

# Off-Label Prescribing in Older Patients

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## Abstract

The practice of off-label prescribing, i.e. prescribing drugs either for unregistered/unapproved therapeutic indications and age groups or using unregistered/unapproved doses or methods of administration, is common in older patients. This may be due to the poor representation of this group in pre-marketing clinical trials assessing therapeutic efficacy and safety of novel therapies or merely to the fact that trials in a particular indication have not been undertaken. Off-label prescribing should not be viewed as scientifically or ethically unsound when there are good clinical data to support a particular therapeutic indication. However, a number of steps should be followed in order to ensure therapeutic efficacy, reducing at the same time, the risk of adverse drug reactions and/or medical litigation. This article discusses the current epidemiology and trends in off-label prescribing in older patients, the scientific and ethical justification of this practice, medico-legal implications, and proposed strategies for risk mitigation.

## 1. Introduction

Off-label prescribing is generally defined as the practice of prescribing drugs either for unregistered therapeutic indications and age groups or using unregistered doses or methods of administration.<sup>[1]</sup> As older people remain poorly represented in clinical trials assessing the pre-marketing efficacy and safety of novel therapies, it is perhaps not surprising that off-label prescribing is particularly common in this group.<sup>[2]</sup> This is further compounded by the often complex patterns of medication intake and co-existing medical conditions in older patients. As a result, it is more difficult to link symptoms and signs to a specific medical condition warranting pharmacological treatment; hence, there is an increased risk of inappropriate prescribing. Significant changes in

pharmacokinetics and pharmacodynamics in old age, combined with a reduced homeostatic reserve and an increased number of co-morbidities, increase the risk of adverse drug reactions (ADRs).<sup>[3,4]</sup>

This article will discuss the epidemiology and the justification of the practice of prescribing off-label drugs in older patients, the ethical and medico-legal implications of such practice, and potential strategies for risk mitigation and standardization.

## 2. Epidemiology of Off-Label Prescribing in Older Patients

### 2.1 Geographical Patterns

The practice of off-label prescribing is common in the older population. The reasons for this become apparent after reviewing a list of drugs

commonly prescribed off-label in this group (table I). An important cause of such prescriptions is the use of antipsychotic drugs in delirium and dementia. However, it is difficult to establish global trends, because of differences in legislation, healthcare settings (e.g. hospital, institution and community), physician training and attitudes, patient characteristics, and availability of medications across countries. Hames and Wynne<sup>[2]</sup> reported that 84% of patients admitted to geriatric medicine wards in Newcastle, UK, were prescribed off-label drugs. Leslie et al.<sup>[5]</sup> investigated antipsychotic medication prescribing patterns from the US Department of Veterans Affairs in 279 778 patients in 2007.

There was no record of a diagnosis for which these drugs are approved in 60% of patients. Bronskill et al.<sup>[6]</sup> showed that 24% of patients without a history of psychosis were prescribed off-label antipsychotic drugs in nursing homes in Canada. Higher rates (86%) of off-label prescribing of second-generation antipsychotics in older, nursing home residents in the US have been reported more recently.<sup>[7]</sup> This is of significant concern because institutionalized patients receive relatively little monitoring by healthcare professionals; hence, there is a potential increased risk of ADRs or other unwanted effects in this group.<sup>[8]</sup>

## 2.2 Relationship with Age

Several studies have addressed potential age-related differences in the prevalence of off-label prescribing. Leslie et al.<sup>[5]</sup> did not detect clinically relevant associations between age and off-label prescribing of either first-generation antipsychotics or indeed any antipsychotic. By contrast, Kamble et al.<sup>[7]</sup> observed a significant effect of increasing age, using age 65–74 years as the reference; the off-label prescribing of second-generation antipsychotics in older, nursing home residents in the US was greater (age 75–84 years: adjusted odds ratio [OR] 1.6; 95% CI 1.2, 2.3; age ≥85 years: adjusted OR 5.0; 95% CI 3.3, 7.5). Alexander et al.<sup>[9]</sup> studied patterns of off-label prescribing of antipsychotic drugs in the US during the period 1995–2008. Off-label prescribing with uncertain evidence was more common in patients aged ≥65 years (67–86%) than in patients aged 18–64 years (44–73%), although no formal statistical comparison was performed. Chen et al.<sup>[10]</sup> conducted a retrospective analysis of off-label prescribing of antidepressants, anticonvulsants and antipsychotics in Medicaid recipients in Georgia, USA. Age ≥65 years was independently associated with off-label prescribing of the three drug classes (antidepressants: OR 5.1; 95% CI 4.8, 5.6; anticonvulsants: OR 4.5; 95% CI 4.2, 5.0; antipsychotics: OR 5.2; 95% CI 4.8, 5.6). Using age 65–74 years as the reference, increasing age was negatively associated with antidepressant overuse in a recent study by Hanlon et al.<sup>[11]</sup> (age

**Table 1.** Examples of drugs commonly used in older patients outside their marketing authorizations

Drug	Comments
Amitriptyline, nortriptyline	Not licensed for neuropathic pain; appropriate and effective second-line agents
Haloperidol, risperidone and other atypical antipsychotic drugs	Not licensed for delirium; with the exception of risperidone, not licensed for behavioural and psychological symptoms of dementia
Gabapentin, topiramate, lamotrigine, carbamazepine, sodium valproate	Amitriptyline, valproic acid and sodium valproate effective but not licensed for prophylaxis of migraine; gabapentin, topiramate and lamotrigine not licensed for trigeminal neuralgia; sodium valproate used but not licensed for the treatment of manic episodes in bipolar disorder (c.f. valproic acid) or migraine prophylaxis
Angiotensin receptor blockers other than candesartan	Not licensed for treatment of chronic heart failure when ACE inhibitors are not tolerated
Spironolactone	Not licensed for resistant essential hypertension
Bevacizumab	Widely used off-label in the treatment of macular degeneration
Midodrine	Not licensed in the UK (for any indication), although licensed elsewhere; used for orthostatic hypotension after non-pharmacological treatments have failed

ACE = angiotensin converting enzyme.

75–84 years: OR 0.89; 95% CI 0.73, 1.09; age  $\geq 85$  years: OR 0.70; 95% CI 0.57, 0.87). A similar negative association between age and off-label prescribing of antidepressants has been reported by Conti et al.<sup>[12]</sup> in a large (>25 million), US, adult patient population. Guillan et al.<sup>[13]</sup> studied the off-label prescribing of intravenous tissue plasminogen activator in patients with acute stroke. Patients receiving off-label thrombolysis were shown to be older in the univariate analysis ( $77.7 \pm 12.5$  vs  $65.1 \pm 13.9$  years,  $p < 0.001$ ); no multivariate analyses were presented.

These studies show contrasting results on the association between advancing age and off-label prescribing of several drug classes. Further studies are also required to address the potential impact of gender, ethnicity, institutionalization and cognitive impairment on possible age-related differences in the prevalence of off-label prescribing.

### 2.3 Other Factors Associated with Off-Label Prescribing

There are relatively few published data on the impact of other factors, e.g. prescriber characteristics, patient attitudes, and institutionalization, on the prevalence of off-label prescribing. In their study on prescribing of second-generation antipsychotics in older, nursing home, US residents, Kamble et al.<sup>[7]</sup> observed that Medicaid was negatively associated with off-label prescribing (OR 0.6; 95% CI 0.5, 0.9). By contrast, self-pay (OR 1.7; 95% CI 1.3, 2.3), history of dementia (OR 3.2; 95% CI 2.4, 4.2), and non-profit facilities (OR 1.5; 95% CI 1.0, 2.2) were positively associated with off-label prescribing of antipsychotics. In a similar study of prescribing of antipsychotics in the US Department of Veterans Affairs Health Care System, Leslie et al.<sup>[5]</sup> observed that female gender (OR 1.28; 95% CI 1.26, 1.31), being African-American (OR 1.13; 95% CI 1.10, 1.15) or Hispanic (OR 1.63; 95% CI 1.58, 1.67) were positively associated with off-label prescribing. Patel et al.<sup>[14]</sup> observed that 41% of the pharmacy claims for off-label prescribing of anticonvulsants were made by primary care providers, 9% by neurologists, 3% by psychiatrists and 46% by other specialties.

## 2.4 Drug Classes Commonly Prescribed Off-Label

### 2.4.1 Antipsychotics

Most of the published evidence on the prevalence and the impact of off-label prescribing has been generated from studies on antipsychotic drugs. The main reasons for this are their frequent use in the older population, particularly in institutionalized patients, and the recent evidence of potential adverse outcomes, particularly in long-term users. Reported adverse outcomes include the development or worsening of diabetes, tardive dyskinesia, extrapyramidal symptoms, stroke and increased all-cause mortality.<sup>[9,15,16]</sup> The main indications for off-label prescribing of antipsychotic drugs in older patients include depression, behavioural and psychological symptoms of dementia, acute agitation and insomnia. These drugs are often continued long term without adequate medication review by either a physician or a clinical pharmacist. The antipsychotic drugs most commonly prescribed off-label in older patients include quetiapine, risperidone, olanzapine, aripiprazole and first-generation antipsychotics.<sup>[5,7,15]</sup>

### 2.4.2 Anticonvulsants

Common indications for off-label prescribing of anticonvulsants in older patients include pain, migraine headache and depression. Gabapentin, topiramate, lamotrigine, carbamazepine, sodium valproate and phenytoin are the anticonvulsants most commonly prescribed for off-label indications.<sup>[10,14]</sup> In particular, gabapentin was reported to be the drug most commonly prescribed off-label (83%) in the US, although specific data in the older population are lacking.<sup>[17]</sup> Chen et al.<sup>[10]</sup> have shown that advancing age is negatively associated with the off-label use of anticonvulsants.

### 2.4.3 Antidepressants

Antidepressants are increasingly used off-label in the general population for the treatment of insomnia, pain, anxiety disorders, premature ejaculation, migraine prophylaxis and fibromyalgia, and in smoking cessation therapy.<sup>[18]</sup> Lai et al.<sup>[19]</sup> studied the off-label prescribing of antidepressants in patients with insomnia, using data from the US national longitudinal database from the 2006

National Ambulatory Medical Care Survey. Off-label antidepressants were prescribed more frequently (45%) than non-benzodiazepine z-hypnotics (43%) and benzodiazepines (12%). The most frequently prescribed antidepressants were trazodone, amitriptyline, mirtazapine, nortriptyline and doxepin.<sup>[19]</sup> In this study, age was not associated with the off-label prescribing of antidepressants. Hanlon et al.<sup>[11]</sup> have recently observed that antidepressants were prescribed in 42% of older, nursing home residents without a clear history of depression that would have met the entry criteria for recruitment into regulatory trials. Selective serotonin reuptake inhibitors were the most commonly prescribed antidepressants (used in 27% of patients without depression).

#### 2.4.4 Anti-Vascular Endothelial Growth Factor Drugs

Anti-vascular endothelial growth factor (anti-VEGF) drugs are increasingly used for the treatment of age-related macular degeneration (AMD).<sup>[20]</sup> The anti-VEGF drug bevacizumab has been prescribed off-label since 2005 for the treatment of neovascular AMD by intravitreal administration.<sup>[21]</sup> A recent clinical trial has demonstrated that bevacizumab and ranibizumab, approved for treatment of AMD, have similar effects on visual acuity at 1 year.<sup>[22]</sup> Brechner et al.<sup>[23]</sup> studied the pharmacoepidemiology of anti-VEGF treatment of AMD by retrospectively reviewing all US Medicare fee-for-service claims for neovascular AMD in 2008. Bevacizumab was administered in 64% of patients, with the remainder receiving ranibizumab. Notably, the overall payments by Medicare were around \$US20 million for bevacizumab and \$US530 million for ranibizumab. A recent pharmaco-economic analysis based on 2010 data in the UK suggested that the National Health Service could save approximately £190 million over 3 years if it were to use bevacizumab to treat an estimated 26 000 new AMD cases each year.<sup>[24]</sup>

### 3. Justification and Rationale for Off-Label Prescribing

Where a drug has an indication not covered by its marketing authorization but there are good clinical data to support the indication, few would

argue against its use. For example, following the publication of the PROGRESS (Perindopril PROtection aGainst REcurrent Stroke Study) trial results, there was good evidence that the angiotensin converting enzyme (ACE) inhibitor perindopril together with indapamide reduced the risk of recurrent stroke regardless of the initial blood pressure.<sup>[25]</sup> Perindopril was widely and appropriately prescribed off-label for this indication, and it was more than a year later that the drug received a marketing authorization for this indication in Europe.

#### 3.1 Scientific Rationale

As in the perindopril example, there needs to be a credible body of evidence to support the off-label prescribing of a drug. The nature of this evidence will clearly differ from the evidence that would be needed to prescribe an unlicensed drug, as the animal toxicity, early clinical development data, and the safety profile in phase 3 and 4 studies would already be known. The fact that safety profiles can differ depending on the indication would of course have to be taken into account. In effect, the prescriber is weighing up the safety and efficacy data in the same way that a licensing authority would. There would, however, be some important differences. First, the prescriber would not be able to rely on the careful data analysis undertaken by the licensing authority. In addition, there would be no concerns over the formulation either in terms of the manufacture or the bioavailability. The prescriber would, however, need to be working well within their area of expertise.

Clearly, there will be situations when the clinical trial evidence base is either inadequate or non-existent, yet a drug offers theoretical advantages. For example, a new antibiotic with limited marketing authorization might be entirely appropriately prescribed in the light of the microbiological sensitivities, particularly where existing antibiotics are either not tolerated or are contraindicated.

#### 3.2 Ethical Rationale

To withhold a drug from a patient when it is judged the most appropriate treatment might be

regarded as ethically unsound. This would apply unless the drug was physically not available for reasons of funding, supply or manufacture. This concept would be relevant in the antibiotic example above in the absence of clinical trial evidence. The clinical priorities would need to be carefully thought through. Thus, the use of an evidence-based, off-label, cytotoxic agent to induce remission after failure of approved agents in the management of haematological malignancy would only be appropriate if aggressive therapy was still indicated rather than a more palliative approach. This issue is particularly relevant in the management of several medical conditions in the older population.

Particularly in the light of the present financial position most countries find themselves in, it could be considered unethical to prescribe a very expensive drug for an indication within the drug's marketing authorization (e.g. ranibizumab versus a much cheaper alternative, e.g. bevacizumab) when the clinical data exist for the alternative but are outside the drug's licence.

#### **4. Risk Management of Off-Label Prescribing**

Within Europe, the European Medicines Agency's (EMA's) Committee for Medicinal Products for Human use (CHMP) is responsible for assessing the efficacy and the safety of a medicinal product and making a recommendation to the Regulatory Authority. Recently, the EMA has established a Geriatric Expert Group, to provide scientific advice on issues related to the elderly. The group is formed of nine European members with expertise in the scientific and regulatory aspects of geriatric medicine. The group contributes to the work of the CHMP and the Agency secretariat by:

- giving advice on guidelines under consultation;
- giving advice on geriatric aspects of the development, assessment or safety monitoring of medicines;
- taking part in meetings where expertise on geriatrics is needed
- contributing to the geriatric implementation plan.

The indication or indications for a drug, as initially proposed by the pharmaceutical company at the time of application, are often changed, and are mostly narrowed down to the profile of the studied patient groups. As a consequence, the original proposed indications are not stated in the Summary of Product Characteristics (SPC), and for the older population, it could be reported as "not studied in elderly patients or lack of sufficient data in elderly patients." Thus, off-label prescribing falls outside of the marketing authorization. However, this does not mean that such use is not supported by scientific data on efficacy and safety. Sometimes off-label prescribing is necessary because of the delay or slow progress of the careful procedures of the regulatory agency, although enough scientific evidence supports a new indication for the drug.

In theory, the practice of off-label prescribing is relatively more risky than prescribing according to the approved indication, although off-label prescribing in clinical situations where there is an evidence base for safety and efficacy minimizes this. On the other hand, older patients with several co-existing medical conditions are usually not included in clinical pre-marketing trials and could suffer adverse reactions not detected in such studies, even though the prescribing is technically within the label. Marketing authorization holders regularly submit Periodic Safety Update Reports (PSURs), providing new information on the safety of a specific drug. A PSUR includes all serious and non-serious ADRs reported worldwide. The PSUR could serve as a basis for changes in the SPC. This is also the case for safety issues related to off-label prescribing. Marketing authorization holders should encourage prescribers to report ADRs associated with off-label prescribing. If such information becomes available, it should then be included in the SPC so that the prescriber is informed and can better assess the risks of off-label prescribing. However, this is a time-consuming procedure, as it might take many months or longer to get the information into the SPC. A quicker way of informing prescribers of potentially more serious adverse reactions is the use of the 'Dear doctor' letter. Recent examples include warnings of severe eye inflammation and sterile endophthalmitis with off-label prescribing of bevacizumab in macular

degeneration and excess all-cause mortality and stroke with off-label prescribing of antipsychotics for behavioural and psychological symptoms of dementia, particularly during the first weeks of treatment.<sup>[26,27]</sup> Despite these reports, recent studies show that antipsychotics are still widely prescribed off-label in assisted living facilities.<sup>[28,29]</sup>

### 5. Strategies to Rationalize Off-Label Prescribing

Doctors treating older patients often prescribe drugs outside their approved indication. However, such practice is not necessarily wrong and might provide significant benefits for the patient. Off-label prescribing could be viewed as a physician's duty if the therapy is considered the best possible treatment for the patient. However, pharmaceutical companies may present results of small, methodologically unsound studies to influence physicians to promote off-label use. In the UK and other countries, pharmaceutical companies are prohibited via the Association of the British Pharmaceutical Industry code (or equivalent) from marketing drugs outside their marketing authorization. Prescribing outside the approved indication cannot be justified if there is no medical or scientific evidence.

Who should pay for off-label use varies between different healthcare systems. The medicines are often reimbursed even if the indication for which they are prescribed is off-label. In addition, this practice might put financial liability on the physician, who might already have a legal liability if the patient was not fully briefed. In a time of increasing medical litigation, this might be a powerful disincentive to prescribe off-label.

A patient prescribed a drug off-label should be adequately informed about the reasons and the potential risks associated with this strategy. In several European countries, the practice of off-label prescribing is regulated by law, whereas in others, it is covered by good practice regulation within the jurisdiction of a regulator.

The following recommendations might assist practitioners when considering off-label prescribing:

- (1) Know the licensed indications of a drug.

These are provided in the SPC and are also

available from the EMA ([www.ema.europa.eu](http://www.ema.europa.eu)).

- (2) Prescribe off-label drugs only if no approved drug is available for this indication or if specific patient characteristics, e.g. age or intolerance, do not allow the prescribing of the approved medicines.
- (3) For references to scientific evidence for off-label drug use, it is advisable to check formularies or guidance documents that specifically evaluate the data to support off-label indications, such as those provided by the National Institute for Health and Clinical Excellence (NICE) [e.g. <http://www.nice.org.uk/Search.do?searchText=off+label&newsearch=true#/search/?reload>].
- (4) If no guideline or formulary is available, discuss potential off-label indications with a clinical pharmacist, clinical pharmacologist and/or a colleague.
- (5) Inform the patient about the reasons for and the potential risks associated with off-label prescribing and ask for 'informed consent'. This might involve discussion with a carer or next of kin if the patient is unable to provide consent.
- (6) Record the off-label prescription and conversation in the medical notes.
- (7) Assess and monitor the expected therapeutic effects of the drug and the adverse effects closely as would be usual for an on-label prescription.
- (8) Regularly assess whether there is still an indication for an off-label prescription.
- (9) Report adverse effects to a pharmacovigilance agency and/or to the pharmaceutical company who holds the marketing authorization and highlight their occurrence as a result of off-label prescribing.

### 6. Conclusions

Off-label prescribing is common in the older population. In the opinion of the authors, this practice will be increasingly adopted in the years to come as evidence continues to accumulate more rapidly than marketing authorizations are updated. In the current financial climate, it is very

unlikely that pharmaceutical companies will fund large, pre-marketing trials looking at the therapeutic efficacy and safety of novel drugs in frail older patients with multiple co-morbidities. It is of potential concern that a significant proportion of institutionalized patients are prescribed off-label drugs, particularly antipsychotics and antidepressants. The limited input and monitoring provided by healthcare professionals in this setting is likely to expose institutionalized patients to a greater risk of ADRs, ultimately increasing the risk of adverse outcomes. These issues notwithstanding, off-label prescribing should not be viewed as scientifically or ethically unsound when there are good clinical data to support a particular therapeutic indication. However, a number of steps should be followed to ensure therapeutic efficacy and safety. The proposed risk mitigation strategies might help practitioners to correctly identify suitable patients and medical conditions potentially requiring off-label prescribing, reducing at the same time the harm to the patient and the risk of medical litigation.

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