EDITORIAL

Off-label Medication Use: A Double-edged Sword

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Off-label use of medication/drug implies its use beyond FDA's approved packaging label or insert. This unapproved/off-label use may be for indications, dose, patient population, or route than those listed. These are often prescribed and administered based on published evidence supporting its unapproved clinical use or lack of robust data with theoretical benefits outweighing potential risks. Off-label use may not be inappropriate when intended to help patients, for e.g. treat a condition because of lack of effective alternatives or exhaustion of approved drugs. However, there can be several concerns such as patient safety, ethical and legal implications. Off-label use cannot be considered illegal as long as ethical and safety concerns are not violated.[1] Off-label medication use is most common in pediatrics and pregnant women due to lack of clinical trials in this subset of population and several medications do not get regulatory approval. The literature is replete with examples from pediatrics reporting a wide range (9–78.7%) of off-label medication use across all settings such as outpatients, wards, and pediatric intensive care units (ICUs).[2,3] There are very few reports evaluating off-label use and adverse drug reactions (ADRs) in adult ICUs.[4,5] Off-label use in adult ICUs is sparsely studied, particularly in India. Patients in ICU are more vulnerable to ADRs because of multitude of factors such as illness severity, preexisting comorbidities, and concurrent use of numerous medications, including several high-alert medications such as vasopressors, antithrombotics, opioids, insulin, sedatives, and neuromuscular blocking drugs.[6] In addition, pharmacokinetics and pharmacodynamics are altered, with implications for medication dose, frequency secondary to organ dysfunction or failure, and renal replacement therapy and possible interactions and incompatibilities. Often, treatment decisions are taken rapidly with the intent to minimize further derangements. Lastly, complex environment involving multidisciplinary teams within the ICU creates a milieu prone for medication errors. Off-label medication use adds another dimension to this complexity. Recently, repurposing of old medications due to the pandemic has led to an increase in reporting of off-label use and associated ADRs. French Pharmacovigilance Network reported an increased risk of cardiac ADRs associated with off-label use of hydroxychloroquine, azithromycin, and lopinavir–ritonavir in COVID-19 patients.[7]

In this issue, Raut et al. have attempted to address certain aspects of off-label medication use in ICU. They evaluated prevalence of off-label drug use, level of evidence for use, and associated ADRs in adult medical ICU. ADRs were also evaluated for causality and severity using WHO-UMC (World Health Organization—Uppsala Monitoring Centre) causality assessment scale and Hartwig and Siegel severity assessment scale, respectively. They reported a prevalence of 41% for off-label indications and 1.8% for off-label dose. Majority of the off-label indications (88%) and off-label dose (91%) were evidence based.

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Overall incidence of ADRs was 9.1% of total off-label drug use (n = 1,518). Majority of the ADRs (88%) occurred with evidence-based off-label use. Causality of ADRs for off-label medications was reported as possible for 64% and probable for 36% of the events. Occurrence of ADRs was associated with significantly longer median ICU length of stay. Most of the ADRs due to off-label use were mild (47.4%) whereas 12% were severe. Severe ADRs needed either additional treatment and/or withdrawal of the offending off-label medication. Five most commonly used classes of off-label medications were gastrointestinal (pantoprazole and ondansetron), bronchodilators, opioids, vasodilators and steroids. Medications most commonly associated with ADRs were ondansetron, heparin, ceftriaxone, fentanyl, and furosemide.

The strengths of this study are evaluation of an often-ignored facet in treatment of critically ill patients and thorough evaluation of ADRs in terms of severity and causality. Although majority of the ADRs were mild to moderate, 12% did require some intervention, which may have contributed to the complexity of treatment. Therefore, a potential for serious harm exists due to off-label medications use. This study does have some limitations. Firstly, important clinically relevant endpoints such as treatment modifications or medication withdrawal following severe ADRs, whether harm was preventable or otherwise, impact on ICU and hospital outcome, quality of life, and costs were not studied. This information may have aided in raising awareness and would have been more convincing for an intensivist. Secondly, authors report significantly longer ICU stay in patients with ADRs. APACHE score was much higher in patients with ADR (21.3 vs 12.5), suggesting greater severity of illness on admission, though the difference was reported as insignificant. To attribute the increase in ICU length of stay solely to ADRs should be interpreted with caution as other confounding variables such as SOFA score, or change in SOFA score, other interventions done during ICU stay, and ICU outcome were not taken into consideration. Lastly, classification of medications would have added more clarity. An abbreviated list of off-label medication incidence is mentioned. This limits

the understanding of various other medications involved. Interested readers should read supplementary material for the entire list of off-label medications used.

Reported prevalence of off-label use in adult critically ill patients in literature ranges from 36 to 43%. Evidence-based prescription of off-label medications ranges from 48 to 62%. Use of high-alert medications such as opioids, anticoagulants, and antimicrobials are most commonly associated with ADRs.[4,5] Raut et al. report similar prevalence (41%) of off-label use and use of high-alert medications associated with ADRs. However, in a striking contrast, 88% of off-label medication use was evidence-based. This can be attributed to differences in the case-mix, methodology, identification, and recording of ADRs.

This study has flagged a very important and most neglected area of concern, while caring for critically ill patients. It has exposed the need for pharmacovigilance and clinical pharmacist during ICU rounds for necessary interventions, such as withdrawal of medication, and/or replacement with appropriate available alternatives. Integrating clinical pharmacist in the multidisciplinary critical care team has been shown to be associated with improved medication safety, reduction in incidence of ADRs due to medication errors, drug interactions, incompatibilities, and reduction in pharmaceutical costs.[8–10]

Kannan et al. evaluated clinician awareness and views regarding off-label prescriptions in a tertiary hospital. They found that though 69% of clinicians were aware of prescribing off-label medication, 28% reported inadequate knowledge regarding off-label use. Prescribing off-label medication was considered illegal by 48%.[11] Liu et al. conducted a nationwide survey regarding off-label prescriptions in ICU. They found 78% clinicians prescribed off-label medications and the proportion of off-label prescriptions ranged from 10 to 25% of all medications prescribed.[12] To date, there are no studies from Indian ICUs that address clinician awareness regarding off-label use of commonly prescribed medications in adult ICU. Clinician awareness of off-label medication use and potential likelihood of ADRs can reduce unintentional harm and its consequences for patients in ICU. Computerized physician order entry, with or without clinical decision support systems, may aid clinicians by increasing awareness about off-label use and thus reduce medication errors.[13] These systems have a learning curve for adaptation, are expensive, and demand a cultural change within an organization.

Prescribing off-label medication use by extrapolating results from other studies may benefit some patients; however, this practice can impede future research in these potential areas. The Drug Controller General of India regulates approval of drugs in India. Currently, there are no guidelines for off-label medication use in India. Considering 41% of prescriptions were off-label use despite under-reporting, raises another question: is it legal to prescribe off-label medications? While the intent for off-label use may be in the patient's best interest, lack or exhaustion of approved treatment options or possibility of ADRs and legal implications places a clinician between a rock and a hard place. Efforts should be led by medical organizations such as Indian Society of Critical Care Medicine to bridge the wide legislative gap between clinical practice and regulatory authorities regarding off-label medication use with scientific rationale and evidence justifying treatment, with built-in safeguards for physicians, pharmaceutical industry, and most importantly not violating ethical and patient safety concerns.

Several lacunae are unmasked regarding off-label medication use in critically ill patients. Off-label prescription in adult ICUs is poorly studied in India. Future studies should address questions such as clinician awareness regarding off-label use and ADRs of commonly prescribed medications in ICU, presence of clinical pharmacist in ICU, consequences of ADRs and its impact on clinically relevant endpoints patient's quality of life and costs.[14]

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