Adverse events associated with off-label medicine use in adults

A large Canadian observational study in people prescribed new medicines found that using medicines for an off-label indication is associated with an increased risk of treatment discontinuation due to adverse drug events, particularly when strong scientific evidence is lacking. This study reinforces the importance of continuing to follow the GMC prescribing guidance and MHRA advice on unlicensed or off-label medicines, and the NICE medicines optimisation guidance which recommends shared-decision making in relation to medicines.

Overview and current advice

‘Unlicensed’ use of medicines describes those that have no licence for use in the UK. A medicine can also be prescribed ‘off-label’. This means the prescriber wants to use it in a different way than is set out in the terms of its licence. This could mean using the medicine for a different condition or a different group of patients, or it could mean a change in the dose or that the medicine is taken in a different way. Unlicensed and off-label medicines are commonly used in some areas of medicine such as in paediatrics, psychiatry and palliative care, but they are also used, less frequently, in other areas of medicine. See NHS Choices for further information about licensing of medicines.

General Medical Council (GMC) prescribing guidance (which reflects MHRA advice) recommends that a medicine should usually be prescribed in accordance with the terms of its licence. However, unlicensed or off-label medicines may be prescribed where, on the basis of an assessment of the individual patient, the prescriber concludes, for medical reasons, that it is necessary to do so to meet the specific needs of the patient. This may be necessary where there is no suitably licensed medicine that will meet the patient’s need, there is no licensed medicine applicable to the particular patient, where a suitably licensed medicine that would meet the patient’s need is not available or the prescribing forms part of a properly approved research project.

The GMC advises that, when prescribing an unlicensed or off-label medicine, prescribers must:

- be satisfied that there is sufficient evidence or experience of using the medicine to demonstrate its safety and efficacy;
- take responsibility for prescribing the medicine and for overseeing the patient’s care, monitoring, and any follow up treatment, or ensure that arrangements are made for another suitable doctor to do so;
- make a clear, accurate and legible record of all medicines prescribed and, where common practice is not being followed, their reasons for prescribing an unlicensed medicine.
The GMC and MHRA also recommend that patients (or their parents or carers) must be given sufficient information about the medicines prescribers propose to allow them to make an informed decision. The NICE medicines optimisation guideline recommends that all people should be offered the opportunity to be involved in making decisions about their medicines. It also recommends that organisations ensure that robust and transparent processes are in place to identify, report, prioritise, investigate and learn from medicines-related patient safety incidents, in line with national patient safety reporting systems – for example, the National Reporting and Learning System.

NICE Evidence summaries: unlicensed or off-label medicines summarise the best available evidence for selected unlicensed or off-label medicines. The GMC has also issued a Hot topic: prescribing unlicensed medicines, which discusses the practical implications of its guidance and lists sources that might help prescribers who are considering the use of unlicensed or off-label medicines. The NICE pathway on medicines optimisation brings together all related NICE guidance and associated products on medicines optimisation into a set of interactive topic-based diagrams.

New evidence

A Canadian prospective cohort study of 46,021 adults with a new prescription for a medicine between 1 January 2005 and 30 December 2009 considered the association between off-label drug use and adverse events. Prescriptions were considered if the same drug had not been prescribed or dispensed in the previous 12 months. They were followed up from the date of the first prescription to the date medicine use was stopped, the end of treatment or the end of follow-up.

Information was taken from a community-based clinical information system that provided a longitudinal electronic health record, and included indications for treatment, reasons for dose changes, discontinuation and the nature of any adverse drug events. In addition, the authors of this study categorised the level of evidence for each off-label drug indication using the US DrugPoints System (Thomson Reuters). Evidence was categorised as strong when the drug was demonstrated to be effective or efficacy was "favoured" for the unlicensed indication, it was recommended for most people with the indication, and the studies used to evaluate efficacy included at least 1 randomised controlled trial (RCT). Adverse drug events were defined as discontinuations of drug use made by physicians due to an adverse drug reaction or an allergic reaction. Prescription follow-up ranged from 1 day to almost 6 years and 46,021 adults (mean age 58 years, 61% female) received 151,305 new prescriptions, 11.8% (17,847) of which were off-label.

Adverse drug events led to physicians stopping 3484 drug treatments overall, giving an incidence rate of 13.2 per 10,000 person-months. This was lower for drug use within licensed indications (12.5 per 10,000 person-months) compared with off-label drug use (19.7 per 10,000 person-months). A 44% relative increase in the risk of adverse drug events was found with off-label drug use compared with drug use within licensed indications (adjusted hazard ratio [HR] 1.44, 95% confidence interval [CI] 1.30 to 1.60).

Off-label drug use was not supported by strong evidence in most (81%) cases. When the association between off-label drug use and adverse drug events was considered according to the strength of evidence available, off-label drug use considered to have strong evidence had a rate of adverse drug events of 13.2 per 10,000 person-months (adjusted HR 1.10, 95% CI 0.88 to 1.38), whereas this was higher at 21.7 per 10,000 person-months (adjusted HR 1.54, 95% CI 1.37 to 1.72) for off-label drug use without strong supporting evidence. When compared with drug use within licensed indications, off-label use without strong evidence was associated with a 54% relative increase in risk of adverse drug events (adjusted HR 1.54, 95% CI 1.37 to 1.72), whereas for off-label use considered to have strong evidence, the increased risk was not statistically significant (adjusted HR 1.10, 95% CI 0.88 to 1.38).
For all drugs, the highest adverse drug event rates were seen with anti-infectives (adjusted HR compared with gastrointestinal [GI] drugs 6.33, 95% CI 4.58 to 8.76) then cardiovascular drugs (adjusted HR 3.30 compared with GI drugs, 95% CI 2.67 to 4.08) and central nervous system drugs (adjusted HR 3.06 compared with GI drugs, 95% CI 2.46 to 3.79). Also, people taking 8 or more drugs had more than a five-fold relative increase in the risk of adverse drug events than people who took 1 to 2 drugs (adjusted HR compared with people taking 1 to 2 drugs 5.29, 95% CI 4.39 to 6.38).

**Commentary**

**Commentary provided by NICE**

As highlighted by the authors, this study is the first to systematically evaluate the association between off-label drug use and the risk of adverse drug events in an adult population. It was an extensive study, including more than 46,000 adults and around 150,000 new prescriptions, followed up for nearly 6 years. Use of the electronic health record making it possible to link the use of medicines with their indication, and identification of reasons for discontinuation are further strengths of the study design.

There are some limitations to this study. Adverse drug events were identified by the people who were prescribed medicines and clinicians and it is possible that some people may not tell their clinician about all adverse events. In addition, some adverse drug events may have been attributed to multiple co-morbidities and, therefore, not recognised as being related to treatment. Severe adverse drug reactions that resulted in hospital admission may not have been documented in the electronic health record. This may have led to underestimation of the adverse events associated with treatment. It should be noted that this study only gives us information about off-label prescribing by indication as it did not consider other types of off-label prescribing, such as off-label dosage, age range or route of administration. Usual clinical practice would be to consider prescribing medicines according to the following hierarchy (where clinical circumstances deem this appropriate): use of a licensed medicine (or medicines) within the terms of its marketing authorisation; followed by use of a licensed medicine off-label; then use of an unlicensed medicine. Unfortunately this study was limited in that it did not look at whether a medicine licensed for the indication had been tried first or any other details about the sequence of prescribing.

The authors adjusted the results to take into account confounding factors, such as number of drugs and participants’ co-morbidities. However, as with all observational studies, there may be other population characteristics or additional factors that might affect the incidence of adverse drug events that were not considered. It is worth noting that the sample cohort was taken several years ago (2005 to 2009) and clinical practice may have changed since then. Additionally, this study was conducted in Canada and the findings may not completely reflect UK practice, where different medicines are licensed and prescribing patterns may vary. Nevertheless, this study suggests that using medicines for an off-label indication is associated with an increased risk of adverse drug events, particularly when strong scientific evidence is lacking.

As highlighted in an accompanying editorial, when prescribing goes beyond the carefully defined confines of a medicine’s product licence, the safety and efficacy is often unknown. This is illustrated by the fact that fewer than 20% of instances of off-label drug use were considered to be supported by strong evidence in this study.

The results of this study reinforce the importance of continuing to follow the GMC prescribing guidance and MHRA advice on unlicensed or off-label medicines, which recommends prescribing an off-label or unlicensed medicine if there is no licensed alternative, being satisfied there is sufficient evidence or experience to demonstrate efficacy and safety and documenting reasons for the prescription, where
common practice is not being followed (see Overview and current advice for details). People should be given the opportunity to be involved in making decisions about their medicines as recommended by the NICE medicines optimisation guideline. In addition, suspected adverse reactions to any medicine, including unlicensed and off-label medicines, should continue to be reported to the MHRA through the Yellow Card Scheme and in line with NICE guidance.

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**References**


**About this Medicines Evidence Commentary**

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