Addressing common legal and ethical concerns with off-label prescribing in Australia

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Introduction

Off–label (unapproved, or unlabelled) prescribing refers to the supply of a medication for an indication, age, dosage or route of administration that is not included in approved product information or registration. [1] Such practice is widespread, occurring at rates of up to 40% in adults and up to 90% in paediatric patients. [2] In some cases, off-label prescribing may be supported by current, high-quality scientific evidence, which has emerged subsequent to publication of approved product information. While Australian data in this area is lacking, data from the USA shows the majority of off-label prescriptions are not evidence-based, with 73% of a surveyed 150 million off-label prescriptions lacking scientific evidence to support their use. [2] This raises a number of legal and ethical issues for both prescribers and patients.

What is the legal status of off-label prescribing?

In a survey of 327 general practitioners, 53% stated they did not know, or gave the wrong answer, when asked about the legal status of off-label prescribing. [1] While it is reasonable to expect the incidence of off-label use to be greater in a specialist setting, comparative data with general practice is lacking. Given the estimated overall high incidence of off-label prescribing, an understanding of its legal status is important for both GPs and specialists.

In the ACT, prescription drugs are controlled under the Medicines, Poisons, and Therapeutic Goods Act 2008 (ACT), which states that a health professional who prescribes a medicine must ensure the supply is for a quantity and purpose consistent with the recognised therapeutic standard appropriate in the circumstances (ch.2, s.7). [3] What is "appropriate in the circumstances" will differ between cases and is decided by the medical practitioner. Nonetheless, prescribing decisions should arguably have an evidence base in order to comply with the Act.

The chief body responsible for regulating pharmaceutical products in Australia, the Therapeutic Goods Administration (TGA), does not regulate the prescription or administration of medicines once they are registered under the Therapeutic Goods Act 1989 and have entered the market. [4] Therefore, off-label prescribing is legal. This was noted in the case of Commonwealth of Australia v Human Rights & Equal Opportunity Commission (1997) 147 ALR 469, which found that off-label prescribing of medicines registered under the Therapeutic Goods Act 1989 would not appear in breach of the Act provided the prescription or administration was not authorised or performed by a sponsor of the medicine. [5] Thus medical practitioners may prescribe approved drugs for any purpose they believe will benefit their patients regardless of the approved terms of use registered by the TGA.

Is off-label prescribing a deviation of the standard of care? Is it litigiously risky?

Off-label prescribing carries the same medicolegal obligations as on-label prescribing. The standard of care remains unchanged. The medical practitioner has a duty to, among other things, inform their patient of all material risks inherent in the proposed treatment as well as those of alternative treatments (see Rogers v Whitaker (1992) 175 CLR 479). If sued for negligence, the practitioner will be judged according to the reasonable nature of their actions in the given

circumstances (in ACT see Civil Law (Wrongs) Act 2002 (ACT)) or by the reasonable body of medical opinion (in NSW see Civil Liability Act 2002 (NSW), encompassing the ratio decidendi of Bolam v Friern Hospital Management Committee (1957) 1 WLR 582).

For a medical practitioner to be found negligent, the patient must demonstrate to the Court that, on the balance of probabilities, the practitioner had a duty of care to the patient, which they breached, directly causing harm to the patient. The off-label status of a drug does not alter these essential elements of negligence, and cannot be used alone as evidence of negligence. An exception to this may exist where a manufacturer clearly warns against a specific off-label use. This was illustrated in the case of Richardson v. Miller 2000 44 S.W.3d 1 (USA) where evidence regarding the off-label use of terbutaline for tocolysis was excluded from the trial because it did not indicate a deviation of the standard of care. This exclusion was, however, reversed at appeal, as the manufacturer explicitly warned against the use of terbutaline for this purpose.

Failure to treat with an off-label drug may also expose practitioners to litigation. Where it becomes standard best practice to administer a drug for an unapproved indication, failure to do so, may be a breach of the duty of care. This is exemplified in paediatric medicine, as the majority (>70%) of registered drugs are not approved for use in children. [6] This is not surprising as it is challenging for drug sponsors to obtain the necessary clinical trial data to support their application for a paediatric indication. The ongoing paediatric exclusivity provisions enacted by the FDA in 1997 aimed to address this issue by providing sponsors with additional patent protection in return for conducting paediatric studies. [7]

In many instances off-label use in children represents the current standard of care, and withholding essential treatment, due to fears of off-label prescribing, would be negligent. [8] This highlights the importance of continuing professional education. Practitioners must remain up-to-date with current clinical evidence to ensure they meet their standard of care.

Perhaps the litmus test for avoiding medical liability in this area is the foremost consideration of the best interests of the patient. [9] Whether prescribing on- or off-label, proposed treatments should be based on scientific and clinical data, with costs, benefits, and alternatives thoroughly explained to patients before gaining consent.

Should doctors inform patients that they are prescribing them a treatment that is off-label?

There are conflicting views around this issue in the medical and legal literature. Some argue that the safety, efficacy, and adverse effects of drugs prescribed off-label are unknown and knowledge of this fact may influence patient's decisions to accept or reject treatment. In this respect knowledge of off-label status may be considered a "material risk" that patients should be informed about. Conversely, some argue that patients may erroneously associate lack of TGA approval with TGA disapproval, and instinctively refuse effective treatment. [10] This latter view reflects an out-dated paternalistic notion that patients are incapable of acting in their own best interest and that practitioners should employ Therapeutic Privilege to protect patients from themselves.

Where the off-label use of a particular drug is best practice and/or supported by quality evidence there may be less onus on the practitioner to inform the patient of a drug's off-label status. However, patients understandably become confused and frustrated when, for example, they are prescribed amitriptyline for neuropathic pain only to read in the enclosed consumer medicines information (CMI) brochure that it is indicated for depression and nocturnal enuresis. [5] This confusion may undermine the therapeutic doctor-patient relationship.

The principle of informed consent promotes patient autonomy and self-determination and acknowledges the central position of the patient in clinical decision-making. Whether knowledge of a drug's off-label status is considered a material risk is yet to be tested in an Australia court, however, in most circumstances, practitioners would be wise to err on the side of caution and inform patients.

Is the promotion of drugs for off-label indications by drug sponsors unethical?

Advertising medicines to practitioners for unapproved indications is both unethical and illegal in Australia. Section two of the Medicines Australia Code of Conduct states that *"the content of all promotional material provided to health professional must be... fully supported by the Product Information."* [11] Adherence to this code is mandatory for all drug sponsors, regardless of their membership with Medicines Australia.

The TGA approval process is expensive, rigorous, and time consuming, but serves an essential role in public protection and safety. Allowing companies to market drugs for off-label purposes removes the incentive to conduct clinical research to prove the safety and efficacy of their products. [12] Pharmaceutical companies have a vested interest in promoting the untested and unapproved use of their products. It is financially advantageous to alter prescribing patters in favour of their product. This may corrupt the therapeutic doctor-patient relationship through the promotion of inappropriate, untested, and potentially unsafe drugs.

The withdrawal of fenfluramine and dexfenfluramine by American Home Products (AHP) from the USA market in 1997, and subsequent class action suit, illustrates the dangers of promoting off-label prescribing. [13] These drugs were initially approved as short-term, standalone weight loss drugs, however in 1992 preliminary evidence emerged suggesting an advantageous combination with another weight loss drug, phentermine (the so dubbed Fen-Phen combination). While both drugs had independent approval from the Food and Drug Administration (FDA), their combination was not approved. Moreover, AHP representatives responded to practitioner enquires by providing research papers, effectively endorsing the off-label combination. [14] In 1997 reports surfaced indicating an increased incidence of pulmonary hypertension and valvular heart disease among those using the Fen-Phen combination. The ensuing case settled for an estimated $16 billion. [14] This case highlights, among other things, the potentially devastating consequences of off-label drug promotion. Such behaviour by pharmaceutical companies bypasses the strict review processes of regulatory bodies (such as the TGA) compromising consumer protection and safety. [15]

More recently, a phenomenal rise in off-label prescriptions for gabapentin (an anticonvulsant) in the USA has been, at least partially, attributed to the illegal marketing practices of pharmaceutical company Warner-Lambert. [16] In 2004, Warner-Lambert was fined $430 million for suppressing negative clinical trials and promoting the off-label use of gabapentin for migraine, bipolar disorder, and neuropathic pain despite having little or no supporting clinical evidence at the time. [17] Using deceptive means to persuade doctors to prescribe costly, unproven, and potentially ineffective drugs is clearly unethical, and ultimately subverts patient health for corporate gains. Prescribers are encouraged to report any unethical behaviour of pharmaceutical representatives to Medicines Australia. [18]

Is the off-label use of drugs a form of human research/experimentation?

The intention of the prescriber determines whether the use of a drug is classified as "therapy" or "experimentation". As outlined in the Belmont Report (1979), clinical practice involves treating a patient with the sole aim of improving their wellbeing. [19] This is distinct from research (or experimentation), which principally aims to test a hypothesis, draw conclusions, gain knowledge and understanding, or to train researchers. [19,20] Research on human subjects must be ethically justifiable – it must have merit, and its researches must have integrity. [20] Additionally, human research is governed by Australian law, imposing responsibilities on investigators and protecting the rights of participants. [20]

Off-label prescribing often blurs the boundary between practice and research, and indeed both may occur simultaneously. Where little or no clinical data is available to guide off-label therapy, practitioners may prescribe drugs with the intention of improving patient wellbeing, but also with the intention of publishing treatment outcomes to provide anecdotal evidence for future prescribers. Such case reports may identify effective new applications of existing drugs, and pave the way for clinical studies.

Lawrence Craven, an American general practitioner, first noted the antithrombotic effects of aspirin in 1950 after observing increased bleeding rates among those who chewed aspirin gum following dental surgery. [21] He soon began prescribing the drug off-label to his patients to prevent myocardial infarction. While his published findings were ignored at the time, they were later supported by large scale clinical trials, eventually leading to the widespread acceptance and approval of aspirin for cardiovascular protection in the 1990s. [21,22] Craven's off-label use of aspirin arguably blurred the line between research and therapy but ultimately flagged an important avenue for further clinical research, and had his findings been appreciated at the time, they may have saved many lives.

When should doctors prescribe drugs off-label?

Off-label use is appropriate when the potential benefits of treatment are deemed to exceed the potential risks in a given clinical context. This will involve a systematic consideration of both the available evidence for safety and efficacy and the seriousness of the condition being treated. [5] In some instances quality evidence supporting use in a particular indication will be lacking, and extensive clinical experience ("expert opinion") may be relied upon. The quantity and quality of evidence required for a favourable risk-benefit ratio will logically be less with more serious diagnoses. Where the TGA has not rigorously assessed a drug for a particular use, the onus is on the practitioner to do so. If they believe a favourable risk benefit ratio exists, they may prescribe treatment once informed consent has been obtained.

In the absence of supporting evidence or expert opinion, off-label use is generally not justified, except when used in the context of formal, approved research, or in exceptional cases with compelling individual

circumstances. [2,5] Such individual circumstances typically involve severe disease refractory to standard treatment. In these cases, there must be some evidence to support the proposed treatment as well as a favourable risk benefit ratio, and approval by an institutional drug committee. [2]

Increasingly, practitioners must consider drug cost when prescribing off-label. For drugs requiring authority approval, the Pharmaceutical Benefits Scheme (PBS) provides subsidised medicines for approved indications only. With the influx of expensive biological agents with narrow listings on the PBS, supply outside of approved indications may incur a high price. It is worth noting that most off-label use currently involves relatively inexpensive drugs for which cost would influence little on the prescribing decision.

Conclusion

Off-label prescribing is both legal and necessary. The TGA approval process lags substantially behind the rapidly emerging clinical evidence supporting novel uses of existing drugs. The clinical data required by the TGA for an extension of indication is difficult and expensive for drug sponsors to obtain, especially in paediatric populations. Lack of TGA approval does not equate to TGA disapproval and in many cases the use of drugs outside of their approved product listing represents the current standard of care. Failure to provide such drugs may constitute medical negligence, and practitioners should remain up-to-date with current clinical evidence to ensure they meet their standard of care. When off-label prescribing is supported by quality scientific evidence and is likely to improve patient wellbeing, it is ethically justified and should be offered to patients.

Disclaimer

The above commentary is not intended to be legal advice and should not be relied upon as such.

Conflicts of interest

None declared.

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