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REVIEW ARTICLE

Off-label prescription: Practice and problems☆

António Vaz Carneiro*, **João Costa**

Centro de Estudos de Medicina Baseada na Evidência, Faculdade de Medicina, Universidade de Lisboa, Lisboa, Portugal

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Abstract Approval of a drug for clinical use requires production of data on efficacy and safety through submission of results from randomized controlled trials (RCTs), in which the new molecule is usually compared with placebo (or an active comparator) for a set of outcomes that will serve as the basis for the drug's indications. These indications are crucial, because drugs are approved on the basis of their net clinical benefit for specific and well-defined diseases and–importantly–only for these. Once the drug is available for use in tens or hundreds of thousands of patients, physicians may realize that some medications can be effective in diseases for which they were not approved, i.e., no studies have been presented to the regulatory authorities, and therefore they are not formally approved for those indications. Convinced of the benefits for their patients, some physicians prescribe them for unapproved indications–off-label prescription.

PALAVRAS-CHAVE
Prescrição *off-label*;
Eficácia e segurança de medicamentos;
Indicações medicamentosas;
Processos regulamentares de aprovação de medicamentos

A prescrição fora das indicações aprovadas *(off-label)*: prática e problemas

Resumo O processo de aprovação de medicamentos para uso clínico implica a produção de provas de eficácia e segurança através da submissão de resultados de ensaios clínicos, em que a nova molécula é comparada habitualmente ao placebo (ou a um comparador ativo) para um conjunto de resultados nos quais se baseará a determinação das indicações. As indicações são absolutamente cruciais, porque os fármacos são aprovados segundo o perfil de benefício/risco que apresentam para tratamento de patologias específicas, bem definidas e - um aspeto muito importante - apenas para estas. Uma vez estando o medicamento disponível para ser utilizado em dezenas ou centenas de milhares de doentes, acontece por vezes que, no decurso do seu uso regular e rotineiro, chega ao conhecimento dos médicos que certas moléculas podem ser eficazes em situações para as quais não foram aprovadas,

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* Corresponding author.
E-mail address: avc@fm.ul.pt (A. Vaz Carneiro).

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isto é, em que não foram apresentados estudos de suporte às autoridades regulamentares e que portanto não estão legalmente aprovadas para essas indicações. Convictos dos benefícios para os seus doentes, alguns médicos vão receitar medicamentos para indicações não aprovadas - a chamada prescrição *off-label*.

Neste artigo discute-se a prevalência da prescrição *off-label*, assim como as suas vantagens e inconvenientes.

Introduction

A drug is only used in clinical practice after a complex process of research and development that lasts on average 12-15 years, of which marketing authorization is the penultimate step. This is granted by the European Medicines Agency for all European countries. For such authorization to be given, evidence must be provided of efficacy and safety through submission of the results of phase 3 randomized controlled trials (RCTs), in which the new molecule is compared with placebo or an active comparator.

In most cases, the last step in the process is the adoption of the drug by national authorities for outpatient and/or hospital use. It is this step that, with rare exceptions, makes the drug available to patients. This decision is taken when the national authority (Infarmed in Portugal) makes a positive appraisal of the new drug's health and/or economic benefits (the latter through economic evaluation studies), compared to the alternative reference therapy used in clinical indications for the disease in question. Only if the new drug constitutes a therapeutic innovation – by filling a therapeutic gap when compared with placebo, no treatment or best supportive care – will it be adopted. A substance is not necessarily a therapeutic innovation simply because it is new.[1]

Central to this process is the definition of indications for the drug in question. These indications are crucial, because drugs are approved (or not) on the basis of their net clinical benefit for specific and well-defined diseases and – importantly – only for these.

Once the drug is granted marketing authorization, the manufacturer can only market it for the approved indication(s); it is illegal to promote, directly or indirectly, or even to suggest, its use for other diseases or other types of patients (although this does happen[2]). Pharmaceutical companies can add new indications to those already approved, but they rarely do, because the clinical trials required are lengthy and expensive and there is little incentive to conduct them, since the drug is already on the market. More common are extensions to the approved indications, such as to other age-groups or to different patient subtypes. Generic drug manufacturers are likewise reluctant to conduct the RCTs needed for new approvals, for the same financial reasons.

Once the drug is available for use in tens or hundreds of thousands of patients, physicians may realize that some medications can be effective in diseases for which they were not approved, i.e., no studies have been presented to the regulatory authorities, and therefore they are not formally approved for those indications. Convinced of the benefits for their patients, some physicians prescribe them for unapproved indications – off-label prescription.

Off-label prescription is thus defined as prescription for an indication, disease, or patient outside the approved indications, or for populations that have not been studied (such as pediatric patients), or using methods of administration or dosages that have not been approved.[3] The rationale for off-label prescription is that the official agencies do not regulate the practice of medicine, and that physicians are free to decide what they consider best for their patients.

There are two types of off-label prescription:

- the use of a drug that is indicated for a particular disease in a completely different condition, such as anti-epileptic agents for neuropathic pain;
- the use of a drug within its indications, but outside the approved specifications, such as sildenafil, approved for erectile dysfunction but used by patients without this condition in order to enhance sexual performance.

The spectrum of off-label use includes guideline-recommended practice (aspirin in diabetes for prophylaxis against cardiovascular disease), last-resort therapy (tacrolimus for autoimmune diseases, in addition to transplantation), and first-line therapy (gabapentin for painful diabetic neuropathy).

Certain types of off-label prescription are of particular concern and require careful scrutiny[4]:

- The off-label use of recently introduced drugs is a major problem, since not only will there be virtually no evidence of their benefit, but safety data from pharmacovigilance will also be scarce, obviously complicating their use.
- Novel off-label use – one that is different from usual clinical practice – has similar problems of lack of data on efficacy and especially on safety, even if the drug itself has been on the market for more than 3-5 years.
- When any drug with known serious or frequent adverse effects is prescribed off-label, this use merits close attention owing to concerns for patient safety.
- Finally, off-label prescription of high-cost drugs raises its own questions, since the financial penalty involved demands particular practical reflection.