone to prevent and reverse opioid-induced constipation. Eur J Pain. **2009**; 13: 56-64.

Melnyk PS, Shevchuk YM, Remillard AJ. Impact of the dial access information service on patient outcome. Ann Pharmacother. **2000**; 34(5):585-92.

Merrill RA. Regulation of drugs and devices: an evolution. Health Aff (Millwood).**1994**; 13(3): 47-69.

Miles CL, Fellowes D, Goodman ML, Wilkinson S. Laxatives for the management of constipation in palliative care patients. Cochrane Database Syst Rev. **2006**; (4): CD003448.

Moerman I, Franck P, Camu F. Evaluation of methylnaltrexone for the reduction of postoperative vomiting and nausea incidences. Acta Anaesthesiol Belg. **1995**; 46: 127-32.

Mold JW, Stein HF. The cascade effect in the clinical care of patients. N Engl J Med. **1986**; 314(8): 512-4.

Moss J, Rosow CE. Development of peripheral opioid antagonists' new insights into opioid effects. Mayo Clin Proc. **2008**; 83: 1116-30.

Moya Garrido M, Nieto Rodríguez MT, Laínez Sanchez MM, Mingorance Ballesteros M, Recalde Manrique JM. Estudio para la identificación y diseño de líneas de cooperación entre los centros de información de medicamentos españoles. Granada: Escuela Andaluza de Salud Pública; **2010**.

Moynihan R. Who pays for the pizza? Redefining the relationships between doctors and drug companies. 1: Entanglement. BMJ. **2003**; 326(7400): 1189-92.

Moynihan R. Independent drug watchdog in Canada under funding threat. BMJ **2008**; 336: 1270.2.

MSC. Ministerio Sanidad y Consumo. Estudio APEAS. Estudio sobre la seguridad de los pacientes en atencion primaria de salud. Madrid: Ministerio de Sanidad y Consumo; **2008.**

Muir Gray JA. Canadian clinicians and patients need clean, clear knowledge. CMAJ. **2006**; 175(2): 129,131.

Mulley AG. Inconvenient truths about supplier induced demand and unwarranted variation in medical practice. BMJ. **2009**; 339: b4073.

Najabat M, Bowey J, Hands D, Brown D. Drug information and patient care. Pharm World Sci.**1999**; 21 Suppl.: A8.

Nektar Therapeutics. Nektar R&D Pipeline Products. Available from: www.nektar.com/product_pipeline/ clinical_trials.html**.**

Nektar Therapeutics. Press release: Nektar Announces Positive Results from Phase 2 Study of Oral NKTR-118 in Patients with Opioid-Induced Constipation (OIC). 2nd March **2009**.

Neumann TA, Van Paaschen H, Marcantonio A, Song Di, Morrison PJ, Eldon MA ,et al. Clinical investigation of NKTR-118 as a selective oral peripheral opioid antagonist. In: American Academy of Pain Management 18th Annual Clinical Meeting: September 27–30, **2007(a)**; Las Vegas, NV.

Neumann TA, Van Paaschen H, Marcantonio A, Song D, Kugler AR, Eldon MA. Evaluation of PEG-Naloxol (NKTR-118) as an oral peripheral opioid antagonist in healthy male subjects: a Double-Blind, Placebo-Controlled, Dose Escalation Crossover Study. In: American College of Clinical Pharmacology 36th Annual Meeting: September 9–11, **2007(b)**; San Francisco, CA.

UKMi. Effective information for managing medicines. National Health Service; **2007**.

OECD. Health care systems: Getting more value for money. **2010**. OECD Economics Department Policy Notes, No. 2.
OECD/European Union. Health at a Glance: Europe **2010**. OECD Publishing; 2010.

Osheroff JA, Forsythe DE, Buchanan BG, Bankowitz RA, Blumenfeld BH, Miller RA. Physicians' information needs: analysis of questions posed during clinical teaching. Ann Intern Med. **1991**; 114(7): 576-81.

O'Connor AM, Stacey D, Entwistle V, Llewellyn-Thomas H, Rovner D, et al. Decision aids for people facing health treatment or screening decisions. Cochrane Database Syst Rev **2003**;(2): CD001431.

Odinecs A, Song Y, Harite S, et al. NKTR-118, an oral peripheral opioid antagonist, has low potential for drug-drug interactions. 2011. In: ACCP 38th Annual Meeting September 13–15, **2009**; San Antonio, TX.

Panchal SJ, Muller-Schwefe P, Wurzelmann JI. Opioid-induced bowel dysfunction: prevalence, pathophysiology and burden. Int J Clin Pract. **2007**; 61: 1181-7.

Pappagallo M. Incidence, prevalence, and management of opioid bowel dysfunction. Am J Surg. **2001**; 182: 11S-18S.

Parker PF. The University of Kentucky drug information center. Am J Hosp Pharm. **1965**; 22: 42-7.

Paulson DM, Kennedy DT, Donovick RA, Carpenter RL, Cherubini M, Techner L, et al. Alvimopan: an oral, peripherally acting, mu-opioid receptor antagonist for the treatment of opioid-induced bowel dysfunction a 21-day treatment-randomized clinical trial. J Pain. **2005**; 6: 184-92.

Pla R, García M, Martín A, Porta A. Información de Medicamentos. In: Gamundi Planas MC: Farmacia Hospitalaria Tomo I; **2002**. 507-540.

Portenoy RK. Constipation in the cancer patient: causes and management. Med. Clin. North Am. **1987**; 71(2): 303-11.

Portenoy RK, Thomas J, Moehl Boatwright ML, Tran D, Galasso FL, Stambler N, et al. Subcutaneous methylnaltrexone for the treatment of opioid-induced constipation in patients with advanced illness: a double-blind, randomized, parallel group, dose-ranging study. J Pain Symptom Manage. **2008**; 35(5): 458-68.

Prescrire. Key opinion leaders: used as a marketing tool by drug companies. Prescrire Int. **2012**; 21(128): 163-5.

Progenics Inc. Press release: phase 3 Clinical Study of RELISTOR presented at American Pain Society Meeting Showed Positive Activity for the Treatment of Opioid-Induced Constipation in Chronic, Non-Cancer Pain Patients. Progenics. 7 May **2009**.

Progenics Inc. Press release: Progenics Announces Clinical Completion of Subcutaneous Methylnaltrexone Safety Study in Chronic Non-Malignant Pain Patients. Progenics. 21 September **2010(a)**.

Progenics Inc. Press Release: Progenics pharmaceuticals initiates oral methylnaltrexone phase 3 trial in patients with chronic non-cancer pain. Progenics. 8 September **2010(b)**.

Prosser H, Almond S, Walley T. Influences on GPs' decision to prescribe new drugs the importance of who says what. Fam Pract. **2003**; 20(1): 61-8.

Puigventós Latorre F, Santos-Ramos B, Ortega Eslava A, Durán-García M.E. Variabilidad en la actividad y los resultados de la evaluación de nuevos medicamentos por las comisiones de farmacia y terapéutica de los hospitales en España. Farm Hosp. **2011**; 35: 305-14.

PwC. Pricewaterhouse Coopers. Top health industry issues of 2012. Pricewaterhouse Coopers; **2011**.

Rahmner PB, Eiermann B, Korkmaz S, Gustafsson LL, Gruvén M, Maxwell S et al. Physicians' reported needs of drug information at point of care in Sweden. Br J Clin Pharmacol. **2012**; 73(1): 115-25.

Raynor DK, Blenkinsopp A, Knapp P, Grime J, Nicolson DJ, Pollock K, et al. A systematic review of quantitative and qualitative research on the role and effectiveness of written information available to patients about individual medicines. Health Technology Assessment. **2007**; (11): 5.

Rodwin MA, Abramson JD. Clinical Trial Data as a Public Good. JAMA. **2012**; 2308(9): 871-2.

Roemer, M.I. Bed supply and hospital utilization: a natural experiment. Hospitals. **1961**; 35: 36-42.

Romano M, Gesualdo F, Pandolfi E, Tozzi AE, Ugazio A. Use of the internet by Italian pediatricians: habits, impact on clinical practice and expectations. BMC Med Inform Decis Mak. **2012**; 12: 23.

Rosenberg JM, Schilit S, Nathan JP, Zerilli T, McGuire H. Update on the status of 89 drug information centers in the US. Am J Health Syst Pharm. **2009**; 66(19): 1718-22.

Rosow CE, Gomery P, Chen TY, Stefanovich P, Stambler N, Israel R. Reversal of opioid-induced bladder dysfunction by intravenous naloxone and methylnaltrexone. Clin Pharmacol Ther. **2007**; 82(1): 48-53.

Saad R, Chey WD. Lubiprostone for chronic idiopathic constipation and irritable bowel syndrome with constipation. Expert Rev Gastroenterol Hepatol. **2008**; 2(4): 497-508.

Shah VP, Besancon LJ, Stolk P, Tucker G, Crommelin DJ. The pharmaceutical sciences in 2020: report of a conference organized by the board of pharmaceutical sciences of the International Pharmaceutical Federation (FIP). Pharm Res. **2010**; 27(3): 396-9.

Schifrin LG, Tayan JR. The drug lag: an interpretive review of the literature. Int J Health Serv. **1977**; 7(3): 359-81.

Schmidt WK. Alvimopan* (ADL 8-2698) is a novel peripheral opioid antagonist. Am J Surg **2001**; 182: 27S-38S.

Schwartz LM, Woloshin S. Making informed decisions about prescription drugs possible. In: Gigerenzer G, Muir Gray JA. Better doctors, better patients, better decisions. Envisioning health care 2020. Cambridge (MA): MIT Press; **2011**. 233-242.

Seidling HM, Schmitt SP, Bruckner T, Kaltschmidt J, Pruszydlo MG, Senger C, et al. Patient-specific electronic decision support reduces prescription of excessive doses. Qual Saf Health Care. **2010**; 19(5): e15.

Senagore AJ. Pathogenesis and clinical and economic consequences of postoperative ileus. Am J Health Syst Pharm. **2007**; 64: S3-7.

Simpson K, Leyendecker P, Hopp M, Müller-Lissner S, Löwenstein O, De Andrés J, et al. Fixed-ratio combination oxycodone/naloxone compared with oxycodone alone for the relief of opioid-induced constipation in moderate-to-severe noncancer pain. Curr Med Res Opin. **2008**; 24: 3503-12.

Slatkin N, Thomas J, Lipman AG, Wilson G, Boatwright ML, Wellman C, et al. Methylnaltrexone for treatment of opioid-induced constipation in advanced illness patients. J Support Oncol. **2009**; 7: 39-46.

Smith R. Medical journals and pharmaceutical companies: uneasy Bed fellows. BMJ. **2003**; 326(7400):1202-5.

SmPC Relistor®: summary of product characteristics.

SmPC Entereg®: summary of product characteristics.

Stacey D, Bennett CL, Barry MJ, Col NF, Eden KB, Holmes-Rovner M, et al. Decision aids for people facing health treatment or screening decisions. Cochrane Database Syst Rev. **2011**; (10): CD001431.

Stubbington C, Bowey J, Hands D, Brown D. Drug Information replies to queries involving adverse events: impact on clinical practice. Hosp Pharm. **1998**; 5: 81-4.

Sucampo Pharmaceuticals. News release: sucampo completes enrollment in Phase 3 pivotal studies of oral lubiprostone to treat opioid-induced bowel dysfunction Phase 3 efficacy data expected in summer 2009. 2 December **2008**.

Sykes NP. Oral naloxone in opioid-associated constipation. Lancet **1991**; 337:1475

Sykes NP. An investigation of the ability of oral naloxone to correct opioid-related constipation in patients with advanced cancer. Palliat Med. **1996**; 10: 135-44.

Sykes NP. The relationship between opioid use and laxative use in terminally ill cancer patients. Palliat Med. **1998**; 12(5): 375-82.

Tan EK, Cornish J, Darzi AW, Tekkis PP. Meta-analysis: Alvimopan vs. placebo in the treatment of post-operative ileus. Aliment Pharmacol Ther. **2007**; 25:47-57.

Tang H, Ng JH. Googling for a diagnosis - use of Google as a diagnostic aid: internet based study. BMJ. **2006**; 333(7579):1143-5.

Theravance. Press release: Theravance Announces Initiation of Proof of Concept Phase 2 Clinical Study with its PUMA Compound, TD-1211, for the Treatment of Opioid-Induced Constipation. 14 April **2010**.

Thomas JR, Von Gunten CF. Management of constipation in patients with cancer. Support Cancer Ther. **2004**; 2: 47-51.

Thomas J. Opioid-induced bowel dysfunction. J Pain Symptom Manage. **2008**; 35:103-13.

Thomas J, Karver S, Cooney GA, Chamberlain BH, Watt CK, Slatkin NE, et al. Methylnaltrexone for opioid-induced constipation in advanced illness. N Engl J Med. **2008**; 358: 2332-43.

Tumwikirize AW, Ogwal-Okeng JW, Vernby A, Anokbonggo WW, Gustafsson LL, Lundborg CS. Use of a pilot drug information centre. African Health Sciences. **2011**; 11: 493 – 498

Wazana A. Physicians and the pharmaceutical industry, is a gift ever just a gift? JAMA. **2000**; 283: 373-80.

Van Paaschen H, Sahner D, Marcantonio A, Eldon MA. Results from a phase 1, double blind, randomized, placebo-controlled, multiple-dose study evaluating the safety, tolerability and pharmacokinetics of oral doses of NKTR-118. **2008**. Available from: http://www.nektar.com/pdf/pipeline/NKTR-118/NKTR-118_Phase_1_APS_Poster_20080507.pdf [Last accessed: 20 august 2012]

Viscusi ER, Goldstein S, Witkowski T, Andonakakis A, Jan R, Gabriel K, et al. Alvimopan, a peripherally acting mu-opioid receptor antagonist, compared with placebo in postoperative ileus after major abdominal surgery: results of a randomized, double-blind, controlled study. Surg Endosc. **2006**; 20: 64-70.

Viscusi ER, Rathmell JP, Fichera A et al. Methylnaltrexone bromide administered postoperatively to patients following segmental colectomy may accelerate bowel recovery and hospital discharge without affecting opioid analgesia. Presented at: Gastrointestinal Cancers Symposium 2007. Orlando, FL, USA, 19–21 January **2007**.

Webster L, Jansen JP, Peppin J, Lasko B, Irving G, Morlion B, et al. Alvimopan, a peripherally acting mu-opioid receptor (PAM-OR) antagonist for the treatment of opioid-induced bowel dysfunction: results from a randomized, double-blind, placebo-controlled, dose-finding study in subjects taking opioids for chronic non-cancer pain. Pain. **2008**; 137: 428-40.

Webster L, Dhar S. NKTR-118 significantly reverses opioid-induced constipation. In 20th AAPM Annual Clinical Meeting; 10 October **2009**; Phoenix, AZ.

Webster L, Jansen JP, Peppin J, Lasko B, Irving G, Morlion B, et al. Alvimopan, a peripherally acting mu-opioid receptor (PAM-OR) antagonist for the treatment of opioid-induced bowel dysfunction: results from a randomized, double-blind, placebo-controlled, dose-finding study in subjects taking opioids for chronic non-cancer pain. Pain. **2008**; 137: 428-40.

Weil A, Duerden M, Schulman S, Tzanis E, Yu D, Manley A, et al. Subcutaneous methylnaltrexone does not affect pain intensity and analgesic use in patients with chronic non-malignant pain and opioid-induced constipation. Journal of Pain. **2010**; 11(4): S46

Wennberg JE, Barnes BA, Zubkoff M. Professional uncertainty and the problem of supplier-induced demand. Soc Sci Med. **1982**; 16(7): 811-24.

Wicks P, Vaughan TE, Massagli MP, Heywood J. Accelerated clinical discovery using self-reported patient data collected online and a patient-matching algorithm. Nat Biotechnol. **2011**; 29(5): 411- 4.

Willcox SM, Himmelstein DU, Woolhandler S. Inappropriate drug prescribing for the community-dwelling elderly. JAMA. **1994**; 272(4): 292–296.

Wolff BG, Michelassi F, Gerkin TM, Techner L, Gabriel K, Du W, et al. Alvimopan, a novel, peripherally acting mu opioid antagonist: results of a multicenter, randomized, double-blind, placebo-controlled, phase III trial of major abdominal surgery and postoperative ileus. Ann Surg. **2004**; 240: 728-34.

Wolff BG, Weese JL, Ludwig KA, Delaney CP, Stamos MJ, Michelassi F, et al. Postoperative ileus-related morbidity profile in patients treated with alvimopan after bowel resection. J Am Coll Surg. **2007**; 204: 609-16.

Wood JD, Galligan JJ. Function of opioids in the enteric nervous system. Neurogastroenterol Motil. **2004**;16 Suppl 2:17-28.

Wyeth and Progenics. Press release: Wyeth and Progenics announce relistor receives Canadian marketing approval. 1 April **2008(a).**

Wyeth and Progenics. Press release: Wyeth and Progenics announce preliminary clinical trial results for Relistor oral and intravenous formulations. 22 May **2008(b).**

Wyeth and Progenics. Press release: Wyeth and Progenics provide update on Phase 3 clinical trial of intravenous methylnaltrexone for postoperative ileus. 12 March **2008(c).**

Yousef SH. Evaluation and cost control of the Welsh Drug Information Centre. MPhil thesis, University of Wales, **1994.**

Yuan CS, Foss JF, O'Connor M, Toledano A, Roizen MF, Moss J. Methylnaltrexone prevents morphine-induced delay in oral-cecal transit time without affecting analgesia: a double-blind randomized placebo-controlled trial. Clin Pharmacol Ther. **1996**; 59(4): 469-75.

Yuan CS, Foss JF, Osinski J, Toledano A, Roizen MF, Moss J. The safety and efficacy of oral methylnaltrexone in preventing morphine-induced delay in oral-cecal transit time. Clin Pharmacol Ther. **1997**; 61(4): 467-75.

Yuan CS, Foss JF, O'Connor M, Osinski J, Karrison T, Moss J, et al. Methylnaltrexone for reversal of constipation due to chronic methadone use: a randomized controlled trial. JAMA. **2000**; 283(3): 367-72.

Yuan CS, Foss JF, O'Connor M, Osinski J, Roizen MF, Moss J. Efficacy of orally administered methylnaltrexone in decreasing subjective effects after intravenous morphine. Drug Alcohol Depend. **1998**; 52(2): 161-5.

Yuan CS. Methylnaltrexone mechanisms of action and effects on opioid bowel dysfunction and other opioid adverse effects. Ann Pharmacother. **2007**; 41: 984-93.

Zeinali F, Stulberg JJ, Delaney CP. Pharmacological management of postoperative ileus. Can J Surg. **2009**; 52: 153-7.

Annex 1

Editorials

Annex 1

Editorial 1

Política de Nuevos Medicamentos: Calidad y Seguridad

Ester Amado Guirado
Laura Diego
Rosa Madridejos Mora

Aten Primaria. 2011;43(6):279-80.

Amado Guirado E, **Diego L**, Madridejos Mora R.

Política de nuevos medicamentos: calidad y seguridad.

Aten Primaria. 2011; 43(6): 279-80.

Annex 1

Editorial 2

Mejorar la Calidad Asistencial no Implica Financiar Públicamente Cualquier Medicamento.

Ester Amado Guirado
Laura Diego
Vicente Ortún

Aten Primaria. 2012; 44(4): 187-9.

Amado Guirado E, **Diego L**, Ortún V. Mejorar la calidad asistencial no implica financiar públicamente cualquier medicamento. Aten Primaria. 2012; 44(4): 187-9.

Annex 2

Drug information bulletins

Full text available from:

Diego L. Novetats terapèutiques 2009 (I). BIT. 2009; 21(7): 37-42
Diego L. Novetats terapèutiques 2009 (II). BIT. 2009; 21(10): 55-60.
Diego L. Novetats terapèutiques 2010 (I). BIT. 2010; 22(7): 41-47.
Diego L. Novetats terapèutiques 2010 (II). BIT. 2010; 22(10): 66-73.
Diego L, Robert L. Novetats terapèutiques 2011 (I). BIT. 2011; 22(5): 25-33
Diego L, Robert L. Novetats terapèutiques 2011 (II). BIT. 2011; 22(10): 56-63
Diego L, Robert L. Novetats terapèutiques 2012 (I). BIT. 2012; 23(6): 32-39