A point-prevalence study of off-label medication use in an Australian adult tertiary intensive care unit

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ABSTRACT

Medications prescribed for indications or at doses, frequencies or durations not approved by the Australian Therapeutic Goods Administration are considered "off-label". Critical illness makes seeking consent for off-label medication use impractical. We aimed to characterise the extent of off-label medication use in a tertiary medical-surgical intensive care unit (ICU) by auditing the electronic health records of all patients admitted over a one-month period. We found 25.4% of 2292 prescriptions made for 142 patients were off-label. Eighty-one (37.2%) of the total of 218 different prescribed medications were used at least once for an off-label indication. Medications commonly prescribed off-label included antacids (pantoprazole, esomeprazole), analgesics (fentanyl, morphine, ketamine, pregabalin), anticonvulsants (levetiracetam), antibiotics (cefazolin, erythromycin), antipsychotics (quetiapine, haloperidol), and cardiovascular agents (metoprolol, clonidine). Nearly all patients (88.0%) received at least one off-label medication during their ICU stay. Most off-label medications were used for conventional (albeit not licensed) reasons, but nine out of 81 (11.1%) were not; for example, acetazolamide for hypertension, aminophylline for oliguria, and dexmedetomidine for seizures. Recognising the challenges of formally registering an indication with the Therapeutic Goods Administration, but also the value of reducing the incidence of medications used for potentially incorrect purposes, we suggest guideline endorsement of what constitutes standard critical care practice as an alternative to regulatory control.

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Medications registered in Australia must be approved for use by the Therapeutic Goods Administration (TGA). The use of a medication for an indication, at a dose, frequency, duration, or for patients not approved by the TGA is considered "off-label". Outside of the critical care environment, there is pressure to gain informed consent before prescribing off-label medications.[1] However, critical illness can render a patient incapable of providing informed consent, and seeking substitute decision-maker assent can become burdensome. For many medications, little published evidence would support such a conversation. One study found 48.3% of off-label intensive care unit (ICU) medication orders had little or no supporting evidence.[2] Despite this, off-label medications seem commonly prescribed in critical care. Almost all paediatric ICU patients (80–97%) receive at least one off-label medication.[3,4] In the absence of trial evidence, physiological rationale, prophylaxis against complications known to be common in critical illness, and extrapolation from related conditions might underpin this practice. There is currently little knowledge of the prevalence and nature of off-label medication use in adult Australian critical care. We therefore aimed to characterise the use of off-label medications in the setting of an Australian adult ICU.

Methods

After obtaining ethics approval (Royal Brisbane and Women's Hospital Human Research Ethics Committee, LNR/19/QRBW/45753), we performed a single-centre retrospective audit of all regular and "as required" medications prescribed to adults (aged ≥ 18 years) in the Royal Brisbane and Women's Hospital medical-surgical ICU in September 2018. Preliminary analysis of several patient charts suggested one month's data would be manageable given the resources available. Fluids, nutritional supplements and repeat prescriptions were excluded. Clinical indications were extracted from the electronic health record. The hospital electronic health record permits, but does not mandate, that an indication is listed for each prescription. Indications were also sought from the narrative clinical notes. Medications were deemed "off-label" if their recorded

indication did not match an approved indication listed on the Australian Register of Therapeutic Goods. In order not to over-represent the number of off-label prescriptions, if a clear indication was not found, the medication was deemed to be "on-label". To minimise bias, the interpretation of the off-label use was completed by a single researcher. Any uncertainty was remedied through consensus discussion. Only differences in indication, not differences in dose, frequency or duration, were flagged as "off-label" use.

Results

In the one-month period of the study, 142 patients were admitted to the ICU, for whom 2292 eligible prescription orders were identified. No patient records were excluded from the study. About one-quarter (583, 25.4%) of these prescription orders were for an indication not approved by the TGA. A mean of 16 different medications were prescribed to each patient during their ICU stay, of which four were for an off-label indication. A total of 218 different medications were prescribed to all ICU patients during this month, and 81 (37.2%) were used at least once for an off-label indication. Table 1 shows the ten most used off-label medications, identifying both their TGA-approved indications and the most common off-label indications observed in this study. These ten medications represent 56.9% of all off-label medications recorded in the study. Among the next ten most used medications, some were in similar classes to those in the top ten (esomeprazole, morphine) and some were prescribed for reasons quite close to their approved indication (methylprednisolone, diazepam, midazolam, ketamine). However, quetiapine and haloperidol were both commonly prescribed for ICU delirium and agitation, while neither is indicated for this condition. Similarly, pregabalin, indicated for neuropathic pain and partial seizures, was commonly used for acute non-neuropathic analgesia, depression and anxiety. Nearly all patients (88.0%) received at least one off-label medication during their ICU stay. Most (69.7%) received more than two, 35.2% received more than five, and 8.4% received more than ten off-label medications. Most off-label medications were used for reasons that would be recognised by the majority of Australian and New Zealand intensivists, but nine out of 81 (11.1%) medications used off-label (mostly in solitary instances) might not (Table 2); for example, acetazolamide for hypertension, aminophylline for oliguria, and dexmedetomidine for seizures.

Table 1. Frequently prescribed off-label medications and their approved indications

Medication	TGA-approved indication(s)	Off-label indication(s)	Number of prescriptions*
Pantoprazole	• Alkalinisation in gastrointestinal disease • Treatment of ulcer/oesophagitis • Maintenance of healed oesophagitis	• Stress ulcer prophylaxis • Gastrointestinal bleed	90 (15.4%)
Fentanyl	• Analgesia in general anaesthesia • Analgesia in regional anaesthesia	• Sedation • Endotracheal tube tolerance	61 (10.5%)
Levetiracetam	• Newly diagnosed epilepsy • Juvenile myoclonic epilepsy • Idiopathic generalised epilepsy	• Seizure prophylaxis • Seizure post-intracranial haemorrhage • New onset seizures • Encephalopathic seizures • Status epilepticus • Seizures after head trauma	32 (5.5%)
Cefazolin	• Respiratory tract infection • Genitourinary tract infection • Skin infection • Bone and joint infection • Septicaemia • Endocarditis	• Infection prophylaxis	27 (4.6%)

(*Continues*)

Table 1. Frequently prescribed off-label medications and their approved indications (*continued*)

Medication	TGA-approved indication(s)	Off-label indication(s)	Number of prescriptions*
Ondansetron	• Nausea from cytotoxic therapy • Nausea from radiotherapy • Postoperative nausea/vomiting	• Nausea/vomiting (various unapproved indications)	25 (4.3%)
Metoprolol	• Intravenous injection: ▸ Dysrhythmias • Tablet: ▸ Hypertension ▸ Angina pectoris prophylaxis ▸ Myocardial infarction ▸ Migraine prophylaxis	• Intravenous injection: ▸ Hypertension • Tablet: ▸ Tachycardia ▸ Atrial fibrillation ▸ Sympathetic storm	24 (4.1%)
Erythromycin	• Upper and lower respiratory tract infections • Skin infection • Diphtheria • Acute pelvic inflammatory disease • Legionnaire disease	• Prokinetic	20 (3.4%)
Insulin (Actrapid; Novo Nordisk)	• Insulin-dependent diabetes	• Glycaemic control in non-diabetics	20 (3.4%)
Clonidine	• Essential hypertension • Renal hypertension • Acute hypertensive crisis	• Agitation • Sedation • Analgesia • Anxiety	18 (3.1%)
Metoclopramide	• Abdominal x-ray adjunct • Intestinal intubation • To aid absorption of certain medications • Gastric retention after gastric surgery • Diabetic gastroparesis • Nausea/vomiting in: intolerance of essential drugs with emetic properties, uraemia, radiation sickness, malignant disease, postoperative vomiting, labour, infectious disease	• Prokinetic • Agitation	15 (2.6%)

TGA = Therapeutic Goods Administration. * Total 583 off-label prescriptions.

Discussion

The off-label rate observed in this study (25.4%) is slightly lower than that in adult ICUs in the United States (43.0%[5] and 36.2%[2]). However, the reported off-label prescription rate in our study might have been underestimated, as medications without a clear indication were considered on-label. Rates might also vary due to different approved indications in the United States in different years, or due to different types of medications used in different ICU populations. We did not explore these possible explanations in detail as their effects are likely to have been small. That 25.4% of Australian ICU medications are prescribed off-label, and that nearly nine in ten patients received at least one off-label medication, is substantial enough to warrant attention.

Many of the medications designated as off-label in this study required nuanced interpretation of ambiguities in TGA-approved indications. The most commonly used

Table 2. Medications prescribed for an off-label indication that did not appear to match conventional practice

Medication	Recorded off-label indication(s)	Number of prescriptions*
Acetazolamide	Hypertension	2 (0.3%)
Aminophylline	Oliguria	1 (0.2%)
Dexmedetomidine	Seizures	1 (0.2%)
Digoxin	Ventricular tachycardia	1 (0.2%)
Dutasteride/tamsulosin (Duodart; GlaxoSmithKline)	Hypertension	1 (0.2%)
Etanercept	After bone marrow transplant	1 (0.2%)
Lamotrigine	Depression	1 (0.2%)
Lithium	Anxiety	1 (0.2%)
Mirtazapine	Bipolar disorder; post-traumatic stress disorder	2 (0.3%)

* Total 583 off-label prescriptions.

off-label medication was pantoprazole for stress ulcer prophylaxis. Although the TGA approves pantoprazole for the treatment and maintenance of gastrointestinal disease, preventing the onset of the disease is not indicated. Curiously, the use of some antibiotics such as cefazolin to prevent infection is considered off-label, while other antibiotics do have TGA approval for prophylactic use. The use of levetiracetam in seizures resulting from traumatic brain injury was deemed off-label, as the approved indication is limited to specific forms of diagnosed epilepsy.

Some argue that informed consent should be obtained (rigorously) before medications are used off-label.[6] To obtain informed consent, patients or surrogate decision makers require education in the level of evidence available to support the off-label use, as well as the associated risks and uncertainties.[1,6] Even if the time pressures associated with critical illness did not prevent this, the number of medications involved and the lack of evidence supporting use in this context would make proper informed consent highly burdensome for both staff and decision makers.

Many of the medications identified, although off-label, are supported by long-standing clinical practice. Extrapolation of experience with similar medications, logical extension of other approved uses, physiological rationale and tradition all support consensus recommendations favouring the use of many off-label medications.[1,7] Formal endorsement of off-label medications from the critical care community, separate to the regulatory process, is a practical alternative to calling for individual informed consent. Facilitating consensus practice (and thereby discouraging unwarranted individual variability) might reduce the low, but nonetheless potentially concerning, incidence of what appeared to be prescribing for incorrect indications observed in this study. A good place to start would be a systematic review of what guidelines exist for the most commonly prescribed off-label medications, and observational studies to confirm that these do, in fact, represent the consensus of what constitutes standard critical care practice.

Competing interests

All authors declare that they do not have any potential conflict of interest in relation to this manuscript.

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