Off-label prescribing in pain medicine practice

Introduction

The ethical and legal framework for off-label prescribing in pain medicine has been a subject of considerable discussion throughout the existence of FPM. The following guidance has been formulated to articulate the consensus views of the faculty leadership as well as reflect legal and ethical principles to inform the professional practice of fellows and trainees.

- The *Therapeutic Goods Act 1989* provides the legal framework for supply and distribution of therapeutic goods in Australia. The *Medicines Act 1981* is the controlling legislation in New Zealand.

- The Therapeutic Goods Administration (TGA) is responsible for maintaining the Australian Register of Therapeutic Goods (ARTG) which lists the therapeutic goods that may legally be supplied, sold or otherwise distributed commercially, and unless explicitly exempted it is illegal to import, export or sell goods which are not on the ARTG for therapeutic purposes as defined by the Act. The New Zealand Medicines and Medical Devices Safety Authority (Medsafe) is the corresponding body in New Zealand which makes recommendations to the Ministry of Health regarding approvals to import and distribute therapeutic goods in that jurisdiction.

- In a technical legal sense, use of a medication for an indication that is not on the ARTG constitutes 'unapproved use' for which an exemption should be sought to prevent an offence occurring, but there has not been a prosecution under the Act which would clarify exactly how the law may apply. The TGA is constituted to regulate products and industry sponsors, NOT to direct medical practice, and hence off-label prescribing falls outside its recognized jurisdiction. The legal principle of *de minimis* is also relevant, as technical breaches of the law which cause no harm (and may in fact be beneficial to the community overall) are not prosecuted.

- Ethically, the case for prescribing existing medicines off-label is based on the argument that as expert clinicians, SPMPs are able to identify evidence-based (or at minimum scientifically plausible) unapproved uses and provide safe and effective treatment that patients would be precluded from if the letter of the law was followed.

- Since the professional judgement of the clinician effectively takes over the role of the TGA, the legal and ethical requirements for clinicians are increased in off-label prescribing.

- The Council of Australian Therapeutic Advisory Groups (CATAG) has produced a suggested framework to guide decisions about the level of risk and therefore the ethical use of off-label medications, introducing the following terms:

  Routine use: for medications with significant evidence base but no regulatory listing for the indication eg Duloxetine for peripheral neuropathic pain. Normal consent requirements apply.

  Exceptional use: individual patient use where pre-specified criteria exist for patient selection but high-quality evidence is lacking or mixed. e.g. use of strong opioids for patients with post-herpetic neuralgia. Written consent with a record of risks and benefits discussed should be obtained.

  Conditional use, with evidence development: Evidence may be low-quality or conflicting, and use of the medicine is conditional upon further evidence of safety and efficacy being developed. Consent should include agreement to collect safety and outcome data for

evidence development in addition to the above. Ketamine infusions for persistent pain are a good example.

Research use: Use within a formal protocol approved by HREC with full consent process for research trial. Scientific plausibility should be adequate to justify use in this setting where little or no clinical evidence of either safety or efficacy may exist.

FPM endorses the adoption of the CATAG terminology and consent requirements for off-label medicine use. Specialist Pain Medicine Physicians are recommended to develop consent procedures in their practices in collaboration with local health service therapeutics advisory committees where possible.

Principles to guide off-label prescribing in pain medicine

Given the slow pace of regulatory and funding approvals by statutory bodies in faculty jurisdictions, as well as the incomplete evidence base for many commonly prescribed treatments, ethical prescribing of off-label medicines to pain patients is of paramount importance to the safe and effective practice of pain medicine.

The faculty has resolved to adopt the seven Guiding Principles for off label prescribing articulated by the Council of Australian Therapeutic Advisory Groups (CATAG) in their 2013 document entitled *Rethinking medicines decision-making in Australian Hospitals; Guiding principles for the quality use of off label medicines* (the Guidelines).

Guiding Principle 1. Consider the off-label use of the medicine only when all other options, including medicines approved by the TGA, are unavailable, exhausted, not tolerated or unsuitable

SPMPs practice in diverse settings, with variable funding arrangements for medicines that are prescribed and variable access to other evidence-based potential treatments. Sensitivity to practice context is essential to making professional judgements regarding the suitability, availability or advisability of individual medications for individual patients. While the Guidelines refer specifically to the Australian context, the principle is generalisable to other countries and health systems. Not listed in the criteria within Guiding Principle 1 is the variable of patient choice, and it should be noted that patient autonomy should be respected if there is a particular reason why they have strong objections to trialling an approved medication.

Guiding Principle 2. Use high-quality evidence to determine appropriateness of off-label medicine use.

In this context, the term 'evidence' may refer to basic science, clinical pharmacology studies or well conducted non-RCT published data. Providing adequate consent for off label use of medications requires is PMP is to be thoroughly familiar and up-to-date with developments in basic science and pharmacology related to drugs which may be of benefit in persistent pain states.

Guiding Principle 3. Involve the patient/carer in shared decision-making when recommending an off-label medicine.

CATAG has developed a decision support tool (appendix 1) to help determine the level of informed consent required to provide ethical prescribing in situations where the evidence being relied upon may be significantly below high quality. Obtaining a consent which goes beyond the basic minimum legal requirement, and includes genuine engagement with the patient or their representatives decision-maker should be routine practice for SPMPs. Documentation should reflect the level of consent obtained in clinical notes.

Guiding Principle 4. Consult the Drug and Therapeutics Committee when prescribing an off-label medicine, except when the use of a medicine off label is considered routine.

This recommendation in the Guidelines refers specifically to hospitals, but the principle of requiring a higher level of scrutiny and accountability for off-label medicine use that is considered Conditional, Exceptional or Investigational is applicable in any area of practice.

Guiding Principle 5. Ensure appropriate information is available at all steps of the medicines management pathway

For pain clinics, no matter what setting, patient information should be provided in written form to support decision-making and discussions around off label medicine use. Due to the frequency of off-label use in pain medicine practice, particularly those classifiable as Exceptional use or Conditional use, accessible information for patients and families should be easily available.

Guiding Principle 6. Monitor outcomes, effectiveness and adverse events.

Informal monitoring of outcomes forms the basis of all clinical practice, however because of the need to provide increased accountability and potentially contribute to evidence development, pharmacovigilance procedures such as audits or presentations of outcomes ought to be routinely performed where provision of off label medicines has become systematised. Monitoring of adverse events is particularly important, given the limited availability of large-scale studies which may uncover unpredicted, uncommon adverse events. Unexpected adverse events which may be related to off label use of medications need to be publicised and appropriately investigated to add to the knowledge base that can be accessible to all SPMP's.

Guiding Principle 7. Consider liability and accountability when using medicines off label.

No matter how well-intentioned off-label prescribing may be, the heightened legal and disciplinary risks surrounding its use need to be acknowledged and respected. Recordkeeping, documentation of consent, collection of both positive and negative outcomes are of enormous assistance if medico legal proceedings are threatened. Contemporary documentation of the decision-making process is critical to protecting against allegations of negligent or unprofessional prescribing.

The commentary above regarding each Guiding Principle should be read in conjunction with the detailed advice provided in the Guidelines, and faculty fellows are encouraged to read the document in full to inform their own practice.