Editorial

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Off-label use of drugs: An evil or a necessity?

Off-label use is the use of pharmaceutical drugs for an indication, age group, dosage, or route of administration that is not approved by the regulatory agencies and is not mentioned in the prescribing information for the drug. A regulatory agency (e.g., Drugs Controller General of India, United States Food and Drug Administration [USFDA]) approves a drug for a particular indication, in a particular dose, dosage formulation and route of administration based on data from clinical trials that have been submitted to and scrutinised by the regulatory agency. Thus, fentanyl is approved as an analgesic for intravenous use, but not for intrathecal or epidural use, making epidural analgesia with fentanyl an off-label use.[1] It is important to understand that off-label use is not illegal. Off-label use is considered as legal unless it violates ethical guidelines or other safety regulations. It is ethical and justifiable to use drugs in an off-label fashion provided such use is based on sound data and evidence. Several prescription drugs and over-the-counter drugs are used in off-label ways to good effect. Off-label prescribing is not necessarily bad. It can be beneficial, especially when patients have exhausted all other approved options. Chemotherapy drugs for cancer are often used off-label, because a drug approved for one type of cancer may actually target many other types of tumours. Off-label use of a drug or combination of drugs often represents the standard of care.[2] The use of β-blockers for heart failure is a standard of care, but was an off-label use for many years. They were initially approved by the USFDA for the treatment of hypertension, before some β-blockers were formally approved to treat heart failure. Thus, it is possible for off-label uses to eventually get approved by the USFDA. The prescribing of drugs for off-label use is entirely proper since the decision regarding how to use a drug is based on what is considered "good medical practice" regardless of whether or not it conforms to the package insert. Drug labelling *per se* is not intended to set a standard for good medical practice.

Although some off-label therapies can be beneficial and even lifesaving for some patients, in many cases, off-label use can be problematic, especially if there is inadequate data regarding drug safety and effectiveness for the off-label use. The combined use of fenfluramine hydrochloride and phentermine hydrochloride (Fen-Phen) is one of the best examples of off-label use with a poor outcome.[2] Individually, they are approved by the USFDA as short-term treatments for obesity. They were prescribed in combination after reports of dramatic weight loss effects of the combination appeared in medical journals. However, its prolonged use lead to severe, and potentially fatal, heart valve damage,[3] and Fen-Phen was withdrawn from the market.[4]

Thus, we emphasise that off-label prescribing has its place in medical practice; however, we also emphasise that off-label use must be backed by strong medical rationale and scientific evidence.

Use of off-label drugs in the perioperative setting is not uncommon. In fact, it is imperative. For instance, small-dose droperidol for prevention of postoperative nausea and vomiting is an off-label use which was widely accepted at a time when ondansetron was very expensive until USFDA placed a "black-box" warning. Ondansetron itself is used mostly off-label for anti-emetic prophylaxis because studies have shown greater efficacy when it is administered near the end of surgery as against the label which states that it should be administered prior to induction of anaesthesia.[5]

The study by Patil *et al*. is an audit of off-label use of perioperative medications in the surgical wards of a teaching hospital.[6] Approximately, one-fifth of drugs prescribed were off-label indications. Inappropriate dose was the most common off-label use followed by inappropriate indication. The authors observed that off-label drug use was practiced with questionable clinical justification in many instances since underdosage can lead to suboptimal treatment. However, anaesthesiologists often adjust doses of induction agents or muscle relaxants based on the patient's condition and patient response. This may result in doses administered that are outside those mentioned in the drug package insert or formulary. The authors also observed a 1.6-fold higher incidence of adverse events in patients in whom drugs were used off-label. However, they did not perform a systematic severity assessment or a causality assessment of adverse events and a thorough risk-benefit assessment. Thus, the impact of off-label use is not very clear in this study. While off-label use may be associated with a greater number of side effects, the benefits may outweigh the risks. Again, off-label practices based solely on intuition are unlikely to be effective as against off-label use supported by clinical evidence. Therefore, future audits of off-label practices should include these metrics in the overall assessment of the utility of such practices. Despite some of these limitations, this is an important study that provides a critical view of some of our practices.

The regulatory agencies do not regulate the practice of medicine, and therefore, they do not regulate the prescribing of drugs for off-label uses. However, some agencies including the USFDA have the authority to regulate the manufacturer's promotion of off-label uses of approved drugs. The recent USFDA guidelines allow "safe harbours" for disseminating information.[7] For instance, pharmaceutical company representatives may circulate peer-reviewed information from high-quality medical journals on the off-label use of drugs and devices amongst doctors, facilitating the practice of evidence-based medicine rather than "limiting" their practice to the information provided in the manufacturer's package insert. On the other hand, promoting off-label uses through mass media such as the internet is not permitted and subject to more regulation. The Indian Medical Association is also extremely tolerant towards off-label drug use and has left such practices to the discretion of the physician.[8]

Ideally, the use of drugs in clinical practice should be based on rational scientific theory, expert medical opinion and well-controlled clinical trials (i.e., evidence-based) rather than the package insert. While the package insert can be a useful source of information about a drug, it is not meant to determine medical practice and is no substitute for sound medical judgement.[9]

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