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OFF LABEL DRUG USE IN CLINICAL PRACTICE

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ABSTRACT

Pharmaceutical companies are not allowed to promote their medications for an off-label use, which has led to several large settlements for illegal marketing. To limit liability, physicians should prescribe medications only for indications that they believe are in the best interest of the patient on the basis of the most credible available evidence, also Health care professionals should continually educate themselves about OLDU to weigh the risks and benefits and provide the best possible care for their patients.

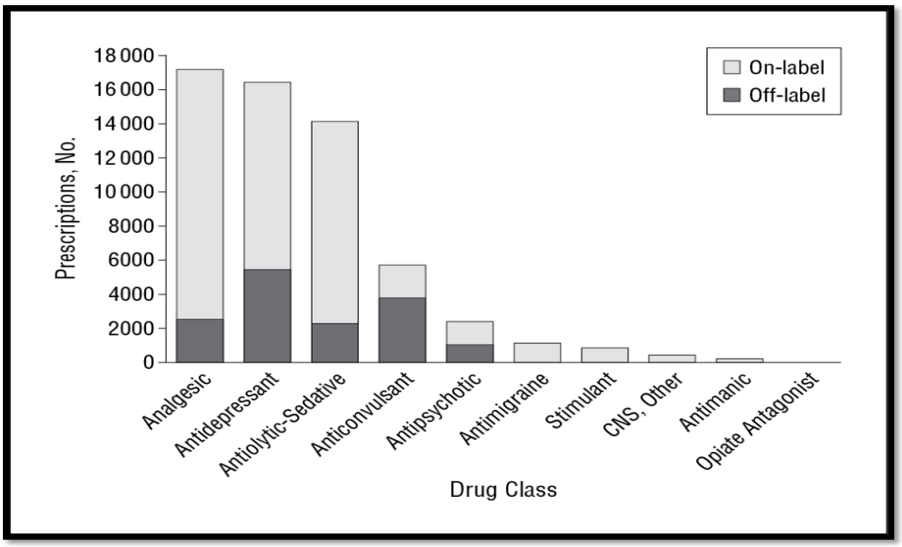
It is well known that a large number of licensed medications are used routinely for unapproved indications or dosages, routes of administrations, or age groups. These applications of medicines which are not described in their package insert are called OFF-LABEL usage. It should be differentiated from using unlicensed, unregistered, or compassionate use medicines, which have not been evaluated or approved by the regulatory authorities. Prescribing medications outside their licenced indications is legal according to many countries law and regulations, however off-label use of medicines is generally not recommended unless validated by high-quality evidence, within the context of a formal research proposal and exceptional use, justified by individual clinical circumstances.

INTRODUCTION

Off-label drug use is legal in many countries, no law prohibits off-label drug use in the United States and Canada, Off-label drug promotion is not allowed in many countries, but it is also not absolutely prohibited. In Germany, the off-label drug use is regulated by either the Medicines Law or the Social Law. According to the British General Medical Council (GMC), off-label prescriptions must better serve patient needs than alternatives and must be supported by evidence or experience to demonstrate safety and efficacy.

Off label drug use is common in many clinical areas such as psychiatry, paediatrics, oncology, Immune Deficiency Syndrome, and intensive care unit, sometimes off-label drug use is the only option for the patient's treatment, however, off-label drug use is not uniformly regulated across the globe.

Some Examples of Widely Practiced Off-label drug use:



Amitriptyline is a tricyclic antidepressant that was developed by Merck and approved in the United States in 1961. It has FDA approval for the treatment of major depression, clinical/endogenous depression, but it is commonly used off-label for other symptoms ranging from chronic pain to bed wetting.

In patients at high risk for postoperative nausea and vomiting, bolus or infused propofol and bolus dexamethasone have gained favour as antiemetic regimens. However, these treatments have never been approved by the FDA for this indication. As such, they represent OLDUs.

Medications for psychiatric disorders are also frequently used for unapproved indications. Selective serotonin reuptake inhibitors have been used off-label for rare or difficult-to-study disorders, such as borderline personality disorder, stuttering, pathologic gambling, and alcoholism.[16] Moreover, selective serotonin reuptake inhibitors (example: paroxetine, sertraline, and fluoxetine) are considered first-line treatments for premature ejaculation, another off-label use. In recent years, antipsychotic drug use for unapproved FDA indications has increased.

For some babies with severe BPD (Broncho pulmonary dysplasia), in whom echocardiography demonstrates pulmonary arterial pressures close to, or greater than, systemic pressure, many neonatologists try sildenafil, as there has been considerable experience using this drug off-label to prevent pulmonary hypertensive crises in babies after cardiac surgery.

Erythromycin induces high-amplitude gastric propulsive contractions that increase gastric emptying. Patients who fail to respond to a trial of metoclopramide and Domperidone should be treated with oral erythromycin (liquid formulation, 40 to 250 mg three times daily before meals. It is an off label use for gastro paresis in diabetic patients.

Prazosin is an antihypertensive drug, which counteracts the scorpion-induced adrenergic cardiovascular effects. It may improve pulmonary oedema through vasodilatory effects.

Lactulose reduce blood ammonia concentration to reduce the degree of portal systemic encephalopathy in Liver Cirrhosis.

Metformin reduces hyperandrogenism through its effect on both the ovary and adrenal gland suppressing their androgen production, reducing pituitary luteinizing hormone and increases the production of sex hormone binding globulin by the liver, it is an off label use for Polycystic Ovary Syndrome with infertility.

Treatment with methotrexate is an especially attractive option when the pregnancy is located on the cervix or ovary or in the interstitial or the cornual portion of the tube, also used to treat Chon's disease, Multiple Sclerosis, SLE and Rheumatoid Arthritis.

Demeclocycline is an antibiotic, which Block the binding of arginine vasopressin (ADH) to its receptor. This inhibition of antidiuretic hormone action causes an increase in the secretion of free water without an accompanying increase in sodium loss, which results in an aquaresis and increase in serum sodium concentration, useful to treat hyponatremia.

COX-2 is the inducible form of the COX enzyme family, is overexpressed in various cancer tissues, and has activity that promotes tumour genesis. A variety of NSAIDs can efficiently block COX activity and have beneficial properties in malignant neoplasms; Celecoxib is having off label use for Fibromatosis.

Category and Drug	Off-label use
Cardiology	
Aspirin	Antithrombosis in atrial fibrillation, Kawasaki disease
Indomethacin	Pharmacologic closure of patent ductus arteriosus
Dermatology	
Azathioprine	Atopic dermatitis, pemphigus; psoriasis
Biologic agents (eg, etanercept, infliximab, intravenous immunoglobulin, rituximab)	Alopecia aerate, atopic dermatitis, Behçet disease, dermatomyositis, hidradenitis suppurativa,
Haematology/oncology	
Alendronate	Hypercalcemia of malignancy
Dabigatran	Venous thromboembolism prophylaxis after orthopaedic surgery
Doxorubicin	Refractory multiple myeloma
Furosemide (nebulized)	Dyspnoea
Rituximab	Idiopathic thrombocytopenic purpura, Waldenström macroglobulinemia
Nephrology	
Acetylcysteine	Prevention of contrast nephrotoxicity
Erythropoietin	Anaemia of chronic kidney disease
Neurology	
Atenolol, metoprolol, propranolol	Migraine prophylaxis
Donepezil	Frontotemporal dementia
Gabapentin	Bipolar disorder, diabetes, fibromyalgia, neuropathic pain symptoms, headache, hiccups, hot flashes, restless leg syndrome
Obstetrics	
Magnesium sulphate	Premature labour
Volatile anaesthetics (eg, enflurane, isoflurane, halothane)	Intraoperative uterine contraction
Paediatrics	
Amoxicillin (high dose)	Otitis media in children
Intranasal desmopressin	Nocturnal enuresis
Psychiatry	
β-Blockers	Social phobia, public speaking
Citalopram	Alcoholism, fibromyalgia, irritable bowel syndrome, obsessive-compulsive disorder, pathologic gambling, stuttering
Fluoxetine	Borderline personality disorder, diabetic neuropathy, fibromyalgia, hot flashes, premature ejaculation
Trazodone	Insomnia in elderly patients
Gastro Enterology	
Metoclopramide	Acute migraine
Omeprazole	Reflux-related laryngitis
Erythromycin	Gastro paresis
Sulfamethoxazole-trimethoprim	Sinusitis

Off Label Drug use in Diabetes

Autonomic neuropathy is commonly encountered in gastro paresis.

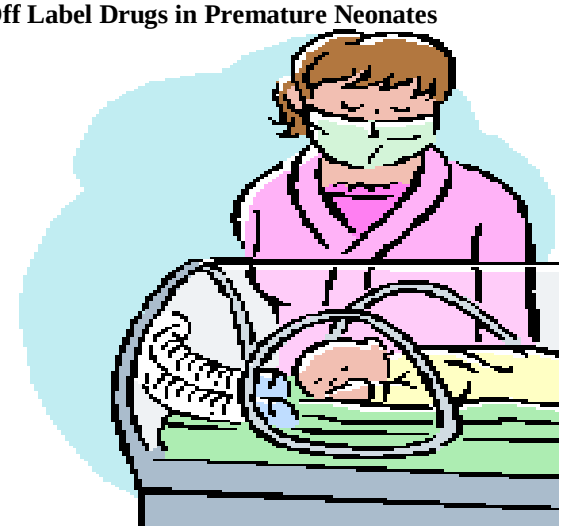
Gastro paresis is a syndrome characterized by delayed gastric emptying in absence of mechanical obstruction of the stomach. The cardinal symptoms include postprandial fullness (early satiety), nausea, vomiting, and bloating.

Diabetic gastro paresis typically develops after diabetes mellitus has been established for > 10years, and patient with type 1 diabetes might have triopathy, that is, neuropathy, nephropathy, and retinopathy. Although gastro paresis appears to be more common in type 1 diabetes compared with type 2. In addition, the use of incretin-based therapy in the latter patients is an additional risk factor for developing gastro paresis in type 2 diabetes.

Erythromycin's prokinetic effect in gastro paresis involves 2 different pathways, activating motilin receptors on cholinergic receptors on neurons and smooth muscle. Erythromycin lactobionate is most effective when given intravenously at a dose of 3mg/kg every 8 hours (by intravenous infusion during a period of 45 minutes to avoid sclerosing veins), as was shown in hospitalized diabetes with gastroparesis.

Intravenous Azithromycine was compared with Erythromycin in study of antral motility (phasic pressure activity) in patients with chronic functional gastrointestinal pain and gastro paresis. The mean amplitude, duration of high amplitude contractions, and motility index were higher with Azithromycine.

Off Label Drugs in Premature Neonates



Approximately 60% of drugs are used off-label in critically ill neonates in the NICU (Neonatal Intensive Care Unit), the pharmacokinetic and pharmacodynamics characteristics of drugs in premature infants are different from the characteristics found in term neonates, older children, and adults. These differences are caused among others by a different body composition, by immaturity of the renal excretion system, the metabolic pathways in the liver and other organ functions as well as immature drug receptors and transporters. After birth, there is a rapid development of many of these functions, besides age and size, co-morbidity, co-administration of drugs and genetic heterogeneity may further contribute to this extensive inter-individual variability in pharmacokinetics and pharmacodynamics of premature infants. There is a critical lack of evidence –based data of drug dosing in preterm neonates.

The parameters to measure the effect of the off label drugs in premature neonates: Fentanyl and paracetamol, used as analgesics, clinical endpoint is pain relief, as routinely measured by the validated COMFORTneo scale and the NRS (numeric rating scale) scale.

Midazolam, phenobarbital and levetiracetam, used as anticonvulsive drugs; clinical endpoint is control of convulsion, measured by Cerebral Function Monitoring using amplitude-integrated EEG (aEEG). Midazolam and fentanyl, used as sedative drug during endotracheal intubation, clinical endpoint is the intubation readiness score (IRS) and a qualitative intubation score and sedation score. Midazolam and fentanyl, used as sedative drug during nursing care is measured by the COMFORTneo scale.

Doxapram, used as treatment for neonatal apnoea, clinical end point is control of neonatal apnoea and endotracheal intubation in case of failure. The first endpoint can be measured by modern monitoring technology, in which central post monitoring data stored after initiation of treatment will reveal the effect of doxapram on the reduction or elimination of apnoea.

Sildenafil, a treatment for PH (Pulmonary Hypertension), clinical endpoints are level of ventilator support, Oxygen need, (repetitive oxygenation index analyses) and BPD (Broncho pulmonary dysplasia) development.

Ibuprofen is used to close patent ductus arteriosus (PDA) in different dosages, orally and intravenously. Endpoints are measured by cardiac ultrasound, ductus closure (yes/NO) , ductal diameter and LA/AO ratio.

Off Label Use of Anticancer Drugs.

Off-label treatment is seen frequently in oncology, in 1976, fluorouracil was approved simply for treatment of solid tumours and metastases but now it is restricted to specific cancers. Off-label prescription of an anticancer drug in the European Union (EU) could be an approved use in the USA (eg, bortezomib for mantle-cell lymphoma in 2007), and vice versa (eg, intravenous vinorelbine is currently approved in the EU but not in the USA for advanced breast cancer).

Off-label anticancer prescription can result in clinical benefit or no effect, either with or without side-effects.

Off-label use is mainly administered with palliative intent.[37] Clinical benefit is supposed to be limited because patients receiving off-label treatment generally have been pre-treated and have advanced disease, which has little hope of cure, However, for some types of cancer, off-label use can be regarded as a standard of care and could sometimes be associated with curative intent, such as etoposide for Ewing's sarcoma or high-dose carboplatin for pre-treated germ-cell malignant disease and paediatric cancers.

Alternative routes of administration to those approved have been associated with clinical benefits. An example is intraperitoneal injection of cisplatin for ovarian cancer with optimally debulked disease. Anticancer drugs have established regimens, which can include a specific number of cycles (eg, for bortezomib or rituximab), a fixed duration of treatment (eg, trastuzumab for early breast cancer), or treatment until progression of disease (eg, cetuximab and bevacizumab for metastatic colorectal cancer, or trastuzumab for metastatic breast cancer). Changing the approved schedule of dosing could be clinically appropriate. For example, administration of paclitaxel every week (instead of every 3 weeks) is beneficial for women with breast cancer.

CONCLUSION

It is reported that more than one in five outpatient prescriptions written in the US are for off-label therapies. Off-label use of drugs can raise the risk of lawsuits should a patient have unwanted side effects. off-label use has been identified as one aspect of problematic drug prescribing, in part because of inadequate data regarding safety and effectiveness for their use. There must be a greater emphasis on evidence-based prescribing, with stricter rules to control off-label drug use. But tightening the reins could delay patients early access to novel therapies. Besides insurers do not always pay for an unapproved, or unproven, product.

RECOMMENDATIONS

The practitioner who prescribes a drug is responsible for deciding which drug and dosing regimen the patient will receive and for what purpose. This decision should be made on the basis of the information contained in the drug's labelling (when available) or other data available to the prescriber.

The use of a drug, whether off or on label, should be based on sound scientific evidence, expert medical judgment, or published literature whenever possible.

Off-label use is neither incorrect nor investigational if based on sound scientific evidence, expert medical judgment, or published literature.

Journals should be encouraged to publish the results of all well-designed investigations, including negative studies.

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