FPM
ANZCA

Use of “off label” or drugs beyond licence in pain medicine

Background

The following summary has been prepared using information from the Association for Palliative Medicine and the Pain Society of Great Britain and Ireland [1]. Their documents highlight the clinical and legal implications of the use of drugs beyond licence.

A discussion paper on this topic was prepared by NSW Therapeutic Advisory Group Inc[2] [3] to assist policy development by NSW Hospital and Area Drug Committees and a similar paper is available from the New Zealand Government’s Medsafe website [4].

Although the use of drugs beyond licence refers to “off-label use”, Fellows of the Faculty of Pain Medicine (FPM) ought also to be aware of regulations relating to the prescription or importation of unlicensed drugs, and the prescribing of medications under the Pharmaceutical Benefits Scheme (PBS), and in New Zealand the Pharmaceutical Schedule, which may impose further restrictions for funding / subsidised prescribing. These are regulated differently, but issues related to them are frequently confused by medical practitioners, who have professional, ethical, social and legal responsibilities related to prescribing that may conflict.

Off-label use

Once evaluated, approved and registered for use, medicines are deemed “labelled” for use as defined in their approved product information leaflet. The term “off-label use” refers to prescriptions for registered medicines for use in a manner not listed in the approved prescribing guidelines such as those released by the Therapeutic Goods Administration in Australia, or the New Zealand Medicine and Medical Devices Safety Authority. The term “off-label use” may pertain to an unapproved indication, route of administration, age group, or dose. The term does not relate to any prescribing conditions outlined by the PBS or PHARMAC in NZ.

Pharmaceutical companies are prohibited from promoting “off-label” medication. The regulatory issues relating to prescribers in section 19 of the Therapeutic Goods Act 1989 (the “Act”) are generally poorly understood and have not been tested in law. It has been argued that section 19 of the Act only sanctions off-label use in the treatment of an individual person or when conducting experimental use in a group of persons, but provides no approval for use in a potentially unlimited number of persons. In response to a request for clarification, the Therapeutic Goods Association (TGA) has indicated that it is not able to interpret legislation or provide any legal advice. However, a previous national manager of TGA indicated that the: "regulation of supply of drugs, in so far as their use and indications are concerned, is confined to supply by sponsors…..The Act neither prohibits or sanctions off-label use of drugs by non-sponsors. Rather, prescribers must accept responsibility for such use. This would amount effectively to an indemnity provision”. [5]

Use of unlicensed drugs

Several mechanisms exist to enable the use of unlicensed and thereby unregistered drugs, as described by the TGA and Medsafe on their websites [6]. These include:

1. The importation of the drugs for personal use;
2. Prescribing medication under Special Access Scheme (NZ:Sect 25); and
3. For use in approved clinical trials.

The use of unlicensed and unregistered medicines may include use of:

- Modified formulations of registered medicines.
- Orphan drugs or those with a niche market (for example, clonidine 30mg/2ml).
- "Not for human use" chemicals.
- Previously withdrawn medications (for example, oral hydromorphone, cyclizine).
- Medications approved elsewhere and/or awaiting registration (eg lignocaine patches); ormedications used in clinical trials.

Orphan drug status may be sought to license the use of unregistered medicines.

Extent of off-label and unlicensed use of medications

Off-label and unlicensed use is common in several areas of medicine particularly where evidence is less readily attainable (for example, paediatrics) or when economic factors limit applications for approval or even when desperation or the desire for innovative medicine drives practice outside the boundaries of established evidence. In Australia, 60 per cent of prescriptions in paediatric hospitals were determined to be unlicensed or off-label [7], and at Peter MacCallum Cancer Centre, 85 patients received at least one medication that was off-label or unlicensed [8]. In palliative care units in the United Kingdom, approximately 25 per cent of prescriptions are off-label [9]. In Sydney 26 per cent of prescriptions in the out patients setting were for off-label medications [10].

Widespread use of off-label drugs and the prescribing of unlicensed medications by pain medicine practitioners may occur without appropriate knowledge or consideration of the medical, legal and ethical implications. Included here would be the use of epidural corticosteroids [11] and most long term intrathecal medications. Such prescribing may not be openly acknowledged for the fear of medicolegal liability. As such, there needs to be clarification to ensure practitioners and patients are aware of the issues, their rights and responsibilities.

Issues to be considered

1. Problems relating to off-label prescribing include a relative lack of readily available information for prescribers, nurses and consumers about the unapproved use of some medications and especially the higher risk of adverse drug reactions [12]. Consumers should give fully informed consent to the use of off-label or unlicensed drug use.

2. Professional groups such as FPM should play a role in guiding health policy pertaining to off-label prescribing in their field of medicine. Hospital administrators and drug committees have been encouraged to establish adequate support tools, including decision-support aids,

to ensure sage and rational use of medications. Some suggested tools have already been developed by the NSW TAG [see appendix I]

3. Although there are frequent misapprehensions about off-label use, influential bodies such as the American Academy of Pediatrics have indicated that the failure to prescribe off-label medications where appropriate may constitute malpractice.

4. There needs to be a delicate balance between formulating policy guidelines independent of pharmaceutical company influence whilst still maintaining a good working relationship to obtain maximum knowledge about unlicensed or off-label use of medications. Potential conflicts of interest should be acknowledged.

5. It is important to rigorously analyse the following:

- Level of evidence supporting use of the off label drug;
- Consideration of risk-benefit ratios; and
- The clinical impact of use or non-use of the drug.

Fellows should aim to collaboratively generate the clinical evidence that may be required to enable potential future use or licensing.

6. Central to the issues to be considered and clarified is the requirement for sufficient information to be presented to the patient for him/her to make an informed choice about their use of the off-label or unlicensed drug. The need for written informed consent should be considered [1].

References

[1] *The Use of Drugs Beyond Licence in Palliative Medicine and Pain Management* the British Pain Society 2005, http://www.palliative-medicine.org and http://www.painsociety.org.

[2] *Off-Label Use of Registered Medicine and Use of Medicines Under the Personal Importation Scheme in NSW Public Hospitals*, 2003, http://www.nswtag.org.au.

[3] Madlen Gazarian, Maria Kelly, John R McPhee, Linda V Graudins, Robyn L Ward and Terence J Campbell *Off-label use of medicines: consensus recommendations for evaluating appropriateness* — Med J Aust 2006; 185 (10): 544-548.

[4] http://www.medsafe.gov.nz.

[5] Vaughan GN, *Non-Approved Indications for Drugs*, 24 Austr J Hosp Pharm 1994, pp 356 – 357

[6] http://www.tga.gov.au , http://www.medsafe.govt.nz/Profs/RIss/unapp.asp.
NZ: *Medicines Act 1981, Sect 25 & 29* makes provision for unapproved medicines and uses, without restrictions. *Code of Health and Disability Services Consumers' Rights is the main determinant of obligations to the patient*. *Health Information Privacy Code, Rule 3*, obligates practitioner to inform patient that information about the supply of unapproved medication will be notified in identifiable form to Medsafe database.

[7] Turner S, *Unregistered and Off Label Drug Use in Paediatric Inpatients*, 29 Austr J Hosp Pharm 1999, pp 265 – 268.

[8] Poole SG & Dooley MJ, *Off-Label prescribing in Oncology*, 12 Support Care Cancer 2004, pp 302 – 305.

[9] *The Use of Drugs Beyond Licence in Palliative Medicine and Pain Management* the British Pain Society 2005, http://www.palliative-medicine.org and http://www.painsociety.org.

[10] Bicknell M & Weeks L, *Off-Label Drug Use in the Outpatient Setting - a Pilot*, 25 Austr J Hosp Pharm 1995, pp 527 - 529.

[11] Epidural Steroid, NZ: http://www.medsafe.govt.nz/Profs/RIss/unapp.asp#Scenario%203.

[12] Stephenson T, *Medicines for Children - the Last Century and The Next*, 85 Arch Dis Child 2001, pp 177 - 179.

[13] New Zealand: *Code of Health and Disability Services Consumers' Rights*. Right 6 – to be fully informed; Right 7 – to give informed consent.

Faculty of Pain Medicine Professional Documents

POLICY – defined as 'a course of action adopted and pursued by the Faculty. These are matters coming within the authority and control of the Faculty.

RECOMMENDATIONS – defined as 'advisable courses of action'.

GUIDELINES – defined as 'a document offering advice'. These may be clinical (in which case they will eventually be evidence-based), or non-clinical.

STATEMENTS – defined as 'a communication setting out information'.

This document has been prepared having regard to general circumstances, and it is the responsibility of the practitioner to have express regard to the particular circumstances of each case, and the application of this policy document in each case.

Professional documents are reviewed from time to time, and it is the responsibility of the practitioner to ensure that the practitioner has obtained the current version. Professional documents have been prepared having regard to the information available at the time of their preparation, and the practitioner should therefore have regard to any information, research or material which may have been published or become available subsequently.

Whilst the College and Faculty endeavours to ensure that documents are as current as possible at the time of their preparation, they take no responsibility for matters arising from changed circumstances or information or material which may have become available subsequently.

Promulgated: 2007

Date of current document: 2007

ANZCA website: www.anzca.edu.au
FPM website: www.anzca.edu.au/fpm

Appendix I

For New Zealand, Summary:

You have a professional ethical and legal obligation to:

- Evaluate the evidence for yourself.
- Inform the patient the drug is unapproved.
- Discuss alternatives.
- Tell patient Medsafe will be informed of unapproved medicine.
- Obtain written consent [14] IF:
    - Use of the medication considered experimental.
    - Minimal evidence to support its use.
    - Equivocal evidence of efficacy or safety if used this way.
    - The use is part of a clinical trial.