Off-label use of medicines: consensus recommendations for evaluating appropriateness

Madlen Gazarian, Maria Kelly, John R McPhee, Linda V Graudins, Robyn L Ward and Terence J Campbell

ABSTRACT

- Off-label prescribing is the prescription of a registered medicine for a use that is not included in the product information. The practice is common, with rates up to 40% in adults and up to 90% in paediatric patients.
- Off-label prescribing is not illegal and may sometimes be clinically appropriate, but is associated with a number of clinical, safety and ethical issues. To date, no explicit guidance has been available to help clinicians assess appropriateness in off-label prescribing.
- We describe the development of a guide for clinicians, policymakers and funders of health care in evaluating the appropriateness of medicines proposed for off-label use.
- Three broad categories of appropriate off-label use are identified:
  - off-label use justified by high-quality evidence;
  - use within the context of a formal research proposal; and
  - exceptional use, justified by individual clinical circumstances.
- An appropriate process for informed consent is proposed for each category.
- If there is no high-quality evidence supporting off-label use, and the medicine is not suitable for exceptional or research indications, its use is generally not recommended. This will reduce inappropriate use, enhance patient safety by reducing exposure to unnecessary risk, and may stimulate more clinically relevant medicines research.

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Off-label (unlabelled or unapproved) prescribing refers to prescribing a registered medicine for a use that is not included or is disclaimed in the product information.[1] Examples include use in a different indication, patient age range, dose or route to that which is approved by regulatory authorities. An *unlicensed* or unregistered medicine is a medicine or dosage form of a medicine that has not been evaluated nor approved in Australia and hence not entered on the Australian Register of Therapeutic Goods.

Much has been published about the extent of, and problems associated with, the off-label and unlicensed use of medicines, particularly in children.[2-8] The extent of off-label prescribing is reported to be between 7.5% and 40% in adults,[2-5] and may be up to 90% in some hospitalised paediatric patients.[6-10] Although the product information may be the main reference for many prescribers, in some cases the best available evidence may not be reflected in the product information,[11] so off-label and yet evidence-based prescribing may be the more appropriate choice. This may be because new evidence has become available after marketing (as there is currently no provision for regular updating of the product information) or because there is insufficient incentive for the sponsor to seek an extension of labelling. However, in most cases, adequate research evidence to support off-label prescribing is lacking. A recent survey of 150 million off-label prescriptions in the United States found that 73% had little or no scientific support, even when sources other than the product information were searched.[12] Thus, only a small proportion of off-label prescribing may be justified by scientific evidence.

While off-label prescribing is not illegal,[13-16] and may sometimes be clinically appropriate (eg, exceptional use in an appropriately informed patient with serious disease, when there are no alternatives and potential benefits outweigh potential risks),[17] it brings with it a number of clinical, safety and ethical issues.[13,15,18] For example, prescribers may expose children to ineffective therapies and to unknown risks of adverse events by extrapolating from adult data.[16] There is now accumulating evidence of resulting harm, with increased incidence and seriousness of adverse drug reactions associated with off-label and unlicensed medicines use in children.[19] Furthermore, some long established off-label uses have been shown to either be ineffective or harmful when subjected to proper evaluation (eg, deaths associated with propofol used for sedation in paediatric intensive care).[20,21]

In contrast to the considerable literature about the extent and consequences of off-label prescribing, there has been no specific guidance to help clinicians trying to make decisions about the appropriateness of such prescribing. Most clinicians perceive off-label prescribing as appropriate and believe that the benefits outweigh the risks.[22] However, their awareness of consequences appears to be minimal, with a low level of concern about risk of side effects, unevaluated efficacy and issues surrounding informed consent.[23] This raises questions about the validity of their risk–benefit analysis when making decisions about off-label prescribing. Recent legislative and regulatory initiatives in the US[20,21] and, more recently, the European Union,[24] have provided incentives and inducements for the pharmaceutical industry to undertake more medicines research in children. Eventually these initiatives may reduce the need to consider off-label prescribing in many instances.[20] Until such time, practitioners are expected to "use their professional judgement" to determine the appropriateness of off-label use in individual patients,[17] although no explicit guidance in exercising such judgement is available. In addition, the legal and ethical ramifications of such prescribing appear to be a source of confusion, with variability in opinions and practice among prescribers and professional organisations.[10,14,17]

We describe the development of a practical and explicit approach to guide clinicians (doctors, pharmacists and nurse practitioners), policymakers (eg, drug and therapeutics committees [DTCs], authors of medicines compendia, therapeutic guidelines developers) and funders of health care (government and non-government organisations) in systematically evaluating the appropriateness of medicines proposed for off-label use. These consensus recommendations are intended to help distinguish between off-label use that is justified by high-quality evidence, and innovative therapy that may be justified in individual clinical circum-

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stances (exceptional use) or that should be pursued in a research context. We also provide guidance on appropriate processes for informed consent.

Consensus development process

Quality use of medicines (QUM) is defined by the Pharmaceutical Health and Rational use of Medicines Committee as selecting management options wisely; choosing suitable medicines if a medicine is considered necessary; and using medicines safely and effectively. New South Wales Therapeutic Advisory Group (NSW TAG) is an independent state government-funded organisation that aims to promote QUM in the state's public hospitals and the wider community through collaboration and consensus. The NSW state public health system provides access to nearly 17 000 beds and is responsible for over 1.5 million admissions annually.[25] NSW TAG's membership comprises clinical pharmacologists, directors of pharmacy and other clinicians, representing DTCs from 50 teaching and non-teaching hospitals.

A working party of NSW TAG (Box 1) was established by identifying areas of expertise considered relevant to address the issue of off-label prescribing and to develop recommendations to guide appropriate practice. Nominations were called from NSW TAG members with expertise or special interest in this area. Gaps in expertise (eg, law and ethics) were identified, and appropriate non-TAG members were invited to join the working party. The final working party included hospital-based doctors and pharmacists with expertise in paediatrics, general medicine, oncology, clinical pharmacology and therapeutics, clinical epidemiology, and evidence-based medicine; a consultant in health ethics and law; a representative from the NSW Department of Health; and a representative from the NSW TAG secretariat. The Chair of the working party was a former member of the Australian Drug Evaluation Committee, and two members of the working party are current members of the Pharmaceutical Benefits Advisory Committee.

Our process of consensus development involved consultation with NSW TAG members; NSW teaching hospitals' DTCs; Pharmaceutical Services Branch, NSW Health Department; and MotherSafe (the Medications in Pregnancy Advisory Service in NSW). Overall, there was no strong dissent and any disagreements were resolved by discussion.

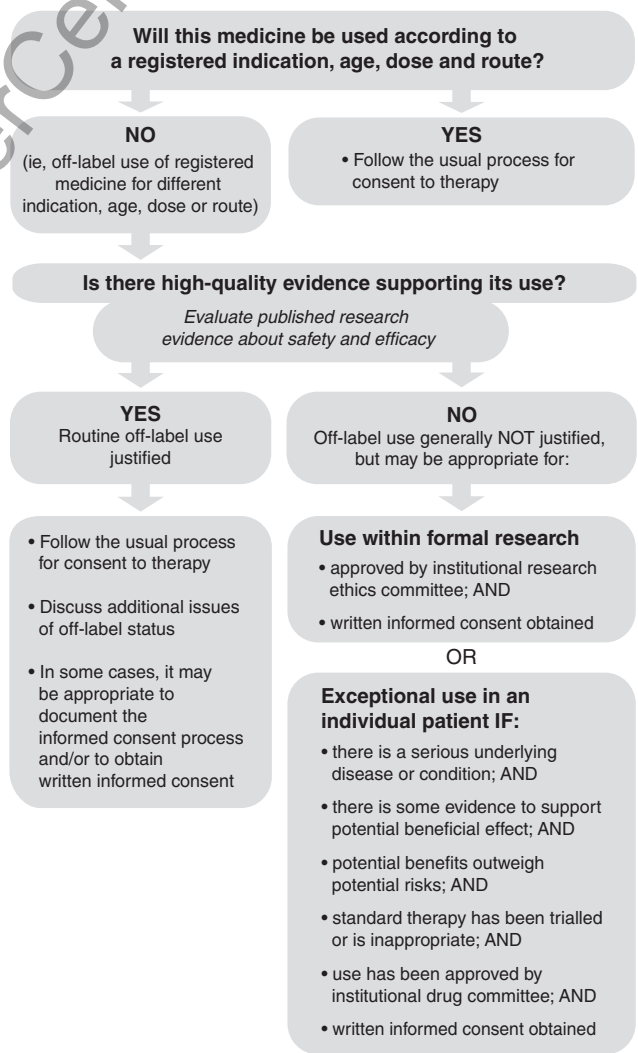
Recommendations

Assessing appropriateness — evaluation of evidence

To provide a systematic process for evaluating the appropriateness of any proposed off-label use, a decision algorithm (Box 2) with accompanying explanatory notes was developed. The notes guide clinicians considering off-label use of a particular medicine in answering the question: "Is there high-quality evidence supporting its use?"

In general, the answer to this question is derived from a critical evaluation of the best available patient-based research evidence on both efficacy and safety. The level of rigour of this evaluation should be similar to that used by the Therapeutic Goods Adminis-

2 Assessing appropriateness of off-label medicines use



tration for clinical evaluation of medicines submitted for registration approval. Accepted guidelines for critical appraisal of therapeutic studies,[26-29] for grading of "strength of evidence"[30,31] and for deciding about applicability of research evidence to individual patient circumstances[32,33] can be used in answering this question. Various Australian bodies, such as state-based therapeutics advisory groups (eg, NSW TAG) or the National Prescribing Service Ltd, are available to help clinicians (in hospital and community practice) and policymakers (eg, hospital DTCs) evaluate the published literature for new medicines or proposed new uses of existing medicines. Special consideration may need to be given to the needs of special populations (eg, paediatric patients). Systematically developed, evidence-based drug information resources such as the *Australian medicines handbook*, *Therapeutic guidelines*, or international resources such as guidance from the National Institute for Health and Clinical Excellence in the United Kingdom or the Canadian Agency for Drugs and Technologies in Health should also be consulted. However, these resources are generally not timely enough to provide useful guidance for very newly marketed medicines,[34] which is the category where many off-label uses initially occur.[35]

Routine off-label use can be justified if there is high-quality evidence supporting efficacy or effectiveness, and sufficient evidence about the medicine's safety profile to suggest an overall reasonable benefit–risk ratio for a given clinical context (eg, need for longer-term outcome data if a medicine is intended for long-term use). This is especially pertinent with newly marketed medicines, as the available evidence about safety at the time of registration is limited, with a more complete profile emerging only after larger numbers of people have been exposed over a longer period of time. The available efficacy and safety data should be weighed against the seriousness of the underlying condition. As a general rule, the less serious the clinical need, the higher the level of evidence needed to support off-label use of the medicine. Individual patient values and preferences should also be considered.[36]

Existing guidelines and systems for ranking evidence are focused mostly on *efficacy* evaluation. The types of studies that should be sought to evaluate the full spectrum of *safety* of a particular medicine are broader. In many instances, only observational studies (eg, cohort or case–control studies) from post-marketing surveillance, rather than randomised controlled trials or meta-analyses, will provide the necessary data. This applies particularly to rare but potentially serious adverse effects (eg, serious sepsis and death associated with anti-tumour necrosis factor therapy[37]) or those which manifest after prolonged exposure (eg, hepatotoxicity with low-dose weekly methotrexate for rheumatoid arthritis[38]) or after a long latent period (eg, infertility after chemotherapy for cancer in childhood[39]).

In some instances, high-quality research evidence supporting the use of a particular medicine (eg, older off-patent medicines) may not be available and may be unlikely ever to become available. However, there may be extensive experience supporting the efficacy and safety of such medicines. Although such data or "expert opinion" is considered to be of lower quality than high-quality research evidence, there are examples where it may be used to inform decisions about off-label use of a medicine. There are several authoritative medicines compendia that make recommendations for appropriate use supported either by research evidence and/or consensus opinion based on extensive experience with various medicines. These include the *Australian medicines handbook*, *Therapeutic guidelines* (Australia) and the *British national formulary for children* (UK). Other "authoritative" sources may include recommendations from professional societies, although the quality and validity of some of these can be quite variable. Less formal sources of support based on "experience" or "opinion" are less acceptable, and caution is recommended when considering this level of support for off-label use.[30,40] It should be emphasised that this category of support for off-label use needs to be systematically reviewed as new research evidence becomes available. For example, some recent US initiatives have stimulated research into off-label uses of medicines in children, generating new evidence about efficacy, safety, and appropriate dosing, with significant implications for long established prescribing practices.[20] The current process for determining the content of the product information should be reviewed to allow more timely collation and effective dissemination of available new evidence to all prescribers.

These issues can be addressed by applying the algorithm (Box 2), which identifies three broad categories of appropriate off-label use:

- use justified by high-quality evidence;
- use within the context of a formal research proposal; and
- exceptional use, justified by individual clinical circumstances (see Box 2 for criteria).

If there is no high-quality evidence supporting off-label use of a particular medicine, and it is not suitable for exceptional or research indications, its use is generally not recommended. Moreover, answering, "yes" to the question "is there high-quality evidence supporting its use?" means that the drug may be used, not necessarily that it should be used in a specific context. Proposed routine off-label uses of new medicines may only be justified if there is evidence from comparative studies showing an advantage in effectiveness and/or safety and/or cost-effectiveness over existing alternatives. For newly marketed medicines, such evidence will only emerge after the passage of time, so caution should be exercised in considering the appropriateness of proposed off-label uses of most new medicines. Policymakers, including DTCs, guideline developers, and authors of medicines compendia and other decision-support resources (eg, electronic prescribing packages), should resist making recommendations for routine off-label uses before such evidence becomes available, as this may encourage widespread off-label use inappropriately and diminish the incentive to conduct the research that is needed.

Patient consent

Previous advice from US and UK professional organisations has been that no special provisions for institutional review or informed consent were needed for proposed off-label uses of registered medicines.[10,17] However, not all categories of off-label use carry the same level of risk, and so a more explicit approach to the type of patient consent process that might be appropriate is also needed.

Usual consent to therapy: When there is high-quality evidence supporting off-label use of a medicine (ie, routine off-label use is justified), the usual process of obtaining consent for treatment should be followed. This includes discussing with the patient/parents/carer the reason for using the medicine, possible alternative therapies and potential side effects. As the medicine is being used off-label, additional information about any uncertainties associated with such use should be given. In some cases, patients

may require additional information to address specific concerns. Documentation of the consent process is recommended and, in some cases, obtaining written consent may be appropriate.

Written informed consent: When there is no high-quality evidence supporting routine off-label use of a medicine, there may still be a case for its use in a particular patient (see "exceptional use" criteria in Box 2), but there may be a higher level of risk. In such cases, an independent evaluation of the medicine's potential benefits and risks should be undertaken (eg, by a DTC) and, if appropriate, approval should be given for individual "exceptional use". Alternatively, use may occur within the context of a formal research proposal that has been evaluated and approved by an institutional research ethics committee. In either case, written informed consent is required.

A more detailed analysis of the legal and ethical dimensions associated with consent and the administration of off-label medicines can be found at <http://www.ciap.health.nsw.gov.au/nswtag/publications/otherdocs/off_label_use_registered_medicines.pdf>.

Conclusions

These recommendations provide a systematic approach for clinicians and policymakers in evaluating the appropriateness of medicines proposed for off-label use, with a number of resulting benefits. First, by helping to distinguish more explicitly between off-label medicines use supported by scientific evidence and innovative therapy, they should help promote evidence-based prescribing. Second, limiting off-label use of medicines to situations where it is justified by prespecified criteria will reduce inappropriate use (including that which may be inappropriately promoted by the pharmaceutical industry)[41] and enhance patient safety by reducing exposure to unnecessary risk. Third, a more explicit process for patient consent will help to better inform patients, parents and carers about the benefits and risks associated with innovative therapy. Fourth, the systematic identification of gaps in knowledge in areas of clinical need will help set the future research agenda, which in turn should result in more useful new knowledge to inform future treatment decisions. Finally, these recommendations may be useful when making decisions about the allocation of scarce health resources.

Although these recommendations were initially developed with a focus on off-label use of registered medicines, the principles apply equally to unlicensed medicines use. Essentially, if sound, evidence-based principles are applied in making clinical decisions about off-label or unlicensed medicines use, then the ethical and legal dilemmas will also have been satisfactorily addressed.

These recommendations have already influenced policy at a number of levels in NSW, including the Department of Health and individual hospital or Area Health Service DTCs, with almost 90% of NSW TAG member hospitals endorsing the recommendations for implementation. Some members of the pharmaceutical industry in Australia also appear to find these recommendations useful for determining appropriate practice. While the recommendations were developed specifically to guide public hospital practice, the general principles are relevant for all prescribers. Wider dissemination should promote broader discussion of the key issues and help contextualise recommendations for a range of settings. Ultimately, wider adoption of key recommendations should promote both better practice (more evidence-based prescribing) and help stimulate more clinically relevant medicines research, which in turn will support better prescribing decisions in an ongoing way.

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Competing interests

None identified.

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