



# Off-licence / Off-label prescribing

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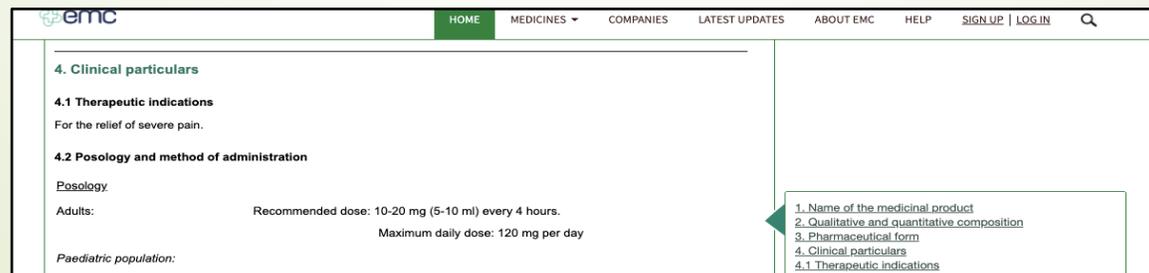


# Aims

- Overview of terminology
  - Why prescribe off-label?
  - Prevalence
  - Why worry?
  - Suggestions for good practice
- 

# Terminology

- A product 'licence' is a marketing authorization
- Products in the UK are licenced by the MHRA
- The marketing authorization includes the product's agreed terms of use 'label'
- The 'label' is described in the SmPC



The screenshot shows the EMC website interface. The top navigation bar includes links for HOME, MEDICINES, COMPANIES, LATEST UPDATES, ABOUT EMC, HELP, SIGN UP, and LOG IN. The main content area is titled "4. Clinical particulars" and contains the following sections:

- 4.1 Therapeutic indications**  
For the relief of severe pain.
- 4.2 Posology and method of administration**  
**Posology:**  
Adults: Recommended dose: 10-20 mg (5-10 ml) every 4 hours.  
Maximum daily dose: 120 mg per day  
**Paediatric population:**

On the right side of the page, there is a table of contents with a red arrow pointing to the "4. Clinical particulars" section:

1. Name of the medicinal product
2. Qualitative and quantitative composition
3. Pharmaceutical form
4. Clinical particulars
- 4.1 Therapeutic indications



# Terminology

- **'Unlicenced'** refers to a product which does not have a marketing authorization for medicinal use in humans
- A **'special'** is a medication that does not have a licence but has been specially manufactured (by a manufacturer with a specials manufacturing licence) or imported to the order of a prescriber for the treatment of an individual patient



# Terminology

- **'Off-licence'** means prescribing a medicine outside of the terms of the SmPC. This includes:
  - Indication
  - Route of administration
  - Age of the patient
  - Dosage
  - Duration of treatment
- **'off-label' = 'off-licence'!**

Today...





# Why do we prescribe off-label?

- Treatment with an approved drug has not been effective / satisfactory
- There is no approved drug for the condition / symptom
- The marketing authorization is unlikely to ever extend to a broader use despite there being evidence of benefit
- Clinical trials are considered more difficult in certain groups eg: palliative care, paediatrics, psychiatry



# How common is off – label prescribing?



- Evidence suggests 14.5% - 35% Of prescriptions in palliative care are off-label
- A U.K survey estimated that up to 25% of all prescriptions for licensed drugs in palliative care are used for off licensed indications (or an off licensed route) [survey 2001]

# How common is off – label prescribing?

*Vol. 38 No. 3 September 2009*

*Journal of Pain and Symptom Management 365*

***Original Article***

## **Off-Label Prescriptions in Italian Hospices: A National Survey**

Franco Toscani, MD, Paola Di Giulio, RN, MSC, Rita Campi, ScD,  
Ivanoe Pellerin, MD, Anna De Luca, MD, and Giuseppe Casale, MD  
on behalf of the End of Life Observatory Research Group

- Italian survey of 53 inpatient units (507 patients) reported:
  - 4.5% all prescribed drugs were off-label for the stated indication
  - 85.4% of all sc injections were off-label



# Common medications

- ▶ Study of off-label medication in the IPU at MD Anderson Cancer Centre
- ▶ 35% prescriptions (201 patients) were off-label
- ▶ 11% of all off-label prescriptions had no literature support or were contraindicated

# Common medications

**Table 4**  
**Frequency of off-label use by drug and associated level of scientific evidence**

Drug Name	Total prescription events N (%) <sup>1</sup>	Off-label prescription events N (%) <sup>2</sup>	Off-label use with strong evidence N (%) <sup>3</sup>
Haloperidol	723 (12)	720 (33)	520 (72)
Chlorpromazine	305 (5)	292 (13)	229 (78)
Dexamethasone	337 (5)	280 (13)	195 (70)
Glycopyrrolate	175 (3)	175 (8)	170 (97)
Hydromorphone	670 (11)	161 (7)	149 (93)
Morphine	518 (8)	156 (7)	156 (100)
Lorazepam	350 (6)	71 (3)	1 (1)
Fentanyl	182 (3)	48 (2)	
Olanzapine	47 (1)	47 (2)	46 (98)
Gabapentin	33 (1)	33 (2)	29 (88)
Metoclopramide	252 (4)	31 (1)	

How commonly do you prescribe or recommend 'off-label'?



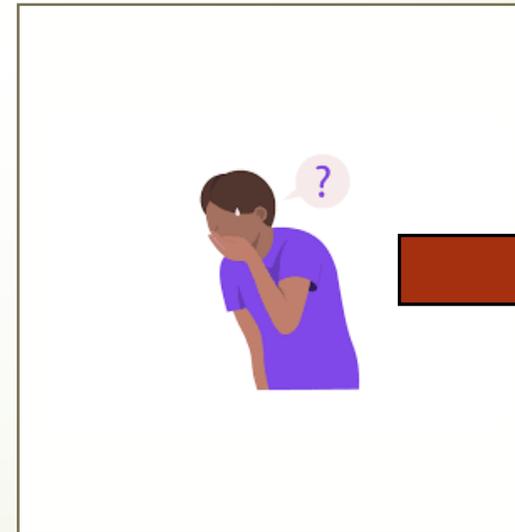
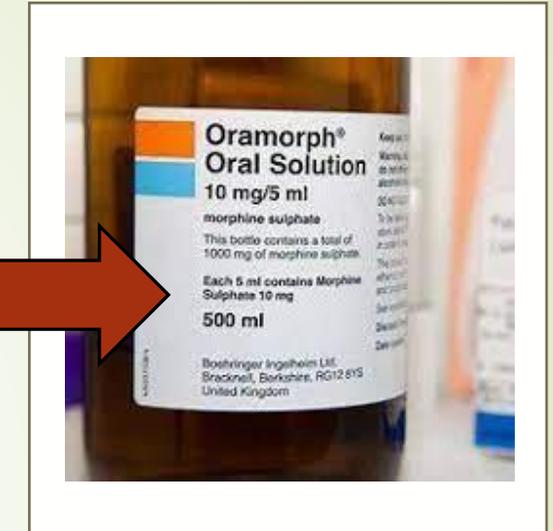
And in which Situations?



"Drug use beyond the licence  
is both risky and offers  
opportunities so requires  
special attention" Hagemann 2019

# Opportunities

- Expands our 'symptom management' options when often limited first line treatments have not been effective





# Opportunities

- Use established pharmacological principles and apply these to the management of symptoms / complications

> [BMJ Support Palliat Care](#). 2019 Dec;9(4):365-366. doi: 10.1136/bmjspcare-2019-001808.  
Epub 2019 Jun 14.

## **Naloxegol for opioid-induced sphincter of Oddi spasm/dysfunction**

[Andrew Neil Davies](#)<sup>1</sup>, [Charlotte Leach](#)<sup>2</sup>



# Opportunities

- ▶ Enables us to use the known side effects of some drugs to bring about benefit
  - ▶ eg. codeine for diarrhoea, erythromycin for gastric stasis
- ▶ Gives options for different routes to suit patients' needs / conditions
  - ▶ eg. sc injections & CSCIs, eye drops po
- ▶ Can lead to therapeutic advances



# Risks : awareness

- Potential lack of awareness of HCPs that we are prescribing / recommending drugs off-label
  - 50% clinicians in one survey were able to correctly identify licensed drugs being used for off licensed use
- Lack of knowledge of policies / patient information in organisations
  - Survey in Australia and NZ highlighted 89% palliative care physicians were not aware of a policy in their organisations
  - Survey in UK highlighted 2% had a policy

# Risks

- ▶ What education is there surrounding off-label prescribing?



# Risks : lack of evidence

## **Off-label prescribing in palliative care – a cross-sectional national survey of Palliative Medicine doctors**

**Timothy HM To** *Discipline, Palliative & Supportive Services, Flinders University, Adelaide, Australia;  
Southern Adelaide Palliative Services; Department of Rehabilitation & Aged Care, Repatriation General Hospital, Adelaide, Australia*

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pmj.sagepub.com  


- Prescribing strongly influenced by:
  - Local practice
  - Anecdote
  - Expert opinion
  
- Other studies have suggested that up to 70% of off-label use has little or no scientific support (Remi et al 2019)

# Risks : off-label marketing

EDITORIAL

## Gabapentin Approvals, Off-Label Use, and Lessons for Postmarketing Evaluation Efforts

Joshua D. Wallach, MS, PhD; Joseph S. Ross, MD, MHS

- 1993 - approved by the FDA for partial seizures
- 2000 – approved for children over 3 years
- 2002 – approved for post-herpetic neuralgia
- Limited evidence for use in other types of neuropathic pain or pain disorders



# Risks : off-label marketing

- 1995 - 2004 sales increased from \$98 million to \$3 billion per year
- Being used to treat varying conditions
- By 2000 top selling anticonvulsant, ranked 17<sup>th</sup> for total expenditures among all drugs
- Gabapentinoid use more than tripled between 2002 – 2015
- 2017 gabapentin ranked as 7<sup>th</sup> most commonly prescribed medication in the US



# Risks : off-label marketing

- ▶ Extensive use due to off-label marketing
  - ▶ Educational programmes
  - ▶ Physician speakers
  - ▶ Industry funded studies
  - ▶ Publications used to promote off-label clinical uses
- ▶ By 2001 gabapentin had the greatest proportion of off-label use among 160 commonly prescribed drugs



# Risks

- ▶ 2004 – Warner-Lambert settled litigation for \$430 million and admitted guilt in connection to charges that the company illegally promoted gabapentin for uses not approved by the FDA
- ▶ An estimated 95% of gabapentin prescribing was for off-label indications



What's the evidence?

- Suggests we need to be concerned about unscientific prescribing not necessarily off-label prescribing



# Off-label drugs in palliative care: a Group Delphi treatment recommendation process

Constanze Remi , Kathrin Weingärtner, Vera Hagemann, Claudia Bausewein, Farina Hodiament

- ▶ First steps in developing a guide for preparing and consenting drug specific recommendations for off-label use in palliative care
  
- ▶ Six domains:
  - ▶ Identification of relevant drugs
  - ▶ Identification of relevant drug uses
  - ▶ Identification and assessment of available evidence
  - ▶ Formulation and presentation of therapy recommendations
  - ▶ Consensus of therapy recommendations
  - ▶ Updating

# Risks : patient education / consent

## ➤ GMC

c. make a clear, accurate and legible record of all medicines prescribed and, where you are not following common practice, your reasons for prescribing an unlicensed medicine.

### **Information for patients about the licence for their medicines**

**107** You must give patients, or their parents or carers, sufficient information about the medicines you propose to prescribe, to allow them to make an informed decision.

## ➤ NMC

- c) You should explain to the patient/client, or parent/carer, in broad terms, the reasons why medicines are not licensed for their proposed use (see the Guidance below)
- d) You make a clear, accurate, and legible record of all medicines prescribed and the reasons for prescribing an 'off-label' medicine



# Patient education / consent

- ▶ Online survey of prescribers within palliative care in the UK
- ▶ 332 responses
- ▶ 15% operated a policy on providing information to patients
- ▶ 65% always make a clear record of the drugs prescribed
- ▶ Drs were better than nurses and pharmacists!
  - ▶ Culshaw et al (2012)

# Patient education / consent

**Table 1.** Respondents' practices regarding off-label prescribing and associated verbal or written consent, and documentation of reasons.

	Always (%)	Sometimes (%)	Never (%)
Do you limit off-label prescribing to consultants only?	29 (29)	39 (39)	31 (31)
Do you obtain verbal consent from the patient/caregiver?	24 (24)	49 (50)	26 (26)
Do you obtain written consent from the patient/caregiver?	1 (1)	23 (24)	74 (76)
Do you document in your notes when prescribing off-label and the reasons for this?	10 (10)	38 (39)	49 (51)



# Patient education / consent

- Important to understand the reason / rationale for the medication (especially when multiple uses for a drug)
- Important to clarify when a review of the medication should take place and by whom



## Risks : AEs

- Risk of AEs increased by an estimate of 44% with drugs used off-label compared to 'on-label' (Kwon et al 2017)
- Risk increases even further when off-label use is not supported by strong evidence

# Risks : AEs



- ▶ 46,000 patients received 150,00 new prescriptions for medicines (2005-2009)
- ▶ 11.8% all new prescriptions (conservative estimate) were off-label
- ▶ Off-label use supported by strong evidence less than 20% of the time
- ▶ Those receiving off-label lacking strong evidence were 54% more likely to experience an ADE significant enough to warrant stopping



# Suggestions for good practice

- Be aware of the evidence base for off-label medications. Practice should be grounded in the best available evidence





# Suggestions for good practice

- ▶ Strategies for collecting data in relation to off-label prescribing should be developed. This could inform:
  - ▶ Education
  - ▶ The development of guidance / policies
  - ▶ Inform areas for future research



# Finally

- Prescribing off-label brings many opportunities to enable improved symptom management for our patients
- There are risks involved the biggest probably being the lack of evidence in relation to some medications