Review Article

Exploring Off-Label Drug Use Across Medical Specialties

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ABSTRACT

Off-label drug use is defined as the use of pharmaceutical drug for an unapproved indication, or an unapproved age group, dosage or route of administration. In pediatrics, off-label prescribing is common due to the lack of specific therapeutic options and limited clinical trials in children. In oncology, off-label drugs provide alternatives when approved options are exhausted, with common medications including carboplatin and targeted therapies like Bevacizumab. The older population often experiences off-label use of antipsychotics, antidepressants, anticonvulsants, and anti-VEGF drugs for conditions such as dementia, insomnia, and macular edema. In weight management, limited FDA-approved drugs for obesity lead to off-label prescriptions, including phentermine, metformin, and topiramate. The COVID-19 pandemic has seen the off-label use of drugs like hydroxychloroquine, remdesivir, ivermectin, dexamethasone, and tocilizumab, with evolving evidence and debates on their effectiveness. Drawbacks of off-label drug use include potential safety concerns, lack of established dosing guidelines, limited efficacy data, and the risk of adverse reactions, emphasizing the need for cautious application etc.

Keywords: Off-label drug use, Paediatrics, Oncology, Older population. COVID-19.

INTRODUCTION

The Term off label drug use (OLDU) is utilized broadly in medical literature. It is a bipolar term since it may be related to potential benefits or harm to patients[1]. Off label drug use is defined as the use of pharmaceutical drug for an unapproved indication, or an unapproved age group, dosage or route of administration. In other words, we can define it as the use of a drug product in patient population, dose, and route of administration for indications that are not reflected in approved product labelling. Off label drug used is a very common practice in different clinical specialities such as paediatrics, oncology, psychiatry and intensive care unit[2]. Sometimes off label drug used is the only option available such as in oncology, when there is no standard or evidence-based treatment options or in patient who have exhausted standard line of treatment. Off label drug used may be advantageous and may provide some potential benefits to the patients. Children and pregnant women are well on the way to be prescribed off label drugs because most of the clinical trials are not conducted in this subset of population due to ethical reasons.[3.] Physician are generally allowed to prescribe the drug in an off-label manner in most regions in the world except in countries such as India where it is illegal.[4] Off label drug use is considered legal except if it disregards ethical guidelines or the safety regulations. It is ethical and justifiable to used drugs in an off-label fashion provided such use depends on sound data and evidence. Several prescription drugs and over the counter drugs are used in off-label ways to great effect.[5.] The main issue with off-label use is that there is insufficient information support to the use of drug, whereas on label drug use is based on scientifically valid and statistically significant evidence indicating potential benefits of drugs[6]. Sometimes it may jeopardize patient safety where a potential health Risk –Benefit ratio not fully established, this is mainly due to the fact that off label drug used is not systemically regulated by the regulatory authority and guidelines policymaker.

The review aims to provide a comprehensive examination of various aspects surrounding off-label drug use, including its prevalence in different countries, prevalence and pattern across different medical specialities such as paediatrics, oncology, geriatrics and in pandemic such as in Covid19. This review will also explore the various factors contributing to the widespread adoption of off-label use such as limited treatment options in oncology, emerging evidence and individual patient needs etc.

TERMS RELATED TO DIFFERENT DRUG USE

Off-label drug use based on little or no scientific evidence is termed as off-evidence drug use.[7] For example, prescribing a drug for an indication in the clinical setting while the result of the clinical trial is yet to be known.

Table 1: Summary of definitions

Terminology	Definitions
Off- label drug use	Clinical practice of prescribing medicines outside the terms mention in the Prescribing Information (PI)
Unlicensed drug use	Drugs which are not subjected to review for their efficacy and safety by drug regulatory agencies.
Investigational Therapies	Drugs are being scientifically studied but are yet to be approved by the licensing authorities for clinical practices.

Compassionate use	Prescribing newly unapproved agents through individual patient use request or expanded access programmes (EAP) to treat life threatening disease for which there are no available treatment.
Extemporaneous preparations	It is the procedure of compounding various ingredients to formulate an unlicensed medication for a single patient in agreement with the prescription.
Drug Repositioning or Repurposing	Investigation of Existing Drugs for new therapeutic purpose.

Table 2: The rate of paediatric off-label prescribing practices in different countries.

Country	Frequency of off-label prescribing practice
Australia	Paediatric off-label prescription rate 54% [19]
France	Paediatric off-label prescriptions equal 42% [20]
United States	16-62% Paediatric off-label/unlicensed prescription. In the neonatal wards setting 55-80%. In the community setting 11-37% [21]
India	27.9-35.7% paediatric off-label/unlicensed prescription.[22,23]
Indonesia	50.8-65.9% paediatric off-label prescription [24]
Brazil	56.0% paediatric off-label prescriptions [25]
Canada	38.2% paediatric off-label prescriptions [26]
Sweden	64% paediatric off-label prescriptions [27]
Italy	60% paediatric off-label prescription [28]
Spain	41.4-53.9% paediatric off-label prescriptions[29]
Jordan	28% paediatric off-label prescriptions [30]
Palestine	35.3% paediatric off-label prescriptions[31]
UK	65% paediatric off-label prescriptions [32]
Malaysia	23% Paediatric off label prescription [33]
China	47.9% of the paediatricians acknowledged that they had prescribed off-label drugs[34]

OFF –LABEL DRUG PRESCRIPTION IN DIFFERENT MEDICAL SPECIALTIES

Paediatrics:

The prescription of off label medicine and unlicensed medicine for children applies especially in neonatal medicine.[8-13] one of the main reasons for prescribing off-label drug in paediatrics is that there are no standard therapeutic options available for a specific disease or condition in children.[14] It can be, due to lack of specific guidelines of dosing and route of drug administration for paediatric age group. Another factor is that there is lack of information about the drug use and its adverse reaction of the drug because most of the clinical trials are done in adults population. There is scarcity of clinical trials in paediatric population due to many reason such as ethical consideration, practical difficulties and objection of the parents to include their children in clinical trials [15]. One of the economic considerations is that conduction of clinical trials in children is not productive for the pharmaceutical industry.[16,17]

The practice of prescribing off-label drugs in paediatrics is a world-wide phenomenon and can be an issue despite the increased awareness and passed legislation.[18]

MEDICATIONS COMMONLY PRESCRIBED OFF-LABEL IN PEDIATRICS

Off-label rates for each drug class include melatonin (100%), Antipsychotic Agent (95.6%), Benzodiazepine (72.7%), Antidepressant (51.1%) and ADHD medication (2.7%).[35] Additionally, it has been reported that 8% of Allergy medications and 22% of the nasal corticosteroids were considered off-label based on child age.[36] Table 3 shows some of the reported data about the classes of drugs to be prescribed off-label manner in paediatrics practices. The source of information of this table is from British National Formulary (2019-20), (BNF) [37]. Drugs which are used in paediatric population and why they are considered as an Off-label manner is also mentioned in Table 3. Some of drug is considered as off-label manner because these drugs are used other than approved condition whereas some of them label as off label because their use is unlicensed in their age group or route of administration or dose. All these information regarding drug and their unlicensed used is taken from BNF 2019-20.

Table 3: Common drugs which are used in OFF-Label Manner in Paediatrics [37]

S.No	Class of Medication	The Mostly Off-Label Used Drugs	Indication	Why use Off-label
1.0	Antiviral agents	Valacyclovir	Valacyclovir is FDA approved for in Pediatric patients as young as 2 years for treatment of chicken pox and Herpes Labialis only	Valacyclovir used off-label manner in the treatment of Herpes zoster and other herpes simplex infections.
2.0 2.1	Antibacterial agents	Meropenem	Aerobic and anaerobic Gram-positive and Gram-negative infections, Hospital-acquired septicaemia, Severe aerobic and anaerobic Gram-positive and Gram-negative infection Exacerbations of chronic lower respiratory-tract infection in cystic fibrosis. Meningitis	Not licensed for use in children under 3 months.
2.2		Imipenem with Cilastatin	Aerobic and anaerobic Gram-positive and Gram-negative infections (not indicated for CNS infections) |Hospital acquired septicaemia Infection caused by Pseudomonas or other less sensitive organisms | Empirical treatment of infection in febrile patients with neutropenia Life-threatening infection, Cystic fibrosis	Not licensed for use in children under 1 year.
2.3		inezolid	Pneumonia (when other antibacterials e.g. a glycopetide, such as vancomycin, cannot be used) (initiated under specialist supervision) Complicated skin and soft-tissue infections caused by Gram-positive bacteria, when other antibacterials cannot be used (initiated under specialist supervision)	Not licensed for use in children.
2.4		Aminoglycosides (Amikacin)	Serious Gram-negative infections resistant to gentamicin (multiple daily dose regimen) Serious Gram-negative infections resistant to gentamicin (once daily dose regimen) Neonatal sepsis (extended interval dose regimen) Neonatal sepsis (multiple daily dose regimen) Fistulating Crohn's disease	With intravenous use Dose for cystic fibrosis not licensed
2.5		Ciprofloxacin	Severe respiratory-tract infections, gastro-intestinal infection Acute exacerbation of bronchiectasis (administered on expert advice) Pseudomonal lower respiratory-tract infection in cystic fibrosis Complicated urinary-tract infection. Gonorrhoea, Anthrax (treatment and post-exposure prophylaxis), Prevention of secondary case of meningococcal meningitis	Not licensed for use in children under 1 year of age. Licensed for use in children over 1 year for complicated urinary-tract infections, for pseudomonal lower respiratory-tract infections in cystic fibrosis. for prophylaxis and treatment of inhalational anthrax. Licensed for use in children over 1 year for other infections where the benefit is considered to outweigh the potential risks. Not licensed for use in children for gastro-intestinal anthrax. Not licensed for use in children for prophylaxis of meningococcal meningitis.
2.6		Vancomycin	Clostridium difficile infection Complicated skin and soft tissue infections. Bone infections and Joint infections Community acquired pneumonia Hospital-acquired pneumonia [including ventilator associated pneumonia] Infective endocarditis, Acute bacterial meningitis, Bacteraemia [occurring in	Use of vancomycin (added to dialysis fluid) for the treatment of peritonitis associated with peritoneal dialysis is an unlicensed route. Not licensed for intraventricular use or inhalation. Not licensed for use by the intrathecal route for the treatment of meningitis.

			association with or suspected to be associated with the licensed indications, Peritonitis associated with peritoneal dialysis, Eradication of meticillin-resistant Staphylococcus aureus from the respiratory tract in cystic fibrosis	
3.0	NSAIDs	Aspirin	Antipletelete Agent, Kawasaki Disease,	Not licensed for used in children < 16 years.
3.1		Acetaminophen (Paracetamol)	Pain / Pyrexia with discomfort Pain in children with risk factors for hepatotoxicity / Pyrexia with discomfort in children with risk factors for hepatotoxicity Post-operative pain. Prophylaxis of post-immunisation pyrexia following immunisation with meningococcal group B vaccine (Bexsero) given as part of the routine immunisation schedule Post-immunisation pyrexia in infants	Paracetamol oral suspension 500 mg/5 mL not licensed for use in children under 16 years. Not licensed for use in children under 2 months by mouth; under 3 months by rectum. Not licensed for use as prophylaxis of post-immunisation pyrexia following immunisation with meningococcal group B vaccine. Intravenous infusion not licensed in pre-term neonates. Intravenous infusion dose not licensed in children and neonates with body-weight under 10 kg
4.0	Beta Blocker	Atenolol	Systemic Hypertension Arrhythmia	Not licensed for used in children <12years
5.0	Antidiuretic hormone	Desmopressin	Diabetes insipidus, Hemophilia A, Willebrand Disease	Nocturnal Enuresis given by intranasal route.
6.0	Phospho diestrase inhibitors	Sildenafil	Erectile Dysfunction	Pulmonary Hypertension in children
7.0	H2 Blocker	Ranitidine	Gastritis, GERD, Gastric ulcer Duodenal Ulcer, Reflex esophagitis	Oral preparation not license for in children 3 years. Intravenous not license for age under 6 month.
8.0	Proton pump inhibitor	Omeprazole	H.Pylori Eradiaction Duodenal and Gastric ulcer Zollinger Ellison Syndrome Acid Releated Dyspepsia	Capsule and Tablet no licensed for used in children except for some ulcerative reflux esophagitis in children over 1 year Intravenous use not licensed for use in children under 12 years.
9.0	5HT3 Antagonist	Ondansetron	For the prevention of chemotherapy or radiotherapy induced vomiting	Outside recommended indication. Intravenous ondansetron used in patient who not on chemotherapy and radiotherapy
10.0 10.1	Others	Chlorpheniramine	Symptomatic relief of allergy such as hay fever, urticaria, food allergy, drug reactions | Relief of itch associated with chickenpox	Injection not licensed for use in neonates. Tablets not licensed for use in children under 6 years. Syrup not licensed for use in children under 1 year.
10.2		Ipratropium Bromide	COPD Reversible airway obstruction Acute bronchospasm Severe or life threatening Asthma	The dose of Ipratropium bromide for severe or life-threatening acute asthma in unlicensed under 6 years.
10.3		Levocetirizine	Symptomatic relief of allergy such as hay fever, chronic idiopathic urticaria, atopicdermatitis	Not licensed for use in children under 2 years
11.0	Osmotic Diuretics	Mannitol	Cereberal edema Peripheral edema	Not licensed for used in children less than 12 years.

Prescribing Off-label medications is a common practice in the paediatric population especially in neonates and younger age groups [38]. Research on more age specific group is highly recommended to confirm medicines safety and effectiveness for the paediatric population. However clinical decision making should be governed by the availability of the best evidence and more data is needed in this regard.

OFF-LABEL DRUG USED IN ONCOLOGY

Off-label prescribing may be advantageous in oncology as it provides an alternative option in a patient when there are no approved drugs for a specific tumour or patient have exhausted standard line of treatments. The main therapeutic intents for off –label drug used in oncology are lack of approved indication for specific tumour type (9%-46%), Modified drug application (10-40%)[39,40], curative intent was reported to be in the range of (10-41%), adjuvant setting (8.5-49%) and palliative care (34-37%).[38,41,42]

OFF-LABEL DRUGS USED PROFILE IN ONCOLOGY

The most commonly administered off-label medicine in oncology were carboplatin, doxorubicin, Fluorouracil , Paclitaxel, Docataxel, Vinorelbine, Gemicitabine and Oxaliplatin.[38-40,42-46] The most common targeted therapies include Bevacizumab, Trastuzumab, Cetuximab, Dituximab,Gefitinib and erlotinib[38,45-53]. Bevacizumab was prescribed in an off-label manner for the treatment of metastatic colorectal carcinoma in the range of (10-62%) of the patients.

Aspirin use was associated with reduced risk of oesophageal adenocarcinoma or high-grade dysplasia[54]. Usually low dose aspirin 75-100mg orally once in a day for patient suffering from colorectal cancer can decrease the risk of progression of stage from B-D. The hypothesis for the use of aspirin in this case is that aspirin has chemoprotective effect early in the adenoma sequence in colorectal cancer development.[55]

The off-label prescribing in oncology is essential and would not disappear soon, as it is not possible to do clinical trials for each and every prescription and getting regulatory approval for it. The healthcare infrastructure needs to be planned in such a way that would maximize benefit risk ratio for the patients, under robust clinical governance guidelines, across all case settings.

OFF-LABEL DRUG USED IN OLDER POPULATION

The Off-label drug used is very common in older population and there is multiple reason for that, such as older population remain poorly represented in clinical trials[56.] Some of them are mentioned below in [Table 4]

Table 4: Several Drugs used in older population

S. No.	Drugs	Comments
1	Amitriptyline, Nortriptyline	Not licensed for neuropathic pain; appropriate and effective second line agents
2	Haloperidol, risperidone and Otheratypical antipsychotic drugs	Not licensed for delirium; with the exception of risperidone, not licensed for behavioural and psychological symptoms of dementia
3	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
4	Angiotensin receptor blockers other than candesartan	Not licensed for treatment of chronic heart failure when ACE inhibitors are not tolerated
5	Spironolactone	Not licensed for resistant essential hypertension
6	Bevacizumab	Widely used off-label in the treatment of macular degeneration
7	Midodrine	Not licensed in the UK (for any indication), although licensed elsewhere; used for orthostatic hypotension after non pharmacological treatments have failed.

DRUGS COMMONLY PRESCRIBED OFF-LABEL IN OLDER POPULATION

Antipsychotics and Antidepressant

The main indications for the off-label prescribing of Antipsychotic include depression, behavioural and Psychological symptoms of Dementia, Insomnia, Depression and Agitations. Most commonly drug prescribed are Quetipine, Resperidone, Olanazepine, Aripriprazole and first-generation Antipsychotics.[56,60,61] Long term use of antipsychotics leads to worsening of diabetes, tardive dyskinesia, extrapyramidal symptoms, stroke and increased all-cause mortality.[57,58,59] Various Antidepressant like Amitryptilline, trazodone, Nortryptilline, Doxepin, Mirtazapine are prescribed off-label in treatment of insomnia and Anxiety Disorder.[60]

Anticonvulsant

The use of anticonvulsant in older population include pain, miagraine, headache and depression. Gabapentin,

topiramate, lamotrigine, carbamazepine, sodium valproate and phenytoin are the anticonvulsants most commonly prescribed for off label indications[62,63]

Anti-vascular endothelial growth factor (Anti-VEGF)

Anti-vascular endothelial Growth Factor drugs are increasingly used for the treatment of Age-Related macular Edema (AMD).[64]Anti VEGF Drugs like Bevacizumab are used off-label for the Neo vascular age related macular edema by intravitreal administration.[65]

OFF-LABEL DRUGS FOR WEIGHT MANAGEMENT

In the last 20 years US food and Drug Administration has approved 208 drugs for cancer, 118 for cardiovascular disease, 168 for neurological disease and 223 endocrine drugs but there are only 6 drugs for obesity, 2 of which was taken off from market[66]. Currently there are 9 drugs approved by the FDA for obesity treatment and that's why the off label drugs prescription for treating obesity is an effort.

Current Strategies for the weight management

Orthodox Paradigm is BMI centric: Pharmacotherapy is applied in a patient with BMI equaling or exceeding either ≥ 30 kg/m^2 or 27 kg/m^2 in presence of an excess adiposity associated disease such as Diabetes. Great emphasis on life style modification and pharmacotherapy is considered a treatment modality ancillary to lifestyle modification. The use of Pharmacotherapy below threshold BMI (≤ 30 kg/m^2) is considered as Off-label.[67]

DRUGS USE IN OFF-LABEL MANNER TO TREAT OBESITY

Phentermine has become the most frequently prescribed medicines for treating obesity. The originally approved indication was to use on short term basis.[68]Phenteramine is used as an off-label drug to use for long term, also as an off-label in patients whose excess adiposity is below the conventional BMI- cut-off. Phentermine doses used are higher than the limit suggested such as more than 37.5 mg per day.[69-75]

Metformin

Primary indication of metformin is as a first line agent in the management of Diabetes mellitus type II. Metformin is known to induce modest weight loss.[76,77]

Topiramate

Topiramate was originally approved By FDA in 1996 for Refractory epilepsy where weight loss was immediately noted as side effect[78]. Topiramate has been used in off-label manner both as monotherapy and in combination of phentermine/topiramate.[79,80]

OFF-LABEL DRUG USED IN COVID-19

The COVID-19 pandemic has ushered in an era of never done before scientific collaboration and exploration of potential treatments. Among the strategies employed, the repurposing of existing drugs for off-label use has garnered significant attention. Several Drugs introduced as Off-label manner for the management of covid 19 pandemic.

Hydroxychloroquine and Chloroquine:

Early in the pandemic, Hydroxychloroquine and Chloroquine emerged as promising candidates due to their established anti-inflammatory properties and in vitro activity against SARS-CoV-2. However, aslarge-scale clinical trials unfolded, including the RECOVERY trial, these hopes were tempered. The evidence revealed no significant benefits in terms of reducing mortality or improving clinical outcomes, with safety concerns, particularly related to cardiac issues, further dampening enthusiasm for their widespread use.

Remdesivir

Originally developed for Ebola, remdesivir became a focal point in the search for effective COVID-19 treatments. The antiviral properties of remdesivir led to its emergency use authorization. Clinical trials, such as the NIAID-sponsored ACTT-1 study, suggested a reduction in recovery time among COVID-19 patients[81]. However, debates persist regarding its impact on mortality. The REMAP-CAP trial indicated a mortality benefit in severe cases. While other studies reported inconclusive findings. The evolving narrative around remdesivir underscores the dynamic nature of off-label drug use in the context of COVID-19.

Ivermectin:

The repurposing of existing drugs with known safety profiles, such as Ivermectin, marked another avenue of exploration. Widely used for parasitic infections, Ivermectin gained attention due to its potential antiviral and anti-inflammatory effects. Numerous studies explored its efficacy, but a lack of robust clinical trials and conflicting results have raised doubts. While some research suggested benefits, regulatory agencies and health organizations, including the FDA and WHO, have not endorsed its routine use for COVID-19, emphasizing the need for cautious interpretation of available data.

Dexamethasone:

Recognizing the role of modulating the immune response in COVID-19, Dexamethasone, a corticosteroid with potent anti-inflammatory properties, gained prominence in severe cases. The RECOVERY trial demonstrated a clear reduction in mortality among patients requiring respiratory support[82]. This landmark finding emphasized the critical role of anti-inflammatory strategies in managing the cytokine storm associated with severe cases.

Tocilizumab:

As the understanding of COVID-19 evolved, the focus shifted to immunomodulatory approaches. Tocilizumab, an interleukin-6 receptor antagonist used for rheumatoid arthritis, emerged as a potential candidate for mitigating the cytokine storms observed in severe COVID-19. Clinical trials, including the RECOVERY trial, demonstrated benefits

in certainpatient populations, leading to the inclusion of Tocilizumab in treatment protocols for severe cases.[83]

The exploration of off-label drug use in COVID-19 treatment reflects the urgency and complexity of managing a novel and highly contagious disease. While some drugs initially showed promise, the evolving evidence base underscores the importance of rigorous clinical trials. Dexamethasone and tocilizumab have emerged as key players, highlighting the pivotal role of anti-inflammatory strategies in severe cases.

As research continues, ongoing evaluation and adaptation of treatment strategies are crucial for optimizing patient outcomes. The dynamic nature of the off-label drug landscape in COVID-19 demands constant vigilance, collaborative research efforts, and a sound understanding of the balance between potential benefits and risks associated with each therapeutic intervention.

CONCLUSION

Off-label drug used is very common practices across different medical specialties, such as in paediatrics, oncology, old age patient and several other areas of medical specialties. Sometimes it is a cornerstone treatment in various conditions such as in oncology where there is no indicated drug for a specific tumour or when patient have exhausted standard line of treatment. It is also justifiable in paediatric population also, when there is lack of information of drug due to lack of clinical trial in paediatric population. It may be justifiable in patient where a benefit risk ratio is established. Off-label drug used is double edge sword it may be beneficial in certain situation such as it allows physician to prescribe medication for rare disease or situation where no treatment options are available. It can generate valuable clinical data , potentially leading to new indication, dosing regimen or treatment strategies. It may be very useful in emergent situation where no standard line of treatment is available or sometime it may provide alternative treatment method which is very cost effective as compared to their standard line of treatment. Off-label used have some potential harms also such as it may lead to adverse effects because there is lack of evidence of use of this drug, lack of regulatory and legal concern also. It may also lead to ineffective treatment, or may it lead to interaction with some other drugs which can cause some hazardous effect for the patient or sometime can jeopardize the patient condition.

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