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Off-label prescribing in palliative care – a cross-sectional national survey of Palliative Medicine doctors

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Abstract

Background: Regulatory bodies including the European Medicines Agency register medications (formulation, route of administration) for specific clinical indications. Once registered, prescription is at clinicians' discretion. Off-label use is beyond the registered use. While off-label prescribing may, at times, be appropriate, efficacy and toxicity data are often lacking.

Aim: The aim of this study was to document off-label use policies (including disclosure and consent) in Australian palliative care units and current practices by palliative care clinicians.

Design: A national, cross-sectional survey was conducted online following an invitation letter. The survey asked clinicians their most frequent off-label medication/indication dyads and unit policies. Dyads were classified into unregistered, off-label and on-label, and for the latter, whether medications were nationally subsidised.

Setting/participants: All Australian palliative medicine Fellows and advanced trainees.

Results: Overall, 105 clinicians responded (53% response rate). The majority did not have policies on off-label medications, and documented consent rarely. In all, 236 medication/indication dyads for 36 medications were noted: 45 dyads (19%) were for two unregistered medications, 118 dyads (50%) were for 26 off-label medications and 73 dyads (31%) were for 12 on-label medications.

Conclusions: Off-label prescribing with its clinical, legal and ethical implications is common yet poorly recognised by clinicians. A distinction needs to be made between where quality evidence exists but registration has not been updated by the pharmaceutical sponsor and the evidence has not been generated. Further research is required to quantify any iatrogenic harm from off-label prescribing in palliative care.

Keywords

Off-label prescribing, palliative care, drug regulation, physician knowledge, iatrogenic harm

Introduction

In Australia, the Therapeutic Goods Administration (TGA) has a similar role to the European Medicines Agency (EMEA) in Europe and Food and Drug Administration (FDA) in the United States in registering *medications*

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(formulation, strength and route of administration) for specific *indications* (population and disease). However, once the medication has been approved, the clinician prescribes and may choose to use the medication in an *off-label* (unlicensed) manner, that is, an unapproved dose, route of administration and/or indication. This is distinct from an *unregistered medication* that is not approved by the regulatory authorities for any indication in their jurisdiction.

Off-label prescribing occurs in three contexts in clinical practice:[1]

1. When approval does not extend to cover the particular dose or indication, although evidence of efficacy is available – often because evidence became available after the medication was registered or after patent has expired, and the label has not been updated;
2. In areas of medicine where high-level evidence is difficult to generate, even for treatments, which are likely to be effective, or because there is a lack of a commercial imperative, for example, rare diseases where adequately powered clinical trials are impossible, or new indications for medications are now out of patent. In these situations, there may be compelling biological plausibility and/or lower level evidence to support prescribing; or
3. When the medication is proven to be ineffective or there is no reason to believe, it is effective.

Off-label prescribing is prevalent in many fields of medicine including general medicine,[2] psychiatry,[3] obstetrics,[4] paediatrics,[5–7] oncology,[8–10] HIV/AIDS[11] and palliative care.[12,13] Off-label prescribing is best documented in paediatrics, with prevalence of 11% in general practice, 72% in a neonatal intensive care unit[5,14,15] and up to 89% of paediatric inpatients.[16] In other populations, estimates of off-label prescribing vary: 8% in psychiatry inpatients,[3] 21% in office-based physicians,[2] 40% in HIV patients,[11] and up to 65% in oncology patients.[10,17,18]

In palliative care, patients often have multiple pathologies and complex symptoms, are frequently on multiple medications[19] and have fragile and rapidly changing health states. Adequately designed clinical trials in this population are feasible but challenging. Consequently, many medications used in palliative care are prescribed off-label in a setting where drug–host and drug–drug interactions[20] are already likely. Patients may also have limited ability to provide informed consent for off-label medications.[21]

Pavis and Wilcock[13] examined the off-label use of medications in palliative care in the United Kingdom in 2001 against General Medical Council (GMC) recommendations, finding low rates of verbal or written consent and poor documentation of reasons for off-label use in case notes. While these GMC recommendations have since been updated,[22] the questions asked by Pavis and Wilcock remain pertinent to quality prescribing. The aim of this study was to examine off-label prescribing in Australian palliative medicine clinicians through a national point prevalence survey.

Methods

Study setting

Specialist palliative care services (SPCS) in Australia span a range of different service delivery models, from large regional multidisciplinary teams to single clinical nurses in small rural locations. SPCS may include public and private hospitals with inpatient and/or consultative services, free-standing palliative care units, outpatient clinics and community care teams. SPCS may be the primary health provider but more commonly work in consultation to support general practitioners, other specialists and community services.

Study design and participants

This cross-sectional study was part of a larger survey looking at prescribing practices. The survey included participants' demographics, scopes of palliative medicine practice, level of experience, and perceptions and experience of off-label prescribing for the three medications in each respondent's practice that he/she most often used off-label (Appendix 1).

An invitation to participate, with a printed version of the survey, was sent in July 2010 to all Australian-based members of the Australia and New Zealand Society of Palliative Medicine (ANZSPM), a medical society open to doctors with an interest in palliative medicine. The letter included a link to the online survey.

Data collection

Survey data were entered by participants using the online survey tool, or if completed on paper were entered by an administrative assistant.

Data analysis

Medication registration and listed indications were obtained from the Australian TGA website (www.tga.gov.au, accessed 9th August 2011). All nominated medication/indication dyads were classified as unregistered, off-label or on-label. In Australia, while the TGA regulates medication approval, the Pharmaceutical Benefits Scheme (PBS) determines medication subsidy, that is, medications approved by the TGA do not automatically receive subsidy from the PBS, and if not, patients must pay full price. Given this distinction and the potential to misconstrue on-label but unsubsidised dyads as off-label, on-label dyads were also grouped into subsidised and unsubsidised

Table 1. Respondents' practices regarding off-label prescribing and associated verbal or written consent, and documentation of reasons

	Always (%)	Sometimes (%)	Never (%)
Do you limit off-label prescribing to consultants only?	29 (29)	39 (39)	31 (31)
Do you obtain verbal consent from the patient/caregiver?	24 (24)	49 (50)	26 (26)
Do you obtain written consent from the patient/caregiver?	1 (1)	23 (24)	74 (76)
Do you document in your notes when prescribing off-label and the reasons for this?	10 (10)	38 (39)	49 (51)

Table 2. Number of occasions of verbal or written informed consent, and documentation of the reason in the notes for off-label prescribing in the last 6 months

Number of occasions	Verbal or written consent[a] *n* = 67	Documentation in notes[b] *n* = 54
0	18 (27%)	23 (43%)
1–5	17 (25%)	18 (33%)
6–10	17 (25%)	10 (19%)
>10	15 (22%)	3 (6%)

[a]Of the 105, 38 (36%) had no response
[b]Of the 105, 51 (49%) had no response

(www.pbs.gov.au, accessed 9th August 2011). Uncertainty in interpretation of listed indications were reviewed by the authors and consensus reached. As the TGA consider any medication registered for parenteral use can be given intravenously, intramuscularly or subcutaneously if administerable without dilution, route of administration was not considered separately in the analysis. Nominated indications by survey respondents were grouped for the purpose of analysis (e.g. nausea/vomiting, pain and delirium/agitation).

Data were analysed using PASW 18.0 (SPSS Corp. Inc., 2008. Chicago, IL. USA). Descriptive statistics were used to analyse categorical variables, and comparisons were done using Chi-square test or Fisher's exact test as appropriate.

The reporting of this survey complies with strengthening the reporting of observational studies in epidemiology (STROBE) criteria for reporting cross-sectional studies.[23] Ethical approval for this study was granted by the Flinders University Social and Behavioural Research Ethics Committee.

Results

In July 2010, 213 of 220 registered Australian and New Zealand Society of Palliative Medicine (ANZSPM) members had a valid contact address, and of these, 105 (49%) provided valid responses for analysis. Thirty-nine percent were male and more than 74% of the respondents were older than 40 years. The majority had been practising medicine for more than 10 years (91%), and palliative medicine for more than 5 years (78%). Respondents worked in a variety of settings: acute inpatient (35%), hospital liaison (64%), community (46%), outpatient (46%) and palliative care unit (55%). Most respondents (91%) saw more than 60 new patients per year.

The majority of respondents reported that their services did not have, or were unaware of, a policy on providing information to patients about the off-label use of medications (89%), nor consistently limited the use of off-label use of medications to consultants (70%). The documentation of consent, verbal or written, was variable but tended to be absent or inconsistent (Table 1). When asked to quantify the number of occasions verbal or written consent was obtained, or reasons documented in the notes, the number of occasions reported was frequently much lower than expected given the numbers of patients seen (Table 2). For example, eight of the ten respondents who reported always documenting reasons for off-label prescribing saw more than 100 patients per year with life-limiting illnesses. However, when asked to quantify consent and documentation, only 7 gave a count of verbal or written consent, with 6 of the 7 reporting 10 or less occasions; furthermore, all the five respondents who gave a count of documenting in the notes reported this 10 or less times. Overall, 20% of respondents never obtained verbal nor written consent, nor documented a reason for off-label use.

The 105 respondents proposed 236 off-label medication/indication dyads for 36 medications (Figure 1, Table 3). Forty-five (19%) dyads for two medications were unregistered (cyclizine and levomepromazine (methotrimeprazine) are not registered in Australia). A total of 118 (50%) dyads were off-label, covering 26 medications for 38 indications. The remaining 73 (31%) dyads were on-label, covering 12 medications for 14 indications. Of these 73 on-label dyads, 31 were of pregabalin or gabapentin for pain, which are registered but not subsidised indications (off-subsidy use).

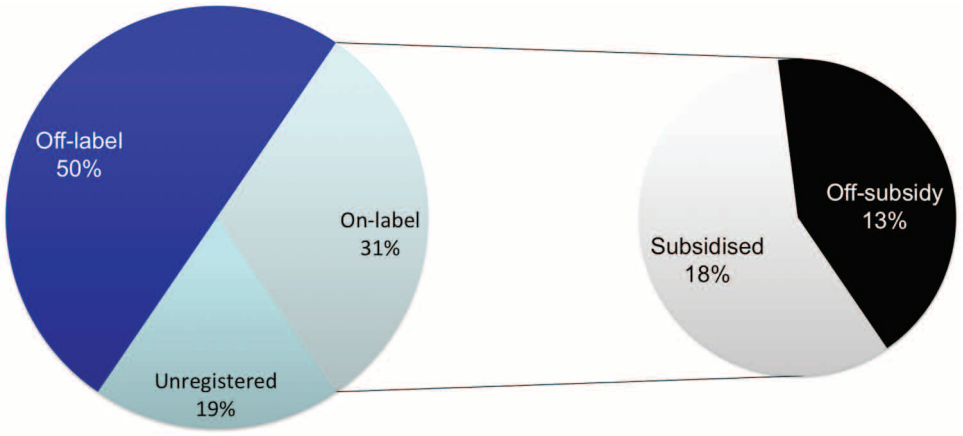

Figure 1. Nominated medication/indication dyads categorised by unregistered, off-label and on-label (n = 236).

Table 3. Top nominated medication/indication dyads categorised by unregistered medication, off-label use and on-label use

Unregistered	Indication	*n*	Off-label	Indication	*n*	On-label	Indication	*n*
Levomepromazine	Nausea/vomiting	19	Ketamine	Pain	24	Haloperidol	Nausea/vomiting	22
	Delirium/agitation	2	Octreotide	Malignant bowel obstruction	20	Gabapentin	Pain	19
	Sedation	1		Nausea/vomiting	2	Pregabalin	Pain	12
	Dyspnoea	1	Clonazepam	Delirium/agitation	7	Midazolam	Sedation	4
	Blank	1		Sedation	6		Agitation	2
Cyclizine	Nausea/vomiting	19		Anxiety	3	Metoclopramide	Nausea/vomiting	5
	Malignant bowel obstruction	1		Pain	2			
	Blank	1		Distress	1			
			Olanzapine	Delirium/agitation	5			
				Nausea/vomiting	3			
			Midazolam	Anxiety	4			
				Dyspnoea	2			
				Pain	1			
			Morphine	Dyspnoea	6			

Discussion

This study has found that palliative care practitioners have a poor understanding of medication regulations and the status of frequently used medications. When asked about 'licensed drugs for unlicensed uses', only 50% of nominated medication/indication dyads were correct.

Nineteen percent of the dyads were unregistered. Previous registration for cyclizine and levomepromazine has expired, and given their limited general use and low commercial value, their sponsors have declined to update and renew their registration. However, these medications are available in Australia using the Special Access Scheme, allowing importation of unregistered medications.

The remaining 31% dyads were on-label. Respondents may have mistaken on-label but unsubsidised medications with off-label use. Furthermore, a number of nominated dyads may have been designated off-label because the route (e.g. subcutaneous) was believed to be off-label. This reflects poor understanding of medication regulation processes that lead to a medication being off-label.

This poor understanding may be, in part, due to a widespread lack of service policies to guide off-label prescribing. Only 11% of respondents reported that their service had policies for the use of off-label medications; however, this was more than British palliative care services (2%) a decade ago[13] but less than American academic medical centres (17%)[24] and Italian hospices (28%)[25] The practices for off-label prescribing are reportedly better than in Pavis and Wilcock's[13] study, with 26% of respondents in this study never seeking verbal consent (compared with 38%) and 76% never seeking written consent (compared with 93%), though never documenting reasons still occurred in approximately 50% of cases.[13] While there may have been some improvement in practices around off-label prescribing since 2001, this survey demonstrates there are still large deficits, though 100% compliance may not be necessary.[22] Establishing a robust policy is a first step, but compliance

with these policies is likely to be extremely limited, given responses reflected into this survey.

What are the issues around off-label prescribing?

Clinically. Off-label prescribing is not a new issue.[26,27] While some cases of off-label prescribing is clinically appropriate, studies have demonstrated that off-label prescribing

- is poorly recognised,[28]
- may lack adequate informed consent processes,[29,30]
- lacks the efficacy achieved in on-label prescribing,[31,32] and
- is more likely to be associated with increased or unrecognised adverse events.[33–35]

While off-label prescribing may have benefits, these must be weighed against harms to define the net clinical effect.

Ethically. The community reasonably expects that prescribing will be for indications approved by reputable regulatory authorities, supported by high-quality evidence, and any deviation from this will be supported by robust policy and informed consent.[36] Off-label medication use may blur the distinction between clinical practice and experimentation, creating significant ethical concerns.[37] Prescribers must understand the potential harms and benefits of a particular therapy (including uncertainties), any alternative therapeutic options and facilitate informed shared decision-making with the patient.

Legally. Once a medication is registered, off-label use is a matter of medical judgement, shifting the focus of ethical and legal responsibility (and hence liability) from manufacturers/suppliers to the prescribing practitioner.[1,38,39] Prescribing off-label is not *prima facie* evidence of medical negligence – negligence requires that the off-label use of the medication for the particular patient was not in line with a reasonable standard of medical care.[40] Regulations prohibit the promotion of off-label uses of medications; however, historically there has been omission or understating of risks, of overstating effectiveness and of unjustifiable comparative claims for off-label medication use.[41–43]

Why does off-label prescribing exist?

The TGA, EMEA and FDA regulate prescription medication marketing, not clinician nor institutional prescribing.[28,43] Given the substantial resources required and evidence base needed to register a medication or update its indications, there will always be off-label prescribing.[44] In some cases, this is supported by studies that underpin particular off-label indications, but regulatory approval has not been sought to cover the indication, dose or route of administration.[29,45]

There are examples where off-label uses of medications have provided patients with improved outcomes, or where such prescribing genuinely reflects leading edge clinical care.[46] Often this is where off-label prescribing was biologically plausible and supported by clinical evidence, although for yet unregistered indications. Examples include imatinib for gastrointestinal stromal tumours,[47] morphine for dyspnoea[48] and immunomodulators in chronic autoimmune/inflammatory conditions.

Expanding indications, or 'indication creep', may provide important therapeutic efficacy data; however, measuring net clinical effect requires systematic assessment of benefits and harms.[49,50] The risk is that practitioners expand indications with limited scientific rationale while the pharmaceutical industry either passively observes broadening indications or actively promotes off-label use even in the absence of evidence of efficacy and safety.[50]

Prescribing is strongly influenced by local practice, anecdote or expert opinion, which may not always reflect best evidence.[51,52] A study of American office-based physicians found that 73% of off-label prescribing had little or no scientific support.[2] Furthermore, as demonstrated in this study, many practitioners do not know whether they are working with registered indications, even in their area of specialty practice.[28]

Off-label prescribing in palliative care?

The available literature on off-label prescribing in palliative care suggests that 12%–26% of prescriptions are off-label,[12,25,53] with low rates of system-level strategies to address off-label prescribing.[25] Off-label prescribing may be biologically plausible, as with octreotide for malignant bowel obstruction, or supported by high-level evidence, as in the case of morphine for dyspnoea.

A number of factors have hindered the building of an evidence base for prescribing in palliative care. This population is often considered difficult to study, due to declining and unstable health, comorbidities, cognitive dysfunction and 'gate-keeping' to 'protect' patients from clinical trials perceived too burdensome despite patient and caregiver support.[54—56] Many of the medications commonly used in palliative care are off patent, and thus, there is little incentive for further research or to expand registration when definitive studies emerge.

Limitations. This study relies on self-report with no easy way to provide third-party verification of the data presented. Furthermore, given the demonstrated poor understanding of off-label prescribing, respondents' self-report may not reflect the extent of their off-label prescribing and are likely to underestimate the prevalence. Furthermore, the sample may be biased, with respondents potentially those most conscious of issues surrounding off-label use, and therefore, the estimates are a more positive picture than the day-to-day reality. Without accurate quantification of the

prevalence of off-label prescribing, the interpretation of these data is limited.

Implications for practice. Ethical off-label use requires at least one of the following:

existing high-level evidence,
the setting of a properly designed rigorous clinical trial
or
exceptional use justified by individual clinical circumstances.[29]

To evaluate the appropriateness of off-label medication use, proposed frameworks consider the level of evidence available and give guidance as to the level of consent, pharmacovigilance and ongoing review required (Figure 2).[22,29,37,57] As with any treatment decision, but especially pertinent in cases with low certainty of net clinical effect, a process of shared decision-making with the patient is required. This should include disclosure of the nature of off-label use, the benefits and harms, the evidence to support the off-label use and why in the particular patient's circumstances, the prescriber believes there is no equivalent or better TGA/EMEA-approved alternative.[36,57] This should be supported by documentation of the informed consent process and discussion in the medical notes.[57,58]

Given the uncertainties of benefits or harms, there is a need to specify treatment goals and to monitor net clinical effect at intervals determined by expected time to response, and requirements for medication titration.[44,59,60] Ideally, formal review of efficacy, safety and cost outcomes should occur to guide further practice.[37] As a minimum, prospective data should be collected on the net clinical effects of the off-label use of medications, and such data aggregated.[61]

While changing clinician behaviour can be difficult,[51] provision of valid evidence and interventions targeting prescribing have been shown to change clinician understanding and prescribing behaviour.[50,62] Other potential strategies include requiring the primary indication when prescribing, which would facilitate post-marketing surveillance.[63] Reducing administrative and financial barriers to approving new indications for registered medications would remove key obstacles to updating registration without lessening the level of evidence required. Professional and regulatory bodies can also guide health policy and influence clinician prescribing.[57] The role of the pharmaceutical industry in promoting off-label prescribing has become more widely recognised in recent cases such as gabapentin,[64] oxycodone[65] and erythropoietin,[66] and substantial penalties have been imposed in an attempt to discourage such actions.

Implications for research. A lack of evidence of effect does not equate to evidence of ineffectiveness. There needs to be prioritisation of research to improve the evidence for medications used off-label in palliative care, particularly those used frequently, with high cost, with significant potential benefits and/or harms, or with little supporting evidence.[67,68] Accurate, prospective determination of the prevalence of off-label prescribing in palliative care, and the medications used, will help guide studies to improve the evidence base.

With regular monitoring of prescribing practice, emerging medication/indication dyads can be identified and appropriate studies performed to build an evidence base. At a minimum, pharmacokinetic studies could be performed in healthy volunteers. Ideally comparative effectiveness studies need to be performed to identify efficacy compared to non-pharmacological and on-label options and to systematically address iatrogenic harm, toxicity and cost-effectiveness, giving an indication of net clinical effect. Should a medication/indication dyad prove beneficial, the dyad should be submitted to the regulatory bodies for registration. Ongoing post-registration evaluation of benefits and harms is required to ensure that the medication is performing as expected.

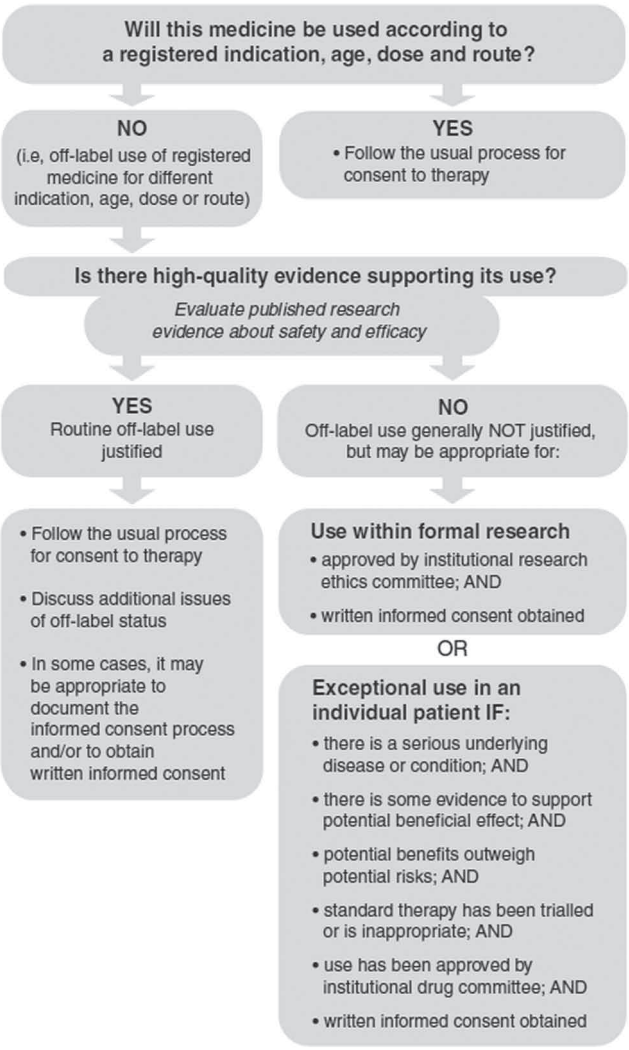

Figure 2. Assessing appropriateness of off-label medicines use.[29]

Further work is required on strategies to optimise prescribing practices and to develop policies around off-label use of medications.

Conclusion

Off-label prescribing in Australian palliative medicine clinicians is poorly recognised and has clinical, legal and ethical implications for the management of palliative care patients.

Two key questions need to be asked in considering off-label use of medications:

Does quality evidence exist but registration has not been updated by the pharmaceutical sponsors? and
Has the evidence not been generated (or exists and suggests that there is no net clinical benefit)?

For clinicians, categorising the medication under one of these two scenarios will guide appropriateness and level of consent, and this should be complemented with subsequent pharmacovigilance for net clinical effect. For policy makers and funding bodies, medications used off-label where there is insufficient evidence should be targeted for further research with a view to updating registration if subsequent studies demonstrate net clinical benefit. More research is required to determine the prevalence and clinical consequences of off-label prescribing in palliative care and to direct intervention for clinicians and patients.

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Conflict of interest

The authors declare that there is no conflict of interest.

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Appendix 1

Survey of the use of licensed drugs for unlicensed uses in palliative care

Section 3: Use of licensed drugs for un-licensed uses in palliative care

Does your service operate a policy on providing information to patients and their carers about the prescribing of licensed drugs for un-licensed u ses/routes?

- ○ Yes
- ○ No

	Always	Sometime	Never
Do you limit the prescribing of un-licensed drugs in this way to consultants only?	○	○	○
Do you obtain verbal consent from the patient/caregiver?	○	○	○
Do you obtain written informed consent from the patient/caregiver?	○	○	○
Do you document in your notes when you are using drugs outside of their license and the reasons for this?	○	○	○

If you answered "*sometimes"* to any of the above please answer the following questions

How often have you obtained verbal or written informed consent from patients/caregivers to use licensed drugs for un-licensed use/routes in the last 6 months?

Times

How often have you documented in the notes the reasons for using unlicensed drugs for un-licensed use/routes in the last 6 months?

Times

Please list the top three licensed drugs for un-licensed use / routes that you use, their indication, and routes of administration.

	Drug	Indication	Route of administration
Drug 1			
Drug 2			
Drug 3			