Walking the tightrope – challenges and risks

Disease management and prescribing outside our comfort zone (beyond licence)

Dr Andrew Wilcock

Outline of session

• Who is ‘uncomfortable’ and why?
• Licensing process
• Use of an licensed drug ‘off-label’
• Use of an unlicensed drug
• Prevalence
• Guidance
• Summary
• Questions/discussion

“Walking the tightrope”

“Life is being on the wire, everything else is just waiting.”

Karl Wallenda

The balancing of pros and cons is an inherent part of life (and prescribing)

Licensing process

• drugs require a marketing authorisation before they can be marketed in the UK
• EU process via the European Medicines Agency (EMEA)
• National process; UK via Medicines and Healthcare products Regulatory Agency (MHRA).

Licensing process: EU

• centralised; EMEA / European Commission grants a single marketing authorisation valid for the whole EU
• decentralised; simultaneous application made to several member states, with one taking the lead; if successful, national licenses are granted in each state
Licensing process: EU

- mutual recognition; application for authorisation in a member state when marketing authorisation exists in another member state.

Licensing process: UK

- MHRA undertakes a medical, pharmaceutical and scientific assessment of the drug
- seek advice from the Commission on Human Medicines (CHM), an independent advisory body
- in turn is assisted by specialist expert advisory groups.

Licensing process: UK

- new drugs may have relatively limited safety information (risk management plan)
- restrictions are imposed if evidence of safety and efficacy is unavailable in particular patient groups, e.g. children
- marketing authorisations are granted for up to 5 years and then reviewed.

Licensing process: UK

- ensures that in relation to the drugs licensed use(s), there has been due consideration of
  - its efficacy, safety and quality
  - benefits outweigh the potential risks
  - appropriate accompanying product information and labelling

Licensing process: UK

- the marketing authorisation defines which conditions and patient groups a pharmaceutical company can market and supply the drug for

Licensing process: UK

- BUT the marketing authorisation doesn't limit what the drug could be used for, i.e. off-label
- clinical experience may reveal other uses
**Licensing process: UK**

- for these to receive a marketing authorisation, evidence would need to be gathered and submitted
- the cost of this, perhaps coupled with a small market for the new indication, often means that a revised application is not made.

It is important to recognize that the licensing process regulates the marketing activities of pharma companies and not a prescriber’s practice.

**Use of a licensed drug ‘off-label’**

- use of a drug is **beyond licence** or ‘off-label’ when it is outside of the specifications of its marketing authorisation
- e.g. for an unlicensed indication, or in doses, formulations or a route not covered by the licence.

**Use of an unlicensed drug**

- various definitions
- use of a drug not covered by a marketing authorisation as medicinal for human use.

**Use of an unlicensed drug**

- new drug used in a clinical trial
- drugs prepared by a licensed manufacturer but not on sale in the UK, e.g.:
  - new drugs, awaiting a MA
  - drugs with abandoned, suspended or revoked MA
  - imported drugs which have a MA in another country but not the UK

**Use of an unlicensed drug**

- specials: drugs obtained from an NHS or commercial supplier who holds a ‘specials’ manufacturing licence
- products made up in pharmacy under the supervision of a pharmacist
- products made by the pharmacy to the order of a doctor for an individual patient.
Prevalence

• in palliative care the off-label use of drugs is widespread, accounting for up to 1/4 of all prescriptions
• not unique to palliative care
• also oncology, paediatrics, psychiatry
• common, ‘usual’ part of practice.

Prevalence

• in palliative care use of unlicensed medicines is even more widespread
• the mixing of 2+ drugs for CSCI is considered the preparation of an unlicensed medicine
• required changes in legislation.

But do you know when you are prescribing off label/an unlicensed drug?

Quiz

Do you know your off-label from your elbow?

10 questions

Licensed (L) Off-label (OL) Unlicensed (UL)

Questions

1. Hyoscine BB SC for drooling?
2. Etamsylate PO for surface bleeding from ulcerating tumours?
3. Diazepam PO for muscle spasm?
4. Midazolam SC for terminal agitation?
5. Levomepromazine SC for pain in the terminally ill patient?

Questions

6. Naproxen PO for cancer pain?
7. Morphine PO for cough?
8. Morphine PO for moderate pain?
9. Morphine PO for breathlessness?
10. Alfentanil nasal spray for pain? (Torbay Hospital)
**Answers**

1. Hyoscine BB SC for drooling? **OL**
2. Etamsylate PO for surface bleeding from ulcerating tumours? **OL**
3. Diazepam PO for muscle spasm? **L**
4. Midazolam SC for terminal agitation? **OL**
5. Levomepromazine SC for pain in the terminally ill patient? **L**

6. Naproxen PO for cancer pain? **OL**
7. Morphine PO for cough? **OL**
8. Morphine PO for moderate pain? **OL**
9. Morphine PO for breathlessness? **OL**
10. Alfentanil nasal spray for pain? (Torbay Hospital) **UL**

**Guidance: Doctors**

In the UK, a doctor may legally:
- use or advise using a licensed drug off-label
- prescribe unlicensed drugs
- and more…

**Guidance: supplementary prescribers**

Nurses, pharmacists and others registered as *supplementary prescribers* can prescribe licensed drugs off-label and unlicensed drugs.

(In the framework of an agreed clinical management plan for a specific patient in partnership with a doctor or dentist)

**Guidance: independent prescribers**

Nurses or pharmacists who are registered as *independent prescribers* can prescribe licensed medicines off-label if this is accepted clinical practice, and unlicensed drugs.
Guidance: mixing drugs
Changes to medicine regulations have recently been made to specifically enable supplementary and independent prescribers to mix, or direct others to mix, two or more drugs prior to administration.

Guidance: mixing CDs
Changes are still required to the Misuse of Drugs Regulations to permit independent prescribers to mix, or direct others to mix, CDs legally.

Guidance: mixing CDs
The MHRA has advised that it: “.would not take enforcement action against those prescribing and administering mixtures of licensed medicines in palliative care unless it would be in the public interest to do so.”

Prescriber’s responsibilities
• the consequences of these actions lies with the prescriber
• must be competent, operate within the professional codes and ethics of their statutory bodies and the prescribing practices of their employers

Prescriber’s responsibilities
When prescribing a drug off-label, a prescriber should:
• be satisfied that such use would better serve the patient’s needs than a licensed alternative (if one exists)
Prescriber’s responsibilities

- be satisfied that there is sufficient evidence/experience of using the drug to show its safety and efficacy
- record the drug prescribed and, when not following common practice, the reasons for its choice in the patient's notes

Prescriber’s responsibilities

- provide sufficient information to the patient/those authorising treatment about the drug’s expected benefits and potential risks to allow them to make an informed decision

Prescriber’s responsibilities

- take responsibility for prescribing the unlicensed drug, for overseeing the patient's care, or arrange for another doctor to do so
- report suspected adverse drug reactions via the Yellow Card Scheme (www.yellowcard.gov.uk).

Pragmatic for palliative care?

Concerns that a detailed approach on every occasion could be:

- impractical
- burdensome for the patient
- anxiety provoking and result in refusal of beneficial treatment.

Pavis and Wilcock 2001

Pragmatic for palliative care?

- a UK survey showed that <5% of palliative medicine specialists always obtain verbal/written consent and document in the notes when using a drug off-label

Pavis and Wilcock 2001

Pragmatic for palliative care?

- about half indicated that they would sometimes obtain verbal consent or document in the notes when using treatments which are not widely used within the specialty, e.g. ketamine, octreotide, ketorolac.
Pragmatic for palliative care?

More recent advice suggests that where current practice supports the off-label use of a drug, it may not be necessary to draw attention to the licence when seeking consent.

GMC 2008

However, information should be given when:

- this is likely to be considered significant to the patient
- the off-label use lacks supporting evidence/experience
- using an unlicensed drug.

GMC 2008

Current practice supports use?

[Image of BNF and PCF3]

Current practice supports use?

Mixing drugs

[Link to palliativedrugs.com]

Current practice supports use?

[Image of APM/Pain Society]

APM/Pain Society statement

- the use of drugs beyond licence should be seen as a legitimate aspect of clinical practice
- the use of drugs beyond licence in palliative care and pain management practice is currently both necessary and common.

Additional information: See PCF3

- NHS Trusts / other institutions have policies and produced information cards or leaflets for patients and caregivers
- a position statement has also been produced by the APM and the Pain Society (due to be updated)
Summary

• doctors and other prescriber’s can prescribe off-label or unlicensed drugs
• it is common practice in palliative care
• there are additional responsibilities on the prescriber, including the provision of information
• make use of existing resources.