Challenges to the validity of using medicine labels to categorise clinical behaviour: an empirical and normative critique of ‘off-label’ prescribing


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ABSTRACT

Rationale, aims and objectives: To determine whether or not the label status of a medicine penetrates into the clinical reasoning of Australian medical practitioners, and to explore the possible reasons for our findings.

Methods: Semi-structured interviews with 14 Australian physicians.

Results: The interviews revealed three broad catalysts for off-label prescribing. The first of these was lack of awareness or understanding of the regulatory process in general and labels more specifically. The second was the perception that labels are not meaningful guides for clinical practice. The third was the
recognition of alternative mechanisms for ensuring safe, rational, and evidence-based prescribing occurs.

**Conclusion:** This research suggests that Australian physicians do not consider whether or not a medicine is off-label to be a reliable measure of the appropriateness of their prescribing practices. Rather, legitimacy of prescribing practices is determined by the abilities, skills, and knowledge base of particular prescribers, by a culture that encourages and supports evidence-based practice, and safe prescribing. While labels are of minimal clinical significance, there are real conceptual, practical and moral problems associated with conflating ‘good’ or ‘better’ practice with ‘on-label’ practice, and ‘bad’ or ‘worse’ practice with off-label prescribing as often occurs. To ascribe greater meaning to the term ‘off-label’ than is warranted can have the unintended consequence of casting suspicion upon, and making it more difficult for physicians to provide, appropriate clinical care. We conclude that labelling can, in some cases, provide assurances to both clinicians and patients that their medications have been demonstrated to be safe and effective, but that clinicians should be able to continue to prescribe responsibly off-label without having any stigma attached to their practice.

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**INTRODUCTION**

Regulatory bodies, such as the US Food and Drug Administration (FDA), the European Medicines Agency (EMA), and Australia’s Therapeutic Goods Administration (TGA) are relied upon to assess medicines for their safety and efficacy on the basis of results from clinical trials in successively larger populations of patients [1]. As part of the approval process a ‘label’ is assigned to each medicine, which tells potential prescribers what disease/s it has been approved to treat, what age groups and doses are appropriate, what administration routes should be used, and how it should be used in pregnancy or other modifying conditions.

Off-label prescribing refers to the clinical use of medicines in a manner that is different to that which is specified in the label. This may be because the medicine is being used for a different disease or age group, at a different dose, and/or via a different route of administration. Pharmaceutical companies generally cannot promote their registered products for off-label uses – although recently the US federal court has ruled that the pharma company Amarin can promote its medicine Vascepa (icosapent ethyl) for ‘truthful’ off-label uses [2]. Doctors, on the other hand, are allowed to prescribe registered medicines in any way they see fit (bearing in mind that off-label prescribing may not be subsidised by public or private insurers).

Off-label prescribing is very common. More than one fifth of all prescriptions in community practice are off-label [3], and in some specialties, medicines or conditions, off-label prescribing can constitute well over half of all prescriptions [3-8]. For instance, recombinant activated factor VII, indicated for patients suffering from specific forms of haemophilia, is used almost exclusively off-label within hospitals to control bleeding in non-haemophilic patients, while cancer drugs such as gemcitabine and rituximab are used off-label the majority of the time [6, 7]. A number of Australian studies show that the proportion of patients that receive an off-label prescription seems to be higher than the number of drugs prescribed off-label (as many patients take multiple medicines of which only one may be off-label) [9, 10].
In recent years, off-label prescribing has become the focus of intense scrutiny following revelations that pharmaceutical companies have illegally promoted their medicines for off-label uses [11-15]. The concern about such off-label promotion has been that doctors’ prescribing practices have been influenced by industry promotion in a manner that is not in the best interests of patients [16-18]. Those who criticize off-label prescribing (whether or not it is industry-driven) worry that off-label uses of medicines have not been sufficiently scrutinized by researchers and regulators, and therefore may be more harmful and/or less effective than expected [19]. They also note that, since we cannot be sure of the cost-effectiveness of these medicines, off-label prescribing could contribute to the wasteful use of scarce health care resources and lead to ‘label-creep’, whereby the clinical usage of a medicine expands, not as a result of evidence of its efficacy in clinical trials but rather as a result of advocacy by doctors, patients and pharmaceutical companies [20]. It has been argued that most off-label prescribing is supported by little or no scientific evidence [3]. More broadly, concerns have been expressed that off-label prescribing bypasses and therefore undermines systems for regulating medicines [17, 21], and may also undermine clinical research as it reduces the incentive for pharmaceutical companies to conduct clinical trials and makes it more difficult to enrol patients into those trials that are conducted [22]. Those who defend off-label prescribing note that if doctors were to strictly adhere to uses that have been approved by regulators, many people would never receive treatments that are likely to be beneficial. This is because the drug development and regulatory approval process is ultimately driven by claims that a drug sponsor—usually a pharmaceutical company—wishes to make [23], and these claims are often driven by profit motives rather than health care priorities [24]. This commercial imperative hinders the development of evidence for certain groups of patients, such as those suffering from rare diseases or so-called ‘diseases of poverty’, which affect mostly people in low- and middle-income countries.

There are also other reasons that regulatory approval might never be sought for certain indications. For example, research might be thwarted by technical difficulties (such as the increasing complexity of trials of ‘targeted therapies’ and their ‘companion diagnostics’) or by ethical challenges (such as the perceived difficulties associated with including pregnant women and children in clinical trials). Furthermore, regulators do not actively seek out indications for which a drug will work, but simply evaluate the claim/s that a drug sponsor puts forward for assessment, meaning that drug labels can quickly become outdated and disconnected from the evolving evidence-base and from clinical needs [25]. Worldwide, there has been relatively little empirical research focused on physicians’ understandings of, and reasons for, prescribing off-label. Those studies that have been conducted do provide some insights into the practice. One study of off-label paediatric prescribing amongst general practitioners in Scotland suggested that, while physicians appeared familiar with the concept of off-label prescribing, they wrongly believed it was not a common practice [26]. This appeared to be, in part, because the primary sources of medicines information they utilised were formularies, personal experience, and the experience of colleagues rather than regulatory labels. Another study utilised electronic health records available in Quebec, Canada, to investigate what factors influenced off-label prescribing in primary care, and discovered that older medicines and medicines with the fewest approved indications are most commonly used off-label [27]. It was also found that younger physicians were more likely to prescribe off-label without scientific support, while (unsurprisingly) the more physicians aligned themselves with evidence-based practice, the less likely they were to prescribe off-label. In a literature-based case study we conducted exploring the emergence of the use of gabapentin use for neuropathic pain, we found that unmet clinical needs, prescribing precedents, and the perception that
gabapentin was a safe alternative to other treatment options were important drivers of off-label prescribing. In this and other case studies we have conducted into off-label prescribing [28-30] we found that, even when confronted with the same body of evidence, stakeholders may come to contrary views about the appropriateness of particular off-label prescribing practices – demonstrating that epistemic and ethical values heavily influence how evidence is interpreted. In this article, we build on our previous work by presenting the results of interviews with practicing physicians with a view to shedding further light on how off-label prescribing is conceptualised and practiced.

METHOD

The first author (NG) conducted semi-structured interviews with physicians practicing in a wide variety of fields including pediatrics (3), obstetrics and gynaecology (3), cardiology (2), general practice (2), mental health care (2), oncology (1), rheumatology (1), respiratory medicine (1) and pain management (1). Given that evidence suggests that physicians are often not aware of the fact they are prescribing off-label [31] physicians were prompted to discuss not only off-label prescribing itself, but also the other ways in which they determine what is good or bad prescribing, the manner in which they deal with epistemic uncertainty, and how they balance risks and benefits. Questions were also asked about attitudes towards regulatory bodies more generally. Sampling was purposive—we were aiming for maximum variation to ensure that no major perspectives were overlooked. In total fourteen physicians were interviewed, representing 9 specialties.

The aggregate duration for all interviews was approximately 12.5 hours, with the average interview duration being approximately 54 minutes (interview durations ranged from 19 min through to 1hr 28 min). Interviews were recorded and transcribed verbatim. Transcriptions were analysed using Morse’s outline of the cognitive basis of qualitative research [32], and Charmaz’s outline of data analysis in grounded theory [33]. Interviews were coded paragraph by paragraph, and a coding tree was generated (using XMind 6) from the themes to allow for higher-level categorization and conceptualization. Half of the interviews were double-coded by IK, ML and/or WL to ensure the validity of emerging themes, categories and concepts. Thematic saturation (the point at which no new themes were emerging) was reached after approximately 10 interviews. Ethics approval for this research was granted by the University of New South Wales Human Research Ethics Committee (Reference number: 2014-7-20) on 19 May 2014.

RESULTS

The interviews revealed three broad catalysts for off-label prescribing. The first of these was lack of awareness or understanding of the regulatory process in general and labels more specifically. The second was the perception that labels are not meaningful guides for clinical practice. The third was the recognition of informal mechanisms for ensuring that prescribing is rational and responsible.

Lack of awareness and understanding of labels and the regulatory system

The interviews demonstrated enormous variation in the degree of understanding that physicians had about off-label prescribing. While many of the physicians interviewed acknowledged that off-label prescribing was important to their practice, many had only a superficial understanding of its implications and meaning. There appeared to be a general lack of awareness and understanding of the medicines governance processes. One experienced physician noted that she had only become aware of the phrase ‘off-label prescribing’ in response to media attention focused on off-label promotion and regulatory failures, and admitted to having been relatively ignorant of the regulator’s role in medicines governance for most of her career:
“Things like the TGA [Australia’s medicines regulator] didn’t seem to have any meaning to me until … latter years in my career and … as governments become more involved in medicine we’ve seen … the TGA get mentioned a lot more and … the varieties of media that we have now enable us to hear a lot more about it. I mean this concept of off label prescribing I’d never – to me, that’s a relatively recent thing.”

Another senior physician expressed the belief that if medicines were available to clinicians, whether or not they were ‘on-label’ was essentially irrelevant. This physician believed that mere fact that a medicine had received marketing approval for any indication was evidence of its potential general utility:

“…the mere fact that they’re available suggests that somebody, or the regulatory authorities, think that they’re not unreasonable to use… The reality is that people don’t look up [information to see whether a drug is on or off-label] – they know it’s available and they prescribe it, and I think it’s not that easy to look up every single drug to see, and I don’t think anyone really looks at it in that respect; if it’s available, it’s available…”

To the extent that physicians were aware of the technical meaning of off-label prescribing, this awareness seemed to stem primarily from the fact that labels often determine which medicines will, and will not be formally subsidised by public and private insurers. For instance, one participant complained about how the privatization of their institution had meant that many patients who would have been provided subsidized off-label treatments in the past through their public hospital now had to pay for these medicines themselves or forgo treatment:

“…that institution there, where I've been for the last [number of decades], used to provide drug committee permission to use the [off-label medicine] – that's being tightened up on. So more and more patients are either being told, “Well, it's up to you if you can pay for it and if you can't, you can't have the drug.” ”

One possible reason for many physicians’ lack of awareness and understanding of off-label prescribing related to the way they had learned to prescribe and utilise information. In this regard, it was noteworthy that none of the participants in our study mentioned regulatory labels, or their accompanying product information, when they described their learning process. Instead, learning was described as occurring through ‘on-the-job’ immersion. Copying superiors and learning from what they did was particularly important in shaping prescribing habits. Specific activities, such as transcribing prescriptions onto medication charts as a junior physician, and being prepared to justify prescribing decisions to one’s superiors, were also important means of learning about prescribing.

Lack of awareness of drug labels also seemed to stem from the rapid growth in online resources and computerised prescribing systems. As one physician stated in discussion about how they would approach prescribing unfamiliar medicines:

“… it’s a very different world these days … The computer just spits up, you know, is the patient pregnant? You are prescribing something that’s a category X drug, make sure the patient is not pregnant. Um, there is a clinical indication it’s high risk, it’s low risk, it’s moderate risk – and it tells you basically what it is that you need to watch out for. So it’s very, you know, it’s very helpful. And previously you had to remember that all going back to the source and look through. It didn’t give you the kind of detail that most computer programs do these days. Which is … hugely helpful.”
The regulatory system is not perceived to be clinically focused and may impinge on practice

Physicians’ lack of interest in using drug labels to guide their practice appeared to reflect, in part, their attitudes towards the regulator and the entire regulatory system. First, they did not believe that medicines regulation was of direct relevance to clinical practice. This perceived disconnect between the role of the regulator and the needs of physicians stemmed in part from recognition of the fact that the evidence used in the regulation of medicines does not reflect the entire evidence base. In this regard, a number of participants noted that the regulatory system neglects entire areas of clinical practice and that, therefore, if the evidence exists for a particular use of a medicine, but this is not an approved use, then the problem lies with the drug development and regulatory system:

“... in my field there’s a lot of stuff that’s off label and it’s not off label because it’s experimental, it’s off label because the pharmaceutical company doesn’t want to go through the time and expense of having it approved by the regulator in this country for that indication... If the scientific evidence exists that the drug is effective and safe, then it should be regulated for, you know, those indications in this country.”

Several participants also pointed to the somewhat arbitrary nature of the regulatory system, noting differences in the approval of drugs internationally, different uses of medicines in the public or private health sector, and the imprecise characterisation of disease:

“I mean, diseases, after all, especially chronic diseases, are really very woolly categories, very woolly categories... So I think the onus does fall ultimately on the prescriber to be able to rationally justify why that drug was prescribed.”

Beyond simply finding medicines regulation to be arbitrary and/or of not direct clinical relevance, many participants suggested that the regulatory process in general, and use of labels in particular, could actually work against good clinical practice.

For example, it was noted that regulators can be passive about what drugs are labelled and for what purposes. One physician, who had experience working in both government and the pharmaceutical industry, took this further, arguing that existing regulatory processes are replete with conflicts of interest and consequently place too much emphasis on the demands of industry. In his words:

“I think the TGA [Australia’s medicines regulator] is useless. I think it’s conflicted in the way it’s structured. It gets its funding and its very existence is dependent upon the medical device manufacturers and pharmaceutical manufacturers that it’s meant to be regulating so I think in its current format, it is completely dysfunctional... they're weak and wishy-washy with controlling things from the manufacturers – yeah, their control is weak over manufacturers and they don’t wield a big stick because they’re dependent on them for their funding.”

This physician also believed that TGA processes for evaluating medicines were therefore not necessarily better than less formal peer driven processes (to be discussed further below).

It was also suggested that there is a disjunction between regulatory approvals (and associated legal determinations of good practice) and what actually constitutes good clinical practice, and that concerns about the legalities of off-label prescribing could lead to poor clinical practice. For instance one physician was concerned about legal liability:
“So that’s another reason where I find the whole TGA [Australia’s medicines regulator] process unhelpful because, you know, stuff that I’m happy scientifically sound prescribing is, yeah, you know, a lawyer can go well that was a flake [since it is not officially on-label]...”

Another interviewee noted how the link between labelling and funding could generate burdens for clinicians—particularly those working in the private sector, where funded indications are limited to those provided by the national insurer. This interviewee complained about how he had to spend more time engaging with pharmaceutical companies to seek subsidised or free access to off-label uses of medicines for their patients:

“The other thing, of course, which is also incredibly tedious and wasteful of time, is actually - I mean I really don't like doing it, actually contacting the industry and seeing if they will let – you know, provide something with an incentive scheme...”

**Informal mechanisms of risk management are just as important as formal mechanisms of control**

**Who is prescribing is just as important as what is being prescribed**

A key theme that arose in the interviews is that the appropriateness of a prescribing decision depends not only on the medicine used, but also upon who is using the medicine. Freedom to prescribe was therefore associated not with what a regulator did, or did not, endorse, but rather with one’s status within one’s field. This view was most explicitly expressed by one interviewee who made it clear that while evidence-based practiced (including, but not only consideration of labels) was important for junior practitioners, and non-specialists, experts should have freedom to prescribe according to their judgement, even if this means prescribing contrary to the information held by ‘the drug authorities’:

“I think there are situations where prescriptions that may be appropriate for a sub specialist who’s considered an expert in his field to take what he perceives as a very small risk, um, but would not be comfortable with, um, general practitioners prescribing... I would certainly, ah, be very keen for experts to be given a relatively free hand by the drug authorities”.

Indeed it seems that to some participants, the very point of being an expert is to have lee-way both to prescribe in areas of epistemic uncertainty and to make use of whatever evidence may be available, whether or not this evidence has been formally assessed by regulatory authorities. As one physician noted:

“Oh, routine practice, absolutely, you know. So every – every day, every decision that I make is usually based around what is the available evidence. Because there are definitely, you know, in my field, there are things where we are absolutely crystal clear on issues – not very many of those –but there are, you know, certainly really strong good evidence base, lots of randomised trials, fantastic work, crystal clear. Most of it is kind of less clear, a little bit grey... it’s the grey zone that’s always the problem, isn’t it?”

Expertise was seen to be associated with a special kind of knowledge and intimacy with particular clinical areas, as well as with medicines recognised as ‘tools of the trade’. Some physicians noted that through prescribing the same medicines over extended periods of time, they became intimately familiar with how particular medicines worked, to the point physicians may even prefer specific brands of the same medicine over others due to subtle differences they have noticed.
“So, I think, not everything on evidence-based is correct, and I think sometimes one needs one’s own judgment ... a very important thing is experience, and if a large pharmaceutical trial shows that there’s no increased incidence of a certain adverse effect, and you commonly get this adverse effect, and it gets better when you stop the drug, well then, you have to be guided by your own experience.”

Indeed, for experts to be too risk averse, and restrict their prescribing to the claims on the regulatory label was seen by some to undermine good prescribing. As one physician noted:

“...I see a lot of what I would call ... poor prescribing from ... fear and hypersensitivity ...” and continues by stating “Um, and just because it’s not [on-label]... doesn’t mean that I as an individual clinician am, you know, not going to prescribe that drug just ‘cause the TGA hasn’t listed it.”

While expertise was seen by physicians to provide greater leeway in prescribing decisions, the application of expertise was more legitimate in the context of prescribing drugs already known to be relatively safe. As might be expected, even experts were hesitant to utilise medicines that were dangerous or had unknown safety profiles in order to gain a benefit for their patient.

**Rational and responsible prescribing can be, and is, encouraged in other ways**

Even expert physicians acknowledged that some epistemic controls over their prescribing were important, and that they needed, at times to be ‘seen’ to be practicing evidence-based medicine in order to develop good habits in less experienced junior doctors. Even here, however, the idea of epistemic control, and the practice of evidence-based medicine were understood in ethical, political and cultural, rather than formal, regulatory terms. One physician distinguished clearly between interventions they believed would work, and what they were permitted to use within a particular practice culture:

“... I cannot take my personal opinion and apply it on the public without any further studies... it can be the truth. But, then, at the same time, it’s not supported in western medicine, you cannot really practice medicine unless it’s supported by evidence.”

This physician also noted the erosion of trust in physicians as influencing how medicine is practiced, a point picked up on by others as reflected by the need to maintain the integrity of medicine by avoiding prescribing in ways that may further undermine trust.

The existence of oversight by peers was also perceived to be an important mechanism of control. For instance one physician shared an instance of how she they had been challenged to justify why she were prescribing a drug in an off-label manner:

“... somebody wrapping my knuckles one day, over me using a certain drug because I actually wanted to use it for its beneficial effect and for its side effects at the same time... I think that physician thought I was going to do something harmful by exploiting the side effects, but backed off with that concern when I justified my position.”

It was also noted that complex decisions were rarely made alone, but only after consultation with peers. One physician noted that as a junior doctor, you would only independently prescribe ‘very obvious drugs’. Hence solidarity was an important mechanism for ensuring legitimacy of prescribing practices. As one interviewee noted:
“I mean, I guess what a lot of people don’t realise in the public is, at a major teaching hospital, complex cases are discussed, you know. Every unit would have a multi-disciplinary meeting once a week where complex patients are discussed. And it may involve different specialties even, as well. And that’s where those sort of decisions are made, where you’ve got someone who’s sick and doesn’t fit into the trial, and this hasn’t worked, they are discussed.”

Some interviewees also described that pharmacists would sometimes vet their prescriptions, and while one interviewee was frustrated by the fact a pharmacist might challenge a decision to use a medicine in a manner contradictory to official information, others recognised the value in having their decisions scrutinised by a third party:

“I sometimes get a phone call from a pharmacist. And I’m delighted when they do do that ’cause they’re just checking whether I really meant that … [However] I think you cannot rely on a pharmacist interpreting what they’re seeing …”

Clinical guidelines and medicines compendia were also considered to be important sources of direction and information, while formularies were identified as an important determinant of practice as they set limits around what medicines physicians (or their patients) may have access to. While these sources of information are obviously derived, to some extent, from regulatory guidance, none of our participants explicitly viewed them this way. Rather, they were seen as part of the process by which one becomes enculturated to be a good prescriber.

“And dosing, again you didn’t really learn that in medical school. I found when I went through that it was when I was an intern, um, that I learned what were the most common medications that were used, and the doses … So we had a formulary, um, in hospital, um, so we would prescribe in that way.”

Discussion

Study limitations

This study has a number of limitations. All participants were recruited in Australia (although a number had also practiced overseas), and therefore the views of these physicians cannot necessarily be extrapolated to physicians practicing in other countries. Most of the physicians interviewed for this project were specialists, and specialists are more likely to prescribe off-label than non-specialists. Therefore these results are not representative of all prescribers. Furthermore the interviewees were recruited from diverse specialties, and therefore the results cannot be said to be representative of any single specialty. As only 14 interviewees were recruited, these results provide only indicative understandings of, and attitudes towards, off-label prescribing.

The clinical significance of a medicine being ‘off-label’

The data from this study suggest that Australian physicians justified off-label prescribing by way of three positive and three negative criteria. On the positive side, they argued first that drugs agreed to be ‘safe’ can be used for conditions not included in the original approval if there is some link – either theoretical or practical – to suggest a possible beneficial effect.

Second, they argued that clinical—particularly specialist—expertise and a sense of responsibility towards patients provides assurance of the safest possible use of off-label drugs. The physicians
interviewed all felt strongly that the commitment involved in specialist practice ensured their capacity to pay conscientious and skilled attention to unwanted side-effects, and to harness clinically useful side-effects of ‘off-label’ medicines.

Third, the physicians declared their respect for evidence-based medicine, but argued that \textit{effectiveness} was the practical criterion that underpinned their prescribing choices, rather than the \textit{efficacy} that determines the authorisation of a drug and its labelling. They thus committed themselves to a social epistemology that depended less on ‘gold standard’ trials, and more on evidence generated at ‘lower’ levels of the EBM hierarchy.

On the negative side, most of the physicians expressed a relative ignorance or indifference to the clinical, ethical or legal implications of labelling. There was some concern about possible legal effects of off-label prescribing, but generally off-label prescribing was simply a part of rational and responsible prescribing, requiring clinical skill, careful monitoring and remaining informed of accumulating information. The precise role of the label was not clear to them.

Second, some of the physicians went further in arguing that labelling and the authorisation processes involved, was \textit{irrelevant} to the actual practice of clinical care, and could in fact be harmful. In the Australian context, lack of regulatory authorisation of a drug for a particular purpose might mean a lack of government subsidy, which imposes significant costs on patients or hospitals. Authorisation and labelling thus impose restrictions on the abilities of physicians to prescribe, and on access to medications for patients.

In addition to restricting what physicians could prescribe, the need to obtain authorisation to prescribe unregistered (and therefore unfunded) medicines created what we refer to as ‘hierarchical dissonance’. By this we mean the apparent disconnect between bureaucratic management and clinical practice. Decisions made around committee tables were seen by practitioners to be decisions made beyond the realities of practice.

Our interviews with Australian physicians suggest that whether a medicine is on, or off-label, does not determine, in their minds, whether a particular prescribing practice is legitimate or not. Rather, legitimacy is determined by abilities, skills, and knowledge base of particular prescribers, and by a culture that encourages and supports rational and responsible practice, and safe prescribing.

This is consistent with the findings of a series of literature-based case studies we conducted into the published discourses surrounding the off-label use of recombinant activated factor VII for uncontrolled bleeding, misoprostol for post-partum haemorrhage, and gabapentin for neuropathic pain, where the fact a medicine was off-label was almost never offered as a reason for not using these medicines [28-30]. Indeed, we could only find one instance where the fact that misoprostol was off-label for post-partum haemorrhage in most countries was raised as a point of concern, as it may increase the potential for dangerous use of incorrect doses due to insufficient official guidance on the most effective and safest dosage regimen [34]. In the case of gabapentin for neuropathic pain, even intense controversy regarding off-label promotion of the medicine did not seem to override the clinical warrants for utilising the medicine off-label, namely the view that it was a safer and a more convenient alternative than medicines already being used for neuropathic pain. In the case of recombinant activated factor VII for management of uncontrolled bleeding, the label was only invoked when some physicians were critical of the FDA’s contradictory position of being reluctant to support research into acutely injured patients, while at the same time not accepting reduced blood loss as a surrogate end-point in clinical trials.
investigating rFVIIa’s efficacy in trauma patients (the FDA demanded evidence of improved survival and hence rejected the results of the Phase III trials) [35].

It could be argued that the knowledge (or lack thereof) and attitudes of fourteen—or even a much larger number—of Australian physicians only describes a deficiency that needs to be rectified with further information and education about the importance of regulatory labels and the dangers of off-label prescribing. We would, however, disagree with this view because the label not only had very limited clinical significance in this study, but also has a general tendency to inadvertently categorize particular prescribing practices as ‘good’ or ‘bad’. This attitude is highlighted in an invited commentary to JAMA Internal Medicine in which Good and Chester interpret one study to imply that off-label prescribing is, in most cases, not in the best interest of patients:

“Although in some clinical circumstances the off-label prescribing is clearly within the best interests of the patient, Eguale and colleagues have documented that this scenario occurs infrequently.” [36], p. 64

We believe this claim is unwarranted on the basis of our study and our previous literature-based research. Internationally, as well as in Australia it must be recognised that while a drug being off-label may imply many things, it does not determine anything specifically. Off-label prescribing may be perceived as non evidence-based (which seems to be the main contention of critics), but may also be based on strong evidence. Off-label prescribing may be construed as poor practice, but it may also be considered best practice. Off-label prescribing may waste limited health care resources, but may also be the most cost-effective use of resources. Off-label prescribing may represent straying from established treatment regimens, or it may represent judicious personalisation to address the needs of patients with complex needs. Off-label prescribing may expose some patients to greater harms, but may also provide benefits that would otherwise have been denied to these patients.

The clinical meaningfulness of the drug label is further called into question by the fact (also recognised by clinicians) that regulators in different countries may come to different conclusions about the scientifically valid uses of the same medicines, using the same evidence to make these determinations. For instance, gabapentin was approved for use of neuropathic pain in Australia in 2000, whereas the United States refused to make it on-label for this general indication due to a perceived paucity of scientific evidence, and therefore only listed it for one form of neuropathic pain - postherpetic neuralgia [30]. This inconsistency between the US and Australian label persists to this day.

Further blurring the clinical significance of the on-label/off-label dichotomy is the fact that respected organisations such as the Cochrane Collaboration and the National Institute for Health and Care Excellence routinely provide evidence summaries for off-label uses of medicines to support physicians [37]. The World Health Organisation also recognises that off-label uses of medicines have a place on the Essential Medicines List, a case in point being misoprostol for post-partum haemorrhage [38]. In addition, while clinical practice guidelines and hospital formulary writers most certainly consider labels, these forms of guidance are not restricted to on-label uses of medicines. It is noteworthy that clinical guidelines are defined by the Institute of Medicine as ‘recommendations intended to optimize patient care’ based on the assessment of ‘the benefits and harms of alternative care options’, neither function of which the label fulfills on its own [39].

What all this suggests is that the term ‘off-label’ is sufficiently vague to be almost meaningless in clinical terms. However, this is not the only problem. As our participants noted, in Australia the labelling status of a drug can also, in theory, expose doctors to greater liability, and in Europe at least, prescribing an
off-label alternative to an on-label drug just because it is more cost-effective may be illegal [40]. Despite the ambiguity around what 'off-label' means, negative connotations are inevitably implied by the term, and this is sustained by blanket demands from some stakeholders for greater consent requirements, and more intensive patient education requirements when utilising medicines in this way [41, 42]. It is also worth noting that there is no agreement between stakeholders internationally on a positive definition of off-label prescribing as pointed out by Neubert and colleagues, although they did manage to get 85% (n=34) of participants to agree on a definition [43]. Therefore the only thing the label can be said to definitely mean is that the regulator has endorsed a particular therapeutic claim based on studies of safety and efficacy, and as our results suggest, this is not necessarily meaningful to physicians.

**The need to remove the stigma attached to off-label prescribing**

This raises the obvious question: if regulatory labels cannot—and should not—be used to distinguish between ‘good’ and ‘bad’ (or even ‘better’ and ‘worse’) clinical practice, what role do labels have beyond simply being a formal record of evidence that a regulatory body has assessed? What the label does provide for physicians is perhaps the best systematic assessment of a medicine’s approved use at the time of market introduction. Therefore the label assists with the safe introduction of a new technology into the health system when there may be little other evidence and experience with it. It also ensures there is a minimum level of evidence available about a new medicine for the medical community to work with – particularly relating to safety and efficacy. Indeed a medicine’s first registration is perhaps the only point at which society can demand a specific standard of evidence from pharmaceutical companies. We contend this socio-political function of setting the tone around the amount and quality of evidence society expects, in general terms rather than in the details, is perhaps the most important role of the regulatory process. However, this does not mean that the regulator has a special epistemic or ethical warrant to determine what is, or is not, an appropriate use of a medicine in any particular clinical case – and as our results suggest, this is definitely not the view of the physicians we interviewed. In practice, we think this means that while labelling can, in some cases, provide assurances to both clinicians and patients that their medications have been demonstrated to be safe and efficacious in clinical trials, clinicians should be able to continue to prescribe responsibly off-label without having any stigma attached to their practice.

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