



OFF-LABEL-USE IN PALLIATIVE MEDICINE

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4	Introduction
6	Definitions and Terms
7	Pharmacotherapy
8	Legal Framework
10	Risks of Off-Label-Use
11	Opportunities of Off-Label-Use
12	Off-Label-Use in Palliative Medicine
16	Recommendations for practice
18	Perspective
19	Guidance for practice

The aim of palliative medicine is to improve the quality of life of patients with advanced disease. Drug management plays a prominent role in the treatment of burdensome symptoms. Up to 50% of authorised drugs prescribed in palliative medicine are used for unauthorised indications and/or by an unauthorised method.

Drugs are prescribed off-label in everyday clinical practice. At the same time, many aspects of off-label-use are not known or there are uncertainties as to when a drug use will no longer be within the authorisation (in-label use) and when off-label-use will begin. In addition, the possible (also legal) consequences of off-label-use are not always known.

The aim of this booklet is to explain the opportunities and risks of off-label-use in palliative medicine and provide information on off-label-use in this field. It is aimed primarily at specialists involved in the care of adult patients receiving palliative medicine.

The suggested forms listed here, e.g. patient information or documentation of off-label-use, are available for download at www.arzneimittel-palliativ.de.

Off-label-use refers to the use of an authorised medicinal product beyond authorisation by national authorities. When a medicinal product is licensed, this marketing authorisation refers both to a specific indication and to a specific group of patients. However, under certain circumstances the medicinal product can also be used for diseases or persons for which it has not been authorised. Such cases are called “off-label-use”. [Federal Institute for Drugs and Medical Devices, Germany BfArM]. However, the understanding of off-label-use may vary in different national contexts.

In general, “off-label-use” refers to all deviations from the approval of a drug, for example with regard to indication, route of administration (incl. crushing tablets for tube administration), dosage interval, duration of treatment and concomitant diseases.

Table 1. Terminology

Type of use	Explanation
Compassionate Use	Free (= provided by the pharmaceutical company) supply for patients with drugs that have not yet been approved. The requirement is a serious or life-threatening disease that cannot be adequately treated with approved drugs.
Unlicensed use	Use of (as yet) unauthorised medicinal products.
Off-Label-Use	Use of an authorised medicinal product outside the marketing authorisation.
Individual therapeutic attempt	Use on a case-by-case basis; the drug is either not yet approved or approved for another area of use.

Irrespective of the approval status of the medicinal products used, the following aspects apply to each treatment:

Patient-specific treatment decision

Each treatment must be adapted to the symptoms of the person being treated, their wishes and views, but also to factors such as age, organ function and comorbidities.

Monitoring of therapy

Each therapy must be evaluated regularly at appropriate intervals with regard to effectiveness, tolerability, and indication.

Taking medical progress into account

New findings on old and new therapies should be taken into account. The argument “we have always done it this way” is insufficient for a therapeutic decision!

The legal framework for off-label-use including obtaining informed consent and aspects of cost coverage are internationally diverse and must be addressed in the respective national context.

Obtaining informed consent

Obtaining informed consent of the patient should be a basic requirement for off-label-use. It should be assessed whether it is possible to abstain from a separate information as far as this is exceptionally dispensable due to special circumstances, especially if the treatment cannot be postponed or the patient has explicitly abstained from being informed about the treatment. If it is a recognized off-label-use, e.g. morphine for breathlessness, a separate patient information on off-label-use can probably be omitted. If the off-label-use is supported by little data, i.e. the more experimental a therapy is, more attention must be paid to individual information of the patient. Especially in the latter cases it is recommended that an individual risk-benefit balance is specifically documented. If, for example, a therapy cannot be justified by large studies or recommendations in guidelines, but the expected risk for the patient is low, or the risk of distress due to a symptom that cannot be adequately treated otherwise is higher, a separate information can be omitted in the individual case. However, there is no place for general assumptions such “subcutaneous administration is always a good alternative”; the assessment must be drug-specific and in the individual context.

When informing patients or their representatives, they should be provided with easy-to-understand information on the difference between the off-label-use of the drug and the conventional use according to the approval, e.g. as specified in the package leaflet. Here it is important not only to inform about the risks but also about the advantages of the therapy.

The following aspects should be included in the information:

- Reason for the need to use the drug outside the authorisation
- Type of drug use in the individual patient (e.g. indication, route of application, etc.)
- Expected effect
- Possible side effects

The template for a possible information form is available for download at www.arzneimittel-palliativ.de.



Off-label-use involves risks at various levels. In addition to costs and liability aspects, drug safety must also be considered. Before a drug is approved, high requirements must be met with regard to efficacy and tolerability. The risks of a drug that has not been tested or has only been tested inadequately can only be assessed to a limited extent.

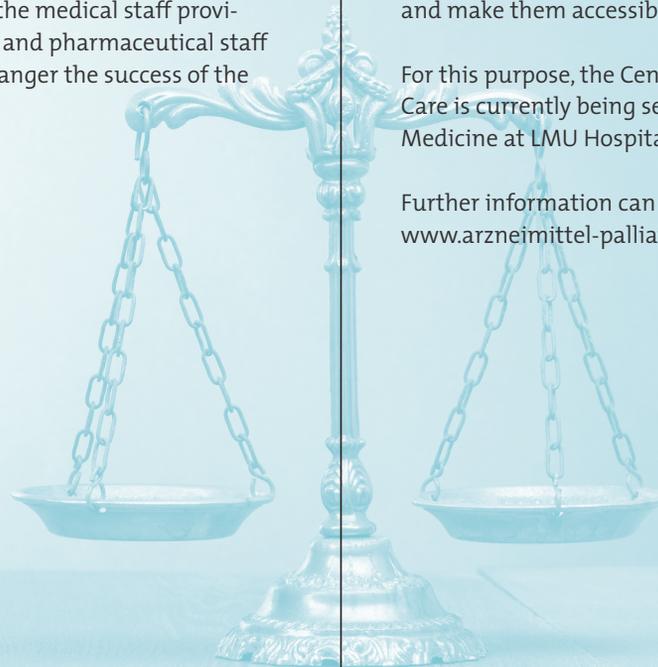
In addition, there is the risk of interruption of therapy due to insufficient communication with other health care professionals involved in the care. For example, the possible use of opioids for breathlessness is not always known. Uncertainties regarding the suitability and safety of the therapy (keyword: respiratory depression) can lead to a situation in which the therapy is no longer prescribed by the medical staff providing further treatment, or medical and pharmaceutical staff can confuse patients and thus endanger the success of the therapy.

Off-label-use is of course not only a risk for the patient, but also offers the opportunity to gain knowledge and thus also an increase in competence. For this purpose, however, off-label-use must be considered consciously, effectiveness and side effects should be documented. A respective documentation form can be found at www.arzneimittel-palliativ.de. Ideally, these experiences are published in a structured form, for example in the form of a case report or a case series.

At the same time, however, they should also be collected and assessed at a central site. This will provide an opportunity to bundle positive and negative experiences, put them in the context of current scientific evidence where appropriate, and make them accessible to a wider professional audience.

For this purpose, the Center for Off-Label-Use in Palliative Care is currently being set up at the Department of Palliative Medicine at LMU Hospital Munich.

Further information can be found at www.arzneimittel-palliativ.de.



The focus of drug therapy and thus off-label-use in palliative medicine is on symptom control. In contrast to other medical disciplines, the primary focus is not on curative or disease-modifying treatment approaches, but on alleviating distressing symptoms.

Every palliative care institution should have a local standard operating procedure for off-label-use.

Table 2. Examples for Off-Label-Use

Drug	Off-Label-Use*	Reason*
Morphine	Breathlessness	Approved only for the treatment of pain
Midazolam	Subcutaneous or intranasal administration	Approved for intravenous, buccal and rectal use only
Haloperidol	Continuous infusion, mixture with other drugs	Approved for injection (i.m.), separate from other medications
Metoclopramide	Administration of 30mg/d over 14 days	Approved for max. five days

*in most countries

Identification of Off-Label-Use

The authorization label of a medicinal product can in general be found in the summary of product characteristics (available e.g. from the pharmaceutical manufacturer or a national drug formulary) and often also on the websites of the responsible licensing authorities, e.g. the European Medicines Agency EMA (www.ema.europa.eu) in Europe or the Food and Drug Administration FDA (www.fda.gov) in the US.

Requirements for Off-Label-Use



The precondition for off-label-use should always be that approved alternatives have been exhausted or are not used in a well justified manner, e.g. due to side effects or contraindications. Based on the data available, there should be a reasonable possibility of treatment success. The risk of treatment complications should be low or proportional to the situation. It must also be taken into account whether it is an off-label use that can be scientifically proven or is purely experimental.

The following requirements should be met:

Indication	Off-label-use cannot be an answer to a request of the patient, but only the consequence of the medical indication provided by the treating medical staff.
Treatment selection	Knowledge of available and approved therapy options must be available; these must be rated as not indicated or already exhausted. Off-label-use is not an answer to a “lack of knowledge”.
Individual decision	The decision for or against off-label-use can only be made in the current and individual context of the person to be treated and is therefore NOT different from the use of approved drugs!

Indication

Only the treating medical staff can provide an indication for a therapy. The request of patients or their relatives for certain treatments should be listened to, but the assessment of the appropriateness and necessity is the responsibility of the treating medical staff.

Treatment selection

The selection of the therapy requires knowledge of the available (pharmacological) treatment options. Authorised drugs should be used preferentially.

Off-label-use is only justified if

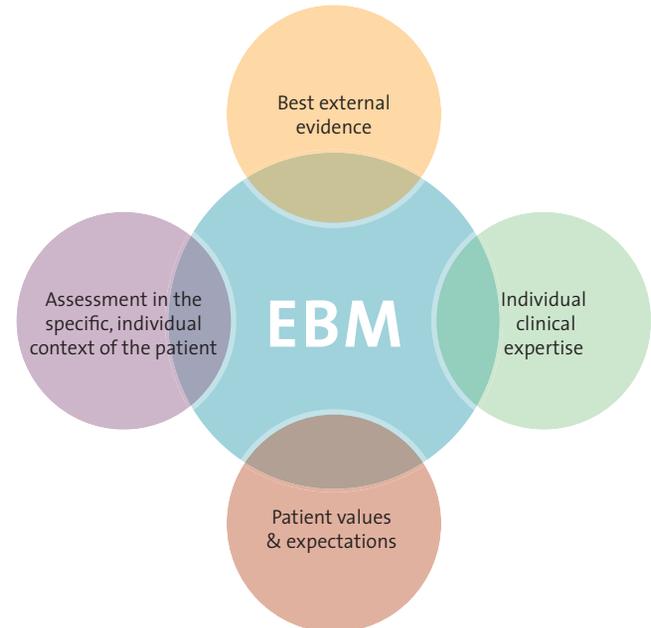
1. approved treatment options are exhausted when symptom control is still inadequate, or
2. are not considered due to side effects, interactions, or other aspects endangering the treatment, or
3. the drug to be used outside the authorization label is the (scientifically) proven better treatment option and
4. the justifiable probability of the intended therapeutic effect exists.

Individual Decision

The decision for or against a treatment can only be made in the current and individual context of the patient.

Off-label-use that is not yet indicated for a patient today can be the treatment of choice for the same person tomorrow. For example, the current disease situation, the response to and tolerance of previous treatments, comorbidities, organ function, age, and the burden of treatment should be taken into account.

Off-label-use should be decided in accordance with the recognized recommendations on evidence-based medicine (EBM) and take the following aspects into account:



The following steps should be followed, especially in the case of potential off-label-use with little or no underlying scientific evidence:

1. Identification of respective (= off-label-use) drugs/therapies
2. Exploiting alternatives
3. Consideration of the current medical standard
4. Information of the patient (informed consent)
5. (Scientifically) plausible treatment attempt after general and individual benefit-risk assessment
6. Documentation
7. Communication
8. Publication

A standardized documentation form offers support in handling off-label-use in clinical practice, which can, for example, consider these steps as follows:

Such documentation can also be used to systematically record experiences with off-label-use and thus make them comprehensible and useful again at a later point in time. The Center for Off-Label- Use at the Department of Palliative Medicine at LMU Hospital Munich also provides such a form for documentation. Ideally, documented experience is provided to the Central Off-Label-Use Office to collect it centrally and make it available to other clinicians.



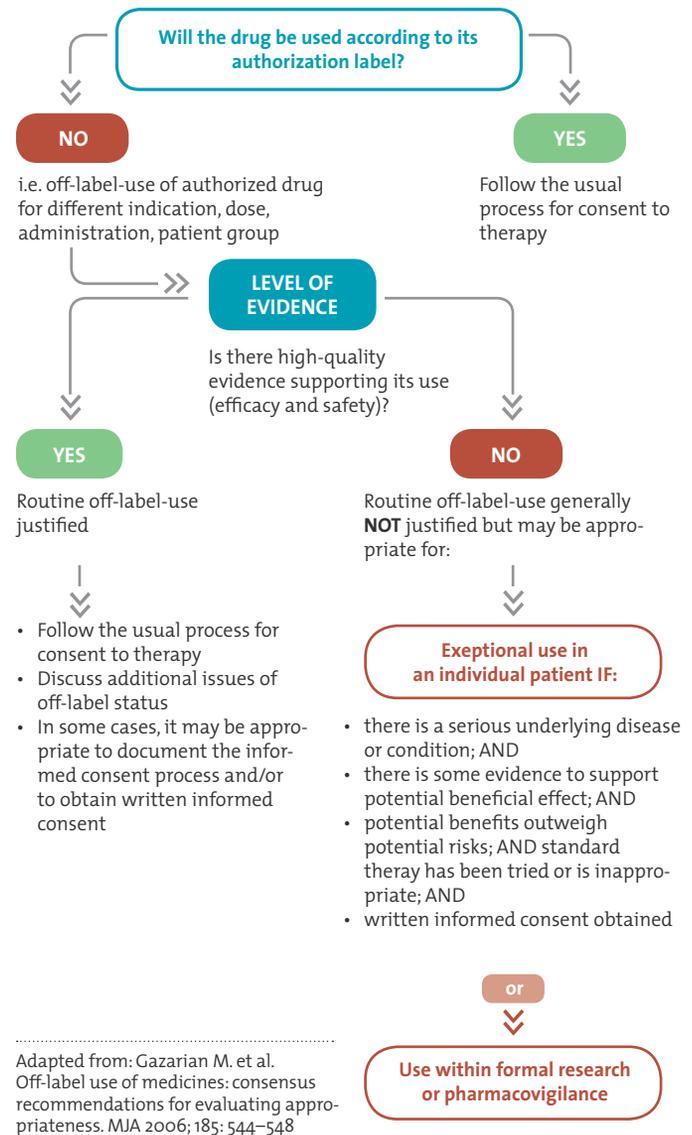
Drug-related information	<ul style="list-style-type: none"> • Drugs used off-label use • off-label indication • Previous treatment attempts (drugs and/or reason why they are no longer used)
Patient-related data	<ul style="list-style-type: none"> • Primary disease of the person treated • Age and sex of the person treated • Current medication (as complete as possible) • Current symptom burden
Monitoring of treatment	<ul style="list-style-type: none"> • Which therapeutic goal is to be achieved with the treatment? • How can this be monitored? • What side effects can be expected? • At what intervals can the therapy be monitored (effect/side effects)? • By whom?
Information	<ul style="list-style-type: none"> • Obtaining informed consent of the person treated or the representing proxy
Treatment effect	<ul style="list-style-type: none"> • Was the treatment goal achieved? (effect level 0 = no effect until 10 = treatment goal completely achieved) • Were blood levels measured? Concentration incl. time of collection (time between last administration and blood draw) • In which time frame was the effect observed? • Which side effects (positive and negative) occurred? • Will the therapy be continued? • If not: why not?

Off-label-use routinely accompanies the clinical daily routine in the care of palliative care patients. These often have a complex disease and symptom course, characterized by physical, psychological, social and spiritual distress of varying magnitude, especially in the specialized care sector. Even though the use of drugs is certainly still the simplest starting point in many cases, it must be borne in mind that there is often little or no scientific evidence to support some palliative medical treatment strategies. The supposedly best possible therapy for the patient must not become an unstructured treatment attempt, which unnecessarily endangers the patient, but does not lead to increased knowledge at the same time. This booklet is part of a project to raise awareness for off-label-use in palliative medicine.

This is a project to

- raise awareness for off-label-use among specialists in palliative medicine;
- collect data on off-label-use centrally, assess it and make it available to other professionals;
- encourage health insurance companies and authorities to rethink their approach and focus on the important treatment goals of “symptom control” and “quality of life”;
- create a forum for professional exchange.

The aim is eventually to make pharmacotherapy in palliative medicine safer and more reliable.



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