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Original Article

Off-Label Prescriptions in Italian Hospices: A National Survey

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Abstract

Off-label prescription is part of routine care in palliative medicine, but no information is available about the situation in Italy. A cross-sectional observational survey was undertaken on all 66 Italian palliative care freestanding inpatient units to describe off-label prescriptions. Data were collected on 507 patients. Each prescribed drug was matched with Italian Marketing Authorization indications: 159 drugs off-label (4.5% of all prescribed drugs) for the stated indication were given to 128 patients (25.2%), and drugs unlicensed for subcutaneous injection were given to 147 patients (85.4% of all subcutaneous prescriptions, excluding insulin and heparin). The off-label prescriptions were subsequently evaluated by referring to the Italian National Pharmaceutical Formulary (INPF) and the British Palliative Care Formulary (PCF2). Although drugs are frequently prescribed off-label in inpatient palliative care units in Italy, this strategy was not always backed by clinical evidence, and in some cases, official/authoritative sources, such as INPF and PCF2 did not support it. Clinical trials and/or agreed international guidelines are needed to support the off-label use of the most widely prescribed drugs in palliation. J Pain Symptom Manage 2009;38:365–371. © 2009 U.S. Cancer Pain Relief Committee. Published by Elsevier Inc. All rights reserved.

Key Words

Off-label, hospice, palliative medicine, SC drugs, prescriptions in hospices, symptomatic prescriptions

This study was supported by a grant from the Luogo di Vitae e di Incontro Foundation of Milan.

A complete list of investigators is reported in the [Appendix](#).

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Accepted for publication: December 10, 2008.

Introduction

Pain and symptom control in end-of-life care often involves the off-label use of drugs.^{1,2} The term “off-label” often is used to refer to the use of a drug outside the indication reported on the product labeling, but actually is the use outside the specifications of its marketing authorization, including prescription for an unlicensed indication and/or administration

by an unlicensed route. Off-label prescription is common in medical practice,^{3–5} even if, in most cases, it is not documented in the clinical records.⁶ Only a few studies have been published on this subject, despite the high frequency of the practice in several medical disciplines, such as oncology, geriatrics, neurology and psychiatry, and pediatrics.

Off-label use is meant to benefit the individual patient, and if properly assessed, it may lead to therapeutic advances. Off-label prescription is very often grounded on established pharmacological knowledge and well-known pharmacological principles. Even if the use of these drugs is not officially approved, in some clinical situations, it is based on scientific evidence, including controlled trials to ascertain efficacy/safety.

When prescribing off-label drugs, doctors need to consider the evidence that the drug may be effective for the unlicensed indication and what risks are involved. In some cases, there is only limited evidence of benefit, and even when their use is likely to be safe, caution is mandatory and patients should be fully informed about their medication.⁷ The off-label use of medications raises important questions about the purpose and applicability of product labeling and its role and ability to provide information on the risks and benefits of commonly prescribed drugs.^{5,8}

In palliative medicine, possibly because of the scarcity of symptom-oriented controlled clinical trials and of drugs specifically designed to control symptoms in end-of-life patients, off-label prescription is an important part of routine care.^{1,2,9} Sometimes, a drug may even be prescribed for one of its side effects, for example, amitriptyline for drooling, which would not be considered “unwanted,” because it controls a symptom not controlled by specific licensed drugs. A drug may also be off-label for the route, in particular, when a drug licensed for intramuscular (IM) and/or intravenous (IV) injection is used subcutaneously (SC). The continuous subcutaneous injection (CSI) by a syringe driver, quite common in terminal and geriatric patients,¹⁰ is very widely used in palliative medicine, with applications that vary across countries (e.g., CSI is much more frequently used in the United Kingdom and Europe^{10–12} than it is in the United States¹³). CSI is used to administer a broad

range of drugs, often in spite of the lack of information on pharmacokinetics, stability, and compatibility.

Information on off-label prescriptions also is limited in hospice settings,^{1,2,7,9} and there is none pertaining to Italian hospices. In Italy, following the directives of the European Union, the Summary of Product Characteristics forms an integral part of the marketing authorization (the Autorizzazione all’Immissione in Commercio [AIC]). The AIC is the official reference for health professionals on how to use the drugs safely and effectively, and is almost fully reported on the package leaflet, making it easy for doctors, and sometimes for patients, to verify indications, dosage and use, and undesirable effects.

In Italy, as in other countries, drugs should be prescribed according to the therapeutic indications and routes specified in the marketing authorization. However, “different” use is allowed if the doctor considers it necessary for the patient and there are no better alternatives, if this use is suggested by strong research evidence, and the patient gives informed consent.¹⁴ Given the rapid development of palliative care and the opening of new hospices in Italy, this national survey of current prescribing practices was undertaken to define the extent of off-label prescribing and to stimulate debate.

Materials and Methods

A cross-sectional observational survey was undertaken on all freestanding palliative care inpatient units (FS-hospices) listed in the directory of the Italian Society for Palliative Care (SICP).¹⁵ To identify them from this directory, and to actually include all palliative care resources available, the following three characteristics were required: 1) dedicated beds for hospice care; 2) freestanding (oncology wards with beds reserved for terminal or dying patients were not included); and 3) a dedicated staff trained in palliative care.

Data on drugs prescribed to inpatients were collected in a predefined time frame (all in the same week). After morning rounds, the therapies prescribed and registered in clinical records were recorded and the doctor was asked to report his/her prescriptions. The

FS-hospice medical directors were asked in a phone interview if there was a policy on off-label prescriptions or on mixing drugs in the same syringe. Drugs were matched with the Italian AIC,¹⁶ and those whose indications and/or routes were not reported there were considered off-label. The interpretation of the stated indications for each prescription was, in some cases, rather broad: for instance, an antibiotic given for dyspnea was considered on-label, assuming that the dyspnea was the consequence of a lung infection, and hyoscine butylbromide was considered on-label if given for abdominal pain in a patient with colic. Any doubt was double-checked and discussed.

For each off-label prescription, we then searched for strong research evidence and/or the "suggestion for use" by official and authoritative sources. The following sources were selected: the Italian National Pharmaceutical Formulary (INPF),¹⁷ which is updated yearly and provided by the Ministry of Health to every Italian physician, and the UK Palliative Care Formulary 2nd Edition (PCF2).¹⁸ Both are based on the British National Formulary,¹⁹ but the first is adapted to the Italian context, and the second is specifically designed for palliative medicine, as a companion to the main textbooks.

Off-label drugs were grouped in four categories following a modified Ferner's classification²⁰ (Table 1). Drugs in each category were designated off-label or on-label. The official and authoritative sources were consulted to clarify the empirical basis for the selected therapies.

Results

Of the 124 palliative care resources listed in the SICP directory, 66 met the inclusion criteria. Fifty-three (80%) agreed to participate in the survey. On the given day, 535 patients were living in the hospices (an average of 11 per hospice; range: 1–27; median: 9). Data were collected on 507 patients; data were not collected for 17 because 13 were very close to death, three died before morning rounds, and one was admitted to hospital; 11 data collection forms were not included because therapies were not recorded. All but 16 were cancer patients, whose average age was

Table 1
Off-Label Drug Categories^a

1. Drugs licensed by AIC for the given indication *but in a different clinical situation, or by a different parenteral route*;
2. Not licensed by AIC for the given indication/route but *INPF and/or PCF2 suggest use*;
3. Not licensed by AIC for the given indication but *a literature-based clinical effect suggests use*;
4. *Contraindicated*.

^aFrom Ferner's classification,²⁰ modified.

69 years (median: 71; standard deviation [SD]: 12; range: 28–96). The average length of stay in the hospice was 26.6 days (median: 13; SD: 53.1).

There were 3555 drug prescriptions, an average of 7 (range: 1–15; median: 7) per patient. These figures include drugs administered on a regular basis or as needed. One hundred and fifty-nine off-label prescriptions were given to 128 patients for indications not reported in the AIC (Table 2).

Only 15 hospices had an internal policy for off-label prescriptions (in nine cases established by the team itself and in six by the hospital or district medical authorities). These mostly involved asking the patients or their relatives, or both, for informed consent. Only four communicated off-label prescription to the hospital or district medical authority.

Excluding insulin and heparin, which were prescribed for concomitant diseases before hospice admission, 185 patients (36.7%) were given an average of 2.2 (median: 2; range: 1–6; SD: 0.9) SC drug injections each; 147 patients received an average of 1.7 (median: 1; range: 1–5) injections off-label for the SC route (Table 3), which accounted for 64.8% of all SC prescriptions. Hyoscine butylbromide in 27 cases, dexamethasone in eight cases, and midazolam in two cases, were prescribed off-label for both indication and route.

Most of the hospices (45 of 53) had a policy for mixing two or more drugs in the same syringe, mostly established by the team (41 hospices), on the basis of the literature or the recommendations of some international scientific board. In 12 of 45 hospices, the number of drugs allowed ranged from 2 to 5 (median: 3), and 41 had a list of compatibilities. Only four hospices checked the solution to determine whether it looked cloudy.

Table 2
Drug Unlicensed for the Stated Indication (Off-Label) According to the Italian AIC

No. of Prescriptions	Drugs	Prescribed for	Category 1, AIC Licensed (for the Given Indication) Only in	Category 2, AIC Unlicensed but Use Suggested by	Category 3, Use Supported by Literature
32	Hyoscine butylbromide IM/IV	Secretion/rattle	Anesthesia ¹⁸	INPF ^a and PCF2	Yes ²³
6	Clonazepam PO	Neuropathic pain	—	Not suggested	No
3	Diazepam PO	Dyspnea	—	INPF ^a	No
23	Morphine hydrochloride IM/IV	Dyspnea	—	INPF ^a and PCF2	Yes ^{24,25}
11	Morphine sulfate PO	Dyspnea	—	INPF ^a and PCF2	Yes ^{24,25}
2	Fentanyl TD	Dyspnea	—	Not suggested	Yes, but only by aerosol ²⁵
1	Bromazepam PO	Dyspnea	—	Not suggested	No
3	Betamethasone PO	Cachexia/anorexia	—	PCF2 (anorexia)	Yes for anorexia No for cachexia
2	Hydrocortisone PO	Asthenia	—	Not suggested	No
15	Prednisolone PO	Cachexia/anorexia	—	INPF ^a and PCF2 (anorexia)	No
49	Dexamethasone IM/IV/PO	Asthenia	—	Not suggested	No
12	Methylprednisolone IM/PO	Asthenia	—	Not suggested	No

PO = *Per os* (by mouth); TD = transdermal.

Category 1: Drugs licensed for the given indication in a different clinical situation, or by a different parenteral route; Category 2: not licensed for the given indication/route but INPF and/or PCF2 supports use; Category 3: not licensed for the given indication but a literature-based clinical effect suggests use. "In the foreword to "Palliative Care."

Discussion

Off-label prescribing in Italian FS-hospices is still limited, and much lower than other countries. To our knowledge, there is no explanation for these differences (similar to the differences in SC administration across countries). The three main off-label indications were the control of secretion/rattle, dyspnea, and anorexia/fatigue. In the first two cases, drugs with a rational basis to support their use were prescribed, even if not licensed for that indication. The mouth-drying effect of hyoscine is a known (side) effect, and its efficacy on death rattle is confirmed by empirical research,²¹ as is the efficacy of opioids in controlling breathlessness.^{22,23} In a few cases, however, benzodiazepines were prescribed for dyspnea, even if this indication is not supported by the literature: Only diazepam is suggested for breathlessness by INPF in its foreword, although it is not clear on what basis. The prescription of steroids is widespread for cachexia/anorexia and fatigue, two conditions that are frequently related and not always clearly distinguished by clinicians. The appetite-stimulant effect of glucocorticoids is claimed, and is probably true, as it is often anecdotally reported. However, it has not

been confirmed by controlled clinical trials, as for megestrol acetate.²⁴ The efficacy of these drugs for asthenia and cachexia is not suggested or supported by research, and should not be considered established. As can be seen from Tables 2 and 3, indications vary across sources, and it is not always easy to understand the rationale.

Patients' informed consent and scientific evidence to back up the prescription are required by law for off-label prescriptions, but the final decision is left to the individual physician, who often seemed unaware of this responsibility, and even of the existence of a specific law.^{7,15} The recommendation for informed consent^{7,15} is probably not workable, because most of these patients are very sick or cognitively impaired. This highlights the need for shared international directives.

The SC route seems to be commonly used in a large majority of Italian hospices. It is easy, and less distressing than the IM and IV routes, especially in patients with poor venous access and scant muscle mass who represent most of the terminal patients. But this route is not risk free; some drugs deliverable by deep IM injection could be histotoxic if injected SC, and hence, contraindicated (e.g., chlorpromazine and most nonsteroidal anti-inflammatory drugs).

Table 3
Drugs Unlicensed (Off-Label) for Subcutaneous Injection According to the Italian AIC

No. of Prescriptions	Drugs	Category 1, AIC Licensed Parenteral Route Only in	Category 2, AIC Unlicensed but Use Suggested by	Category 3, Use Supported by Literature	Category 4, Contraindicated
2	Ranitidine	IM/IV	Not suggested	No	—
43	Hyoscine butylbromide	IM/IV	INPF ^a and PCF2	Yes ²⁴	—
16	Metoclopramide	IM/IV	INPF ^a and PCF2	No ¹²	—
3	Alizapride	IM/IV	Not suggested	No	—
7	Furosemide	IV	Not suggested	Yes, but no evidence ¹²	—
1	Chlorpromazine	IM deep	Not suggested	No	Yes
16	Ketorolac	IM	PCF2	Yes ^{27,28}	—
1	Ketoprofen	IM deep/IV	Not suggested	No	—
3	Promazine HCL	IM/IV	Not suggested	No	Yes
54	Haloperidol	IM/IV	INPF ^a /PCF2	No ¹²	—
1	Levosulpiride	IM	Not suggested	No	—
1	Lorazepam	IM/IV	Not suggested	No ¹²	—
3	Chlormethyldiazepam	IM/IV	Not suggested	No	Yes
14	Midazolam	IM/IV	INPF ^a and PCF2	Literature reports its use, but low level of evidence ¹²	—
67	Dexamethasone	IM/IV	INPF ^a and PCF2	Literature reports its use but no controlled clinical trials ¹²	—

Category 1. Drugs licensed for the given indication in a different clinical situation, or by a different parenteral route; Category 2: Not licensed for the given indication/route but INPF and/or PCF2 supports use; Category 3: not licensed for the given indication but a literature-based clinical effect suggests use. ^aIn the foreword to "Palliative Care."

Some drugs injected SC off-label do have a rational justification, such as metoclopramide, midazolam, haloperidol, and dexamethasone. The SC use of these drugs is backed by clinical experience. But often, for these drugs too, controlled clinical trials are lacking or weak.¹⁷ Even official sources do not always agree; for instance, for ketorolac and hyoscine, SC use is supported by the literature,^{25,26} and suggested by the PCF2, but not supported by INPF. A recent French publication²⁷ recommends furosemide and ketoprofen for SC injection (in contrast to the INPF and PCF2), and ketorolac (suggested by the PCF2 but not by INPF). In some cases, use of the SC injection was a mistake, as recorded in this study for chlorpromazine (one case), promazine HCl (three cases), and chlormethyldiazepam (three cases), as this route is specifically contraindicated for these drugs.

Although we did not collect this information, it is likely that most SC drugs were mixed in the same syringe. Syringe drivers and elastomeric disposable pumps are an irreplaceable aid for administering a broad range of drugs, often mixed in the same syringe mostly with opioids.²⁸ However, there have been concerns about both SC injection²⁹ and the compatibility and

stability of mixtures.^{30,31} The tendency to mix as many drugs as possible in the same syringe is understandable but not always rational or safe.³² Most interviewed physicians take this problem into serious account, but information on compatibility and stability of drugs is still insufficient.

Limitations

The borderline between wrong and off-label use of a drug is sometimes blurred, and this study could not go deeply into this matter. For instance, an antibiotic was considered "on-label" if prescribed for cough, because cough can be a consequence of lung infection. Any antibiotic prescription for infection was considered "on-label," but we were unaware whether the drug was used against a microorganism indicated by the AIC. Thus, the scale of off-label prescribing may have been underestimated.

Data were collected on an index day but prescribing practices may vary widely across hospices and physicians, and not all prescriptions are necessarily part of routine care. Also, the use of drug cocktails in the same syringe was not studied and this deserves further, specifically designed investigations.

Conclusions

Off-label prescriptions are a routine part of palliative medical therapies in Italy. Their use is not always supported by clinical evidence. Even when their benefit is grounded on clinicians' shared experience, often research evidence is lacking, and this should call for caution and their use only when there are no alternatives.

At present, palliation is not an appealing market for the pharmaceutical industry, and only in a few cases (mainly analgesics) is research oriented to developing and marketing new drugs specifically designed for controlling symptoms in terminal patients. In some cases, the AIC should be updated, but the procedure is expensive and time consuming, and the limited number of patients involved means pharmaceutical companies have no gain—hence no interest—in doing it. It is thus likely that off-label prescription will continue to play a role in palliative medicine.

Even if research difficulties make controlled clinical trials supporting off-label use very difficult, finding supporting evidence for or against what is usually only a matter of personal experience and opinion should be encouraged. National and international medical associations should produce consensus-driven and up-to-date guidelines, avoiding contradictions among official/authoritative sources, and palliative care/hospice units should set formal procedures for off-label prescription to arouse physicians' awareness about potential problems connected with this kind of prescription, and stimulate discussion among palliative medicine specialists.

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