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Off-label prescribing of antidepressants

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TITLE

Off-label antidepressant prescribing and the extrapolation of evidence

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In most countries, medicines have a product licence that describes how they should be used. Licencing is intended to assure that medicines meet acceptable standards of efficacy, safety and quality for a particular indication in a particular group of patients.[1] 'Off-label' use occurs when a drug is prescribed for an unlicensed indication, to an unlicensed patient group (e.g. children), and/or as an unlicensed dosage or formulation. In the linked paper, Wong and colleagues found that almost a third of antidepressants were prescribed for off-label indications, most commonly pain, insomnia and migraine.[2]

Physicians can legally prescribe off-label, and professional licencing agencies recognise that off-label use is necessary if licenced medicines are ineffective, are associated with adverse effects, or if the licenced dose or formulation do not meet the patient's needs. Professional responsibility in these circumstances is fundamentally the same as for on-label prescribing. As the United Kingdom medical regulator says: "We expect you to carefully consider any treatment that you prescribe, and we expect you to be able to justify your decisions and actions when prescribing, administering and managing medicines regardless of whether they are licensed or unlicensed."[3] Although off-label prescribing may need more explicit justification, the evidence supporting prescribing is actually more important rather than the licence per se.

Only 16% of the off-label prescribing identified by Wong and colleagues was directly supported by strong evidence, with a further 40% having indirect support from strong evidence for other drugs in the same class.[2] Although it may seem odd that off-label prescribing can have strong evidence, this frequently occurs when new indications for old drugs are evaluated in trials, but pharmaceutical companies have not judged it worthwhile to alter existing marketing authorisations because the drug is off-patent and the required regulatory process is complex and expensive. Amitriptyline use for chronic pain is an example of evidence-based[4] and guideline recommended off-label prescribing[5] and accounted for 14% of off-label antidepressant prescribing in the linked study.[2] Extending the range of uses of long-established medicines like this way is attractive for health care professionals and patients alike, because they are perceived to have familiar safety-profiles and are cheaper. Similarly, clinical guidelines may recommend antidepressant drug classes for extended indications like anxiety rather than only specific licenced medicines,[6] even though this requires a fairly strong assumption that all drugs in the same class are equally effective or equally safe.

Clinical and shared decision-making is complicated by these mismatches between licencing, evidence and guidelines within countries, further confused by licencing and guidelines varying between

different countries, even to the point of inconsistency in which adverse drug events are considered significant for licenced drugs.[7] For all prescribing, patients (or their parents or carers) should be provided with enough information to allow them to make an informed decision to take a medicine (or not). This should include whether the intended use is off-label, but more importantly should account for the evidence base underlying the prescriber's recommendation.[3] How often this occurs in practice remains uncertain. Electronic prescribing systems offer opportunities to provide more point-of-care information to prescribers and patients, including whether an intended use is off-label and/or lacks evidence in the patient in front of them. However, such systems need careful design and evaluation to avoid unintended consequences of implementation in time-constrained clinical workflows.

Off-label prescribing matters because it is usually (but not always) associated with significant uncertainty about the balance of benefit and harm.[8] Prescribers should therefore be cautious when they prescribe an off-label medicine based on an extrapolation of evidence for a different indication, in a different patient group, and/or for a significantly different dose or formulation. Equally though, *on-label* prescribing also often involves extrapolation, most commonly because the patient in front of the prescriber is very different from the patients included in trials. For example, on-label use of antidepressants to treat depression is based on trials carried out in people with more severe depression and less psychiatric and physical comorbidity than is typical in everyday practice.[9,10] As a result, most people with well-characterised Major Depressive Disorder in everyday practice would be ineligible for the antidepressant treatment trials on which licencing and treatment recommendations are based.[11] There is also evidence that those ineligible for trials are less likely to respond to antidepressants and more likely to experience adverse events.[12] Off-label prescribing clearly matters because it often lacks any strong evidence or relies on extrapolating evidence from one situation to another, but prescribers and patients should be cautious about all extrapolations of evidence whether on- or off-label.

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