# Considerations on preventable drug-related morbidity in Primary Care

## Part I – Impact of preventable drug-related morbidity

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*ABSTRACT*

*Objective: To review the evidence on the magnitude and implications of preventable drug-related morbidity in primary care.*

*Methods: Multiple formats were used to systematically search the literature on preventable drug-related morbidity (PDRM) in primary care. We looked for studies in adults examining avoidable morbidity caused by primary care usage of drugs. Nine electronic databases were searched and references of retrieved papers scanned. In an attempt to find Portuguese data we conducted a hand-search in a Portuguese journal and mailed requests to experts.*

*Results: More than 100 articles were identified as potentially relevant. False positives included studies investigating inpatients and papers not providing quantitative estimates for preventability of drug-related morbidity. References that met our inclusion criteria were subsequently divided into reviews and original articles. Given the space available for this work original articles were excluded where relevant reviews had been published. Preventable drug-related hospital admissions are the most well studied issue (n=5 meta-analytic reviews), followed by preventable drug-related emergency department visits (n=1 systematic review); little is known about preventable drug-related morbidity that is managed in primary care facilities (n=3 original studies). We found evidence that PDRM resulting in hospitalisation is a common problem; less serious drug-related injuries appear to be even more frequent. More than half of drug-related hospitalisations are avoidable (if drug-related morbidities other than ADRs are considered); data suggests that more severe events are the most likely to be preventable. Reviews on the costs of drug-related injuries (n=2) show that management of PDRM consumes significant resources.*

*Conclusions: PDRM may be a leading cause of hospital admissions in industrialised countries. A large proportion of drug-related morbidity is avoidable. The economic implications of PDRM are so great that even expensive interventions to tackle this problem may be cost-effective.*

**Key-Words:** *Morbidity; Primary Care; Safety; Therapy; Preventability; Costs.*

### INTRODUÇÃO

It has been suggested that drug-related morbidity in primary care in developed countries is a significant problem, causing considerable human suffering and economic waste. North-American and British Government policy documents on patient safety and medical errors, although more focused on secondary care, have acknowledged the existence of similar problems in primary care[1;2].

The literature is prolific in descriptions of negative clinical outcomes of drug therapy, such as adverse drug reactions and adverse drug events.

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Since no standard terminology is available the same term may be used with different meanings. An adverse drug reaction (ADR) is generally regarded as an "unintended response" to a drug occurring at the doses normally used in clinical practice[3]; this definition excludes unapproved indications and inappropriate doses. An adverse drug event (ADE) is a broader concept, encompassing other than normal doses and patient injuries caused by errors in the way the drug is used[4]. The term drug-related morbidity[4] has the widest scope, including not only drug-induced injuries, but also the outcomes of non treatment (failure to prescribe a needed drug, failure to dispense or non adherence) and under-treatment (lack of effectiveness). In fact, although ADRs are by far the most recognized negative clinical outcome of drug-therapy, adverse outcomes of non-treatment and ineffectiveness may be more prevalent than safety injuries[5].

A proportion of drug-related morbidity is unavoidable and its occurrence has to be accepted as part of the risk--benefit considerations for drug usage. For example, idiosyncratic reactions (such as Stevens-Johnson syndrome in a patient on allopurinol) cannot be predicted, and may account for 20% of medication related illness which result in hospital admissions[6]. However, awareness has been raised about the preventability of many negative clinical outcomes of drug therapy. Interestingly, the problem is not new, as shown by a medical journal editorial in 1971, where the author wrote: "If most drug reactions resulted from hypersensitivity, idiosyncrasy or the inevitable risk assumed when toxic drugs are used... one could lament the facts, being powerless to change them. However... 70 to 80 percent are predictable. Most of these are preventable without compromise of the therapeutic benefits of the drug"[7].

Drug-related morbidity is not necessarily an unavoidable hazard nor should it be regarded as an inevitable price patients and the society have to pay for the benefits of drug-therapy. *Preventable* drug-related morbidity (PDRM) represents a waste of resources for the health care system and an *unnecessary* loss of health and quality of life for the patient.

PDRM can be reduced with changes in practice. It has been suggested this requires a shift to a new paradigm, which takes into consideration the complexity of the medication-use process in primary care, acknowledging that adverse events commonly result from more than one failure in a system comprised of several components: equipment, people and procedures[8].

This paper is part of a series of two papers on considerations on preventable drug-related morbidity in primary care. In this first article we aim to review the evidence on the magnitude and implications of preventable drug-related morbidity in this setting. We divided the present work into two main sections. The first section presents the epidemiology of PDRM in primary care, while the second section is devoted to the burden of PDRM to the healthcare system. The next paper will address the causes of PDRM and possible strategies to alleviate this problem, focusing on the system level.

## METHODS

For the purpose of this review drug-related morbidity is used as a general term for negative clinical outcomes of drug-therapy, comprising ADRs, ADEs, non treatment and under-treatment. Preventability was considered as defined in each study by the authors.

Systematic searches were conducted in nine databases:

1. Medline (1996 to 11/2003)
2. EMBASE (1996 to 11/2003)

3. CINAHL (1982 to 11/2003)
4. SIGLE (1980 to 11/2003)
5. Lilacs (1982 to 11/2003)
6. Cochrane Library
7. Science Citation Index (1981 to 11/2003)
8. Pharm-line (1978 to 11/2003)
9. e-Pic (1992 to 11/2003)

The criteria for searching are presented in Table I. Publications in languages other than English were considered in order to minimize the "English language bias". Various iterations and combinations of free vocabulary terms and controlled vocabulary terms were used for identifying studies, with the aid of advanced search options. The titles and abstracts of identified references were reviewed for inclusion by one of the authors. References were entered into Reference Manager Software version 10. Potentially relevant articles were obtained in full. The literature search was then expanded by scanning the bibliographies of retrieved papers.

A hand search was conducted in *Revista Portuguesa Clínica Geral* (RPCG), from 1984 to 03/2004).

In an attempt to overcome the absence of Portuguese literature on the topic a letter was sent in March 2004 to four Portuguese individuals identified on the basis of their expertise in iatrogenic disease associated with medicines usage. Experts were asked for references of published or unpublished literature on PDRM in Portugal.

Data were summarised by a single reviewer by means of data extraction forms.

**TABLE I**

**CRITERIA FOR CONSIDERING STUDIES FOR PDRM REVIEW**

**Inclusion criteria**
Studies in English, Portuguese, Spanish or French
Studies examining preventable drug-related morbidity in primary care or caused by primary care prescribing/usage of drugs
Studies in adults

**Exclusion criteria**
Studies on drug related-morbidity in secondary care
Studies not providing quantitative estimates of preventability
Studies on drug-related mortality
Studies in children

## RESULTS

More than 100 articles were identified by the search strategy as potentially relevant; the majority of them originated from electronic searches. The hand search in RPCG did not reveal any relevant studies. Response to the information requests was obtained from two experts, leading to the identification of one Portuguese study on adverse drug reactions in primary care[9]. After analysis of the full papers the major reason for rejecting an article was its focus on hospital setting; other false positives included studies not assessing preventability. The remaining references were subsequently divided into two groups: reviews (systematic and meta-analytic) and original articles. For the purpose of this paper original articles were excluded where relevant reviews had been published. Furthermore, studies were classified in one of the three following categories: PDRM managed in primary care facilities, PDRM leading to emergency department visits and PDRM causing hospital admissions.

Studies on drug-related hospital admissions have attracted more interest, since these have a greater clinical, economic and humanistic impact both at a patient and system-level. However, drug-related hospital admissions provide an incomplete picture of the phenomenon, as many patients who experience PDRM might visit primary care facilities or emergency departments, and do not necessarily require hospitalisation.

On these grounds it was chosen to include the first two categories of studies in the present review.

## Epidemiology of preventable drug-related morbidity (PDRM) in primary care

### A) PDRM IN PRIMARY CARE FACILITIES

Ghandi and colleagues[10] conducted a 17-month retrospective observational study in 11 US ambulatory clinics. The medical records of 2858 randomly selected patients (20–75 years old) were reviewed and the patients surveyed by telephone on aspects such as health care utilisation and drug complications within the past year. ADEs identified on chart review by a trained nurse were verified by a physician; the causality and severity of ADEs was further established by one physician-reviewer. Patient reported drug-complications were cross-checked with the Physicians' Desk Reference (PDR), an authoritative drug information source. Chart review revealed a 3% incidence of ADEs but 18% of the patients reported drug complications, less than half of which were documented in the PDR. 13% of ADEs were previously recorded in the patient chart (allergy or other reaction to the causative drug) and therefore were deemed preventable by the authors. Only 48% of patients with problems or symptoms related to their prescribed medicines sought medical attention. 5% of the patients with an ADE required hospitalisation. The number of medical problems and failure to have side effects explained before treatment were independently correlated with patient reported drug complications. As expected, overall patient satisfaction with care was lower in patients who had experienced drug complications.

A more recent 7-month observational study by Ghandi and co-workers[11] in four US primary care practices surveyed 661 patients (19–100 years) by telephone in two points in time: about ten days after receiving a prescription and three months after the first inquiry. In addition medical records were reviewed at three months by a nurse; possible ADEs were then assessed by two independent physicians and classified in terms of severity and preventability. In this study[11] the term ADE was used for both patient reported and reviewer detected adverse events, probably because the prospective design enabled the collection of more detailed data to established causality based on patient information. About a quarter of the patients experienced an ADE (incidence of 27% per three months), of which 11% were judged preventable. Only a minority (28%) of the total number of ADEs was identified by reviewing charts. About a tenth (13%) of the ADEs considered serious led to hospitalisation or emergency department visits. The number of medications the patient took was a predictor of ADEs.

Gurwitz *et al*[12] carried out a 12--month retrospective observational study in the ambulatory clinical setting of US Medicare practice. 30397 patients (all Medicare enrolees, >65years) were screened for ADEs applying multiple methods, such as computer generated signals and review of administrative incident reports concerning medication errors; whenever a signal of drug-related incident was detected medical records were reviewed by four trained clinical pharmacists. Possible ADEs were then assessed by two independent physicians for causality, severity, preventability and effects on the patient. The overall rate of ADEs was 5% per year, about a quarter (27.6%) of which were preventable. Almost 40% of the ADEs identified were categorized as serious, life-threatening or fatal.

Medical record review by a qualified professional is generally considered the gold-standard for evaluation of the process of care. However, studies relying mostly on medical records are limited by their incompleteness, caused by not

recording and by lack of awareness of patients' medication[6]. For example, 500 medical records analysed by Maria *et al*[9] in the 12 months prior to the beginning of a study in Portugal showed no record of ADRs. Moreover, only a minor proportion of ADEs is identified from either the medical records or the patient[10;11], which illustrates the importance of combining sources of data.

Several approaches may be taken to the review of clinical data. Explicit review, such as applying the Naranjo criteria for ADRs[13], is almost rater independent; it yields highly reproducible results but clinical nuances may be overlooked[14]. In the other extreme is implicit review, where a judgement is made based on the reviewer's "knowledge, opinions and beliefs"[14]; this approach is greatly dependent on the reviewer proficiency and reproducibility tends to be poor. Structured implicit review attempts to capture the strengths of the two approaches described by guiding the reviewer without providing strict directions[14]. In addition, if more than one reviewer is used the procedure to reach a final decision on causality may vary from a consensus based decision to the exclusion of cases where discrepancies exist. Two of the studies reported previously[11;12] applied a sound methodology to assess possible ADEs, including measuring inter-rater agreement by kappa statistics and resolving disagreement by consensus.

It is noteworthy that all of the studies looked at drug-related morbidity in a narrow sense, considering only ADEs. Such an approach may underestimate the magnitude of the problem. Furthermore, the definition of preventability used in one of the studies[10] was extremely narrow, which may also underestimate the problem.

**B) PDRM CAUSING EMERGENCY DEPARTMENT (ED) VISITS**

Patel and Zed systematically reviewed the literature on drug-related ED visits[15]. Twelve observational studies covering almost a decade (1992-2001) were included in this work, with a predominance of North-American studies. Eight retrospective studies revealed a frequency of drug-related visits to ED from 0.41% to 10.6%, while prospective studies ranged from 4.3% to 28.1%. Hospitalisation subsequent to the ED visit varied between 8.6 and 24.2%. Only three studies assessed preventability; 52% to 70.4% of ED visits were deemed preventable. Women and elderly patients appear to be at greatest risk of drug-related visits to an ED[15].

Such a broad range of results may be explained by different study designs, samples, and procedures to assess causality between drug-therapy and the visit to an ED. Retrospective studies may underestimate the true frequency of medication related visits because of the incompleteness and or inaccuracy of medical charts[15]. In addition, some studies were concerned only with ADRs and non-compliance, while others assessed also injuries caused by untreated indications and lack of effectiveness. The focus of one study was older patients, which predictably will yield a higher estimate of drug-related ED visits compared to the whole adult population. The lowest frequency of drug-related ED visits (0.41%) was based on ADE diagnosis code in a US survey comprising data from 474 hospitals[15]. This improves external validity, by enabling a more representative sample; however internal validity is reduced, not only due to incompleteness of chart information but also by the subjective judgement of multiple physicians. The highest estimate of drug-related ED visits (28.1%) is yielded by a prospective study[15] which applied an intensive multidisciplinary detection method, included sequential patient interviews by a triage nurse, two pharmacists and a physician.

**C) PDRM CAUSING HOSPITAL ADMISSIONS**

Several meta-analyses on drug-related hospital admissions have been published[16-20]. The focus of some reviews is ADR related hospital admissions only[16-18] while others include other types of drug-related morbidity, such as therapeutic failure. These meta-analytic reviews are complementary, both in their approach to the literature and in the studies included. The fact that studies use an array of diverse methods and definitions makes direct comparisons among studies impossible. For instance, incidence is a measure sensitive to a specific time period, and therefore incidences calculated for different periods are not directly comparable.

Winterstein and co-workers[19] reviewed 15 studies from eight countries conducted over a period of almost 20 years (1980-1999). Trials not providing a quantitative estimate of preventability were excluded. The median prevalence of drug related hospital admissions (DRA) was 7.1% (Inter-quartile range [IQR] 5.7-16.2%) and over half of these were preventable (median 59%, IQR 50--73%). The authors chose not to compute meta-analytic summary estimates because study results were highly heterogeneous.

Alonso *et al*[20] reviewed 22 studies published between 1990 and 2000 from 12 countries; only seven studies assessed preventability. Incidence of drug--related hospital admissions had a median of 4.2% and a meta-analytic median of 7.2% (IQR 2.5-11.0%); more than half of drug-related morbidities were preventable (meta-analytic mean 57.5%, IQR 47.0-66.8%). The salient feature in these two reviews, which included studies with a broad definition of DRM, is that a large proportion of drug-related admissions is preventable.

Beijer and De Blaey[16] examined 68 observational studies on ADR related hospital admissions spanning almost 3 decades; of which 12 assessed preventability. They found a mean proportion of ADR related hospital admissions of 4.9±0.1% (mean±confidence interval), with just under a third being preventable (mean 28.9%±0.02%). As anticipated, the rates of hospital admissions secondary to ADRs are lower than those associated to a wider concept of drug--related morbidity. The lower preventability rate is not unexpected either, since only type A ADRs* are traditionally considered preventable whereas drug-related morbidities such as therapeutic failure and non treatment are potentially preventable. Muehlberger and collaborators[18] derived a median frequency of ADRs causing hospital admissions of 4.1% (IQR 2.5-5.9%), based on the review of 25 observational studies (1972--1996). Goettler and colleagues[17] worked on this review to estimated preventability; they found that about a third of ADR related hospital admissions were preventable (mean 35.4%±13.4%).

Studies pooled in these reviews have highly heterogeneous results, which is not surprising given the diversity of methodological approaches pursued. Several factors may account for this heterogeneity (Table II), whose discussion is out of the scope of this paper.

There are no reasons to believe that drug-related hospital admissions are a country-specific problem. Data were pooled from a number of countries, and

**TABLE II**

**STUDY CHARACTERISTICS THAT MAY AFFECT THE ESTIMATION PDRM CAUSING HOSPITAL ADMISSIONS**

- Type of ward
- Type of admissions sampled
- Type of hospital
- Subjects' age
- Type of drug-related morbidity considered
- Detection methods
- Definition and assessment of both causality and preventability

although there is a predominance of studies from Europe, the US and Australia even nations such as Iran and Lebanon appear not to be immune to this phenomenon. No apparent association exists between studies originated in the US and the prevalence of PDRM leading to hospitalisation[19]. Moreover, there is no evidence of improvement over time.

There seems to be an upward trend in the preventability rate for more severe drug-related injuries, since many studies on drug-related admissions and ED visits show higher estimates of preventability than studies on PDRM managed in primary care facilities. This is corroborated by work reported previously[12], which found that more serious adverse drug events are more likely to be preventable.

Results of the meta-analytic reviews are consistent in suggesting that PDRM in primary care is at least as significant as in hospital patients. The milestone Harvard Medical Practice Study, which analysed the incidence and types of adverse events in 51 randomly chosen hospitals in New York State in 1984, found that adverse events due to medical mismanagement occurred in 3.7% of hospitalised patients[22]; drug adverse events were a common class of injuries, representing about a fifth (0.7%) of all adverse events[22]. 69.6% of the events were judged preventable[23]. These findings were corroborated by the Utah and Colorado Medical Practice study in 1992[24].

No Portuguese data on *preventable* drug-related admissions were found (or other studies on PDRM in primary care). This may reflect limitations of the search strategy, or, more likely, the absence of such studies in Portugal. In addition, data sources that could be used to generate estimates of PDRM in primary care are either non-existent (e.g. litigation claims databases) or of unknown value (e.g. complaints data) in Portugal. Assuming international data is applicable to the Portuguese health system (Table III) it can be extrapolated that around 43000 patients per year are admitted to hospital with *preventable* drug-related morbidity in Portugal, i.e. approximately five patients unnecessarily admitted to hospital per hour. This estimate is purely theoretical, but highlights the fact that PDRM is likely to be at least as relevant as injuries caused by motor vehicle accidents in Portugal (4852 injured individuals, 2001 data)[25]. The latter problem, however, receives considerable attention from the public opinion and the Government, while PDRM has attracted little attention.

There is some agreement in the literature on the drugs most commonly associated with drug-related hospital admissions (Box 1); which may be proportional to drug usage in developed countries. As anticipated the drugs or

**TABLE III**

**ESTIMATE OF THE MAGNITUDE OF PREVENTABLE DRUG-RELATED MORBIDITY REQUIRING HOSPITAL ADMISSION IN PORTUGAL**

| | |
|---|---|
| Hospitalisations per year (2001)[31] | 117,3 hospitalisations per 1000 inhabitants<br>Portuguese population ≈ 10 000 000<br>in total ≈ 1 000 000 individuals hospitalised |
| Median prevalence of preventable drug-related hospital admissions[19] | 4.3% |
| Number of patients per year admitted to hospital due to PDRM | 43 000<br>(hospitalisations per year × prevalence) |

**BOX I**

**DRUG CLASSES FREQUENTLY IMPLICATED IN PREVENTABLE DRUG-RELATED HOSPITAL ADMISSIONS (ADAPTED FROM16;26)**

- Cardiovascular (including diuretics, cardiac glycosides and beta-blockers)
- NSAIDs and analgesics
- Psychotropics
- Antibiotics
- Antiplatelets
- Antiepileptics
- Hypoglycaemics

* The simplest classification of ADRs is into types A and B[21]. Type A reactions result from augmented responses to the pharmacological action of a drug (e.g hypoglycaemia with an antidiabetic agent), while type B reactions are often caused by immunological and pharmacogenetic mechanisms (e.g. aplastic anaemia with cloramphenicol).

drug classes involved more frequently in hospital admissions are broadly similar to the ones causing ED visits[15], since up to a quarter of ED visits can result in hospital admissions. In the Alonso review studies assessing non compliance and therapeutic failure as a cause of hospital admissions found that cardiovascular drugs (including diuretics), bronchodilatadors and antiepileptics were the drugs most commonly implicated, leading to hospitalisation due to uncontrolled heart failure, asthma or epileptic crisis. A more recent study[26] is consistent with these findings, indicating that loop diuretics, antiepileptics, corticosteroids, nitrates and insulin were the drug classes most commonly associated with PDRM due to adherence problems.

### COST OF PDRM IN PRIMARY CARE

Several studies[17;20;27;28] have discussed the economic impact of adverse outcomes resulting from drug usage in primary care, focusing on its more serious side (hospital visit or stay). Original studies are not directly comparable because of differences in the definition of adverse drug outcome; many focus on ADRs only. Preventable drug-related injuries are consistently recognised as incurring more health care utilisation costs than non-preventable injuries[27;28], presumably due to the greater severity of the former[20].

The values yielded by pharmacoeconomic analysis differ according to the perspective taken in a study. Generally studies perform economic evaluations from an institutional perspective; cost from the patient perspective is poorly explored. In a societal perspective all relevant costs of drug-related morbidity are considered. Direct costs consist of the value of additional health care resources needed to respond to DRM. Indirect costs are defined as the value of production lost to society and the individual, such as loss of productivity, absenteeism and lost wages, whereas intangible costs are related to loss of well-being for the individual, like forgone leisure time and stress, which is sometimes measured as quality of life[28]. Most studies have determined only direct costs of adverse drug outcomes, which probably reflects methodological problems in estimating indirect and intangible costs (e.g. employment status of the patient often unknown, reduction of health related quality of life is difficult to quantify)[17].

In a review Rodríguez-Mongió et al[27] concluded that ED visits without hospitalisation cost the hospital $US 329-422 per adverse drug event, while treating an episode that leads to hospital admission has an estimated average cost of $US 3066 (2000 values). This cost varies from one country to another and the type of event studied.

Johnson and Bootman[27] developed a conceptual model of drug-related morbidity and mortality to assess costs from a provider perspective in US ambulatory care. The cost-of-illness model considers drug-related morbidity and mortality as a disease. Based on this proba-

bility pathway model it was estimated that drug-related morbidity and mortality cost US$ 76.6 billion in 1994, with drug-related hospital admissions accounting for about 62% of the total cost. The comparison of this figure with the annual expenditure on drug-therapy for the same year (US$73 billion) yields the popular dollar-for-dollar rule: for every dollar spent on ambulatory medications in primary care another dollar is spent to treat new health problems caused by the medication[27]. This conceptual model relied on an expert panel to define the incidence of ADEs and the proportion of patients that as a consequence would require different types of healthcare services, and not on original studies. The figures generated have been criticised as excessive[27] and this model is not directly applicable to countries other than the US, because of differences in health care systems. Nonetheless, this study has brought public attention to the fact that drug-related morbidity and mortality is a financial burden to the healthcare system. Recently an updated study using the same model revealed that the cost of drug-related morbidity and mortality exceeded US$177.4 billion in the year 2000; the cost had more than doubled in about five years[27].

Although data on the cost-efficiency of interventions to reduce PDRM appears not to be available, the magnitude of potential savings (estimated for ADRs only) suggests that any intervention will be cost-efficient even if a considerable sum of money is spent[17].

### Limitations of the literature review methodology

One of the strong points of our review is the comprehensive perspective we took, by including studies examining avoidable morbidity from drug usage in primary care facilities and leading to hospital visit or stay. Nevertheless, the review deals with two major limitations: publication bias and unpublished data. The former is defined as the trend journals have to publish articles with "positive or interesting" conclusions, failing to publish studies with "negative or unremarkable" results[29]; researchers tend not to submit "negative articles" either. The impact of publication bias can be estimated as small if high quality published work is both large in number and consistent in results. In spite of methodological weaknesses there is a considerable body of literature on drug-related morbidity in primary care, especially on ADRs; studies consistently point to the existence of an important problem with high preventability rates. Unpublished data may assume several formats, such as accessible final reports and studies with poor quality, negative or uninteresting results[29]. The last ones are often referred as "grey literature"[30]. In order to minimize the potential impact of unpublished data SIGLE, a database for Information on the grey literature, was searched.

This review can be described as a mapping exercise; a critical appraisal of the studies will be discussed in future work.

## CONCLUSION

PDRM may be a leading cause of hospital admission in developed countries. Less serious avoidable drug-related injuries, which cause visits to emergency departments or primary health care centres, appear to be even more common. In an era where economic resources are scarce given the skyrocketing health expenditure, the cost implications of PDRM deserve serious attention.

The evidence available should encourage extensive research on strategies to reduce the risk of PDRM, and not simply at characterising this problem.

## REFERENCE LIST


1. Kohn LT, Corrigan JM, Donaldson MS, editors. To err is human: building a safer health system. Washington DC: National Academy of Sciences, 1999.

2. Department of Health. An organisation with a memory. London: The Stationery Office, 2000.

3. World Health Organisation: Technical Report no 498. Geneva: 1972. [as cited in reference 4]

4. Hepler CD, Segal R. Preventing medication errors and improving drug therapy outcomes. Boca Raton: CRC Press, 2003.

5. Baena MI. Problemas relacionados con los medicamentos como causa de consulta en el Servicio de Urgencias del Hospital Universitario Virgen de las Nieves de Granada; Tesis doctoral, Universidad de Granada, España [Spanish: Drug-related Problems as a cause of emergency department visit at the University Hospital Virgen de las Nieves in Granada; Doctoral thesis, University of Granada, Spain]. 2003.

6. Atkin PA, Veitch PC, Veitch EM, Ogle SJ. The epidemiology of serious adverse drug reactions among the elderly. Drugs Aging 1999; 14(2): 141-52.

7. Melmon KL. Preventable drug-reactions: causes and cures. New Engl J Med 1971; 284: 1361. [as cited in reference 4]

8. Reason JT. Understanding adverse events: the human factor. In: Vincent C, editor. Clinical risk management - enhancing patient safety. London: BMJ Books, 2001.

9. Maria VAJ, Carvalho ML, Pimpão MV, Azevedo JS, Carreira MA, Victorino RMM. Estudo clínico-epidemiológico de reacções adversas a medicamentos em cuidados de saúde primários [Portuguese: Clinical-epidemiological study of adverse drug reactions in primary healthcare]. Arquivos do Instituto Nacional de Saúde 1988; XIII: 145-72.

10. Gandhi TK, Burstin HR, Cook EF, Puopolo AL, Haas JS, Brennan TA et al. Drug complications in outpatients. J Gen Intern Med 2000; 15(3): 149-54.

11. Gandhi TK, Weingart SN, Borus J, Seger AC, Peterson J, Burdick E et al. Adverse drug events in ambulatory care. New Engl J Med 2003; 348(16): 1556-64.

12. Gurwitz JH, Field TS, Harrold LR, Rothschild J, Debellis K, Seger AC et al. Incidence and preventability of adverse drug events among older persons in the ambulatory setting. JAMA 2003; 289(9): 1107-16.

13. Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA et al. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther 1981; 30(2): 239--45.

14. Ashton CM, Kuykendall DH, Johnson ML, Wray NP. An empirical assessment of the validity of explicit and implicit process-of-care criteria for quality assessment. Med Care 1999; 37(8): 798-808.

15. Patel P, Zed PJ. Drug-related visits to the emergency department: How big is the problem? Pharmacotherapy 2002; 22(7): 915-23.

16. Beijer HJM, De Blaey CJ. Hospitalisations caused by adverse drug reactions (ADR): A meta-analysis of observational studies. Pharm World Sci 2002; 24(2): 46-54.

17. Goettler M, Schneeweiss S, Hasford J. Adverse drug reaction monitoring—cost and benefit considerations. Part II: cost and preventability of adverse drug reactions leading to hospital admission. Pharmacoepidemiol Drug Saf 1997; 6 Suppl 3: S79-S90.

18. Muehlberger N, Schneeweiss S, Hasford J. Adverse drug reaction monitoring—cost and benefit considerations. Part I: frequency of adverse drug reactions causing hospital admissions. Pharmacoepidemiol Drug Saf 1997; 6 Suppl 3: S71-S77.

19. Winterstein AG, Sauer BC, Hepler CD, Poole C. Preventable drug-related hospital admissions. Ann Pharmacother 2002; 36(7-8): 1238-48.

20. Alonso HP, Otero Lopez MJ, Maderuelo Fernandez JA. Ingresos hospitalarios causados por medicamentos: incidencia, características y coste [Spanish: Drug-induced hospital admissions: Incidence, characteristics and cost]. Farm Hosp 2002; 26(2): 77-89.

21. Beard K. Introduction. In: Anne Lee, editor. Adverse Drug Reactions. London: Pharmaceutical Press, 2001.

22. Bates DW. Frequency, consequences and prevention of adverse drug events. J Qual Clin Pract 1999; 19: 13-7.

23. Thomas EJ, Brennan TA. Errors and adverse events in medicine: an overview. In: Vincent C, editor. Clinical risk management - enhancing patient safety. London: BMJ Books, 2001.

24. Thomas EJ, Studdert DM, Burstin HR, Orav EJ, Zeena T, Williams EJ et al. Incidence and types of adverse events and negligent care in Utah and Colorado. Med Care 2000; 38(3): 261-71.

25. Instituto Nacional de Estatística. Indicadores estatísticos gerais - população e condições sociais - acidentes de viação. Dezembro 2001. www.ine.pt. 2002. Accessed on 22/02/2005.

26. Howard RL, Avery AJ, Howard PD, Partridge M. Investigation into the reasons for preventable drug related admissions to a medical admissions unit: Observational study. Qual Safe Health Care 2003; 12(4): 280-5.

27. Rodriguez-Monguio R, Otero MJ, Rovira J. Assessing the economic impact of adverse drug effects. Pharmacoeconomics 2003; 21(9): 623-50.

28. White TJ, Arakelian A, Rho JP. Counting the costs of drug-related adverse events. Pharmacoeconomics 1999; 15(5): 445-58.

29. Fink A. Conducting research literature reviews: from paper to the internet. USA: Sage, 1998.

30. Bowling A. Research methods in health - investigating health and health services. 2nd ed. Maidenhead: Open University Press, 2002.

31. Fragata J, Martins L. O Erro em Medicina - perspectivas do indivíduo, da organização e da sociedade [Portuguese: Error in Medicine: perspectives of the individual, the organisation and the society]. Coimbra: Almedina, 2004.

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***CONSIDERAÇÕES SOBRE MORBILIDADE EVITÁVEL RELACIONADA COM MEDICAMENTOS EM CUIDADOS PRIMÁRIOS***
***PARTE I – IMPACTE DA MORBILIDADE EVITÁVEL RELACIONADA COM MEDICAMENTOS***

***Objectivo:*** *Caracterizar a magnitude e implicações da morbilidade evitável relacionada com medicamentos em cuidados primários.*

***Metodologia:*** *A literatura sobre morbilidade evitável relacionada com medicamentos (MERM) em cuidados primários foi revista de forma sistemática utilizando vários métodos. Foram incluídos estudos que reportassem morbilidade evitável causada pelo uso de fármacos em adultos em cuidados primários. Pesquisaram-se nove bases de dados electrónicas e as bibliografias dos artigos obtidos. Para localizar dados portugueses procedeu-se a uma pesquisa manual numa revista de referência e enviaram-se pedidos de documentação a peritos.*

***Resultados:*** *Foram identificados mais de 100 artigos potencialmente relevantes. Entre os falsos positivos incluíam-se estudos que investigavam doentes hospitalizados e trabalhos que não quantificavam a evitabilidade da morbilidade relacionada com medicamentos. As referências que obedeciam aos critérios de inclusão foram divididas em revisões e estudos originais. Dado o espaço disponível para este trabalho os estudos originais foram excluídos quando existiam revisões publicadas. O tópico mais bem estudado são os internamentos hospitalares evitáveis causados por medicamentos (n=5 revisões meta-analíticas), seguido de artigos sobre visitas evitáveis à urgência hospitalar causadas por medicamentos (n=1 revisão sistemática). Conhece-se pouco sobre morbilidade evitável relacionada com medicamentos tratada em cuidados primários (n=3 estudos originais). Existe evidência de que a MERM grave, responsável por internamento hospitalar, é um problema comum; formas menos graves de MERM parecem ser ainda mais frequentes. Mais de metade das hospitalizações causadas por medicamentos são evitáveis (quando se consideram outros tipos de morbilidade relacionada com medicamentos que não apenas reacções adversas medicamentosas). Os dados disponíveis sugerem que formas mais graves de MERM têm maior probabilidade de serem evitáveis. Revisões sobre o impacte económico deste fenómeno (n=2) mostram que o tratamento da morbilidade relacionada com medicamentos é responsável por um consumo significativo de recursos.*

***Conclusões:*** *A MERM pode ser uma das principais causas de internamento hospitalar nos países desenvolvidos. Uma proporção significativa dos casos de morbilidade relacionada com medicamentos é evitável. As implicações económicas da MERM têm tal magnitude que é possível que intervenções dispendiosas para combater este problema sejam custo-efectivas.*

**Palavras-Chave:** *Morbilidade; Medicamento; Cuidados Primários; Segurança; Evitabilidade; Custos*