Scienxt Journal of Pharmacy and Drug Research (SJPDR)

Is The Use of Drugs Off-Label, an Unauthorized Abuse as Stated by FDA, or Is It a Professional Duty? "Comprehensive Review"

Wafa Mahmoud Alshaiby*[1], Mabroukah Amr Ishrayhah[2], Einass Ragab Ibraheim[3]

[1,2,3]*University of Zawia, Faculty of Pharmacy, Department of Pharmacology, Zawia, Libya.*

***Corresponding author: Wafa Mahmoud Alshaib**

ABSTRACT

In continuing medical education activities and medical journals, the phrase "off-label drug" (OLD) is widely used. Many healthcare professionals do not, however, fully understand what it is, how common it is, and what effects it has. Off-label drug use (OLDU) is the act of giving a patient a prescription for a condition that the medication has not been approved to treat. Every area of medicine is currently affected by OLDU, however it may be more common in specialties like pediatrics, pregnancy, or psychiatry where the patient population is less likely to take part in research studies. Pharmaceutical businesses are not allowed to promote their goods for a use other than that which is prescribed, which has led to numerous sizeable settlements for unlawful marketing. Doctors should only provide medications when they need them to lessen liability. Additionally, in order to assess the advantages and disadvantages and give their patients the best care possible, healthcare practitioners should educate themselves about OLDU. Our review's objective is to explain the significance and value of using prescription medications outside of their allowed use by outlining the advantages and hazards of doing so. *Methodology:* The review is based on information from prior research, investigations, and reviews of digital materials (websites, scholarly journals, Google search).

Keywords: Off-label drugs use, FDA regulations, ethics and legal consideration

INTRODUCTION

Off-label drug (OLD) is a drug that has been approved for one use but can be used to treat a different disease or medical condition. For example, when a chemotherapy is approved to treat one type of cancer, but healthcare providers use it to treatdifferent types of cancer. This also entails switching up the modes of administration, such as when an oral solution is used to provide a medication that was originally approved as a capsule.(1) Prescriptions written off-label are rather prevalent; in the United States, over 20% of all prescriptions are written off-label; in the United Kingdom, about 11% of medications prescribed for children are used off-label; this is also true in the Netherlands (29%) and France (33%). In several clinical specialties, including psychiatry, pediatrics, oncology, and intensive care, off-label drug use is widespread. Off-label usage is sometimes secure and efficient. There could, however, be certain hazards associated with, It is crucial to be aware that the FDA must receive clinical data and other information from a company before a medicine can be approved. The manufacturer of the drug must demonstrate that it is both effective and safe when used as directed. A medicine being "safe" does not imply that it has no side effects. In its place, it indicates that the FDA has decided the advantages of using the medicine for a certain purpose exceed the possible hazards.(1,2)

What justifies the use of an approved medicine outsideof its intended purpose?

When a medicine is approved by the FDA, healthcare professionals can often prescribe it for an unapproved purpose if they believe it is medically necessary for their patient. You might be wondering why your doctor would want to prescribe a medication for an illness or ailment that the medication is not

approved to treat. One explanation is that there may not be a medicine that has been approved to treat your illness or medical condition. Another possibility is that you tried every treatment that was authorized but got no results. In some circumstances, you and your healthcare practitioner may discuss using an approved medicine for a purpose other than what has been approved to treat your illness or medical condition.(1)

How does the FDA approve a drug?

The manufacturer of a medicine must submit specific data to the FDA in order for it to receive FDA approval. This contains dataon the following clinical trials:

Ailment that the medication can successfully address. The maximum dosage that people should take.Proof of the medication's effectiveness and safety, including possible side effects and adverse events.(1)

Why do doctors recommend medications that are off-label?

1. A person's illness cannot be treated with a medicine that hasreceived FDA approval.
2. The FDA-approved medication for a certain disease did notwork for the patient.
3. The FDA-approved medications for a certain disease are prohibitively priced or otherwise unavailable.
4. A person cannot use the FDA-approved medication because of adverse effects or potential drug interactions.
5. The physician has seen proof that a specific medication is effective for a specific off-label purpose.(1) The freedom to prescribe medications outside of the approved label has significant benefits. It allows for innovation in clinical practice, especially when tried-and-true treatments are ineffective. It permits doctors to adopt new practices based on developing evidence and gives patients and physicians earlier access to potentially beneficial drugs. and it may provide "orphan" disorders the only treatments that are now available.(4)

How Are Prescription Drugs Off-Label Used?

It is a recognized medical practice to write prescriptions for so-called off-label purposes, which frequently demonstrates cutting-edge clinical knowledge. This is true, for instance, of the usage of cancer drugs, more than half of which are prescribed off-label. When a medication was evaluated for the treatment of one condition and then given to try and prevent or treat another, when it was tested at one dose and then used at greater or lower doses, or when it was tested in an eight-week study and then prescribed for long-term usage, these instances are all examples of off-label uses.(3)

The Development of FDA Off-Label Promotion Regulations

The FDA is able to control how pharmaceutical companies promote their products because to the Federal Food, Drug, and Cosmetic Act (FFDCA) of 1938. In order to prevent drug companies from improperly influencing prescribing practices, FDA laws have made an effort to strike a balance between allowing doctors to use their best clinical judgment and preventing this from happening.(12) As a result, doctors may prescribe medications for off-label applications in accordance with FDA standards, but pharmaceutical companies may not advertise such usage. In order to ensure that marketing and advertising strategies are truthful, balanced, and devoid of false information while still being backed by evidence from clinical experience, FDA regulations were created. FDA laws do not expressly forbid the advertising of off-label usage; nonetheless, two measures indirectly accomplish this goal. Pharmaceutical firms are not permitted to introduce a medicine into interstate commerce unless the FDA has authorized the drug and its label. Manufacturers are not allowed to introduce misbranded medications into interstate commerce, according to a second clause. When a drug label describes an unauthorized application, is deceptive, or is insufficient to support the safe use of an approved indication, misbranding is deemed to have taken place. Whether or whether they are included in product labeling, materials distributed by the manufacturer to describe the uses of the drug are regarded to be part of the labeling for that product. According to FDA regulations, pharmaceutical companies must submit safety and efficacy data and get FDA permission before selling a new drug indication in order to avoid participating in inappropriate promotion. However, the FDA Modernization Act of 1997 (FDAMA) created regulations that contained a clause that permitted pharmaceutical and medical device companies,

subject to specific conditions, to disseminate academic research on off-label usage.[9,12,11,14,15]

Drug use outside of the recommended dosage range is not an uncommon occurrence; it is widespread. Previous studies have shown that this practice can be as prevalent as 90% in children or 40% in adults. It has been discovered that neonates, infants, and premature and low birth weight newborns are more likely to utilize drugs off-label and without a prescription. Drugs are reportedly used off-label in oncology at a rate of up to 50%. When off-label use is supported by science and medicine, doctors advance the interests of their patients by administering off-label medications. Off-label prescribing is done without sufficient scientific evidence, and the primary focus should be the safety of the drug for the specific ailment.[16,17,18,19,20]

Situation involving off-label prescriptions

In the majority of countries, pharmaceutical companies are not permitted to advertise their products for non-approved indications in prescribing information or promotional materials, but doctors are free to recommend any approved drug for any indication, even if it has not been approved by regulatory bodies, if there is an emergency, there is no approved treatment for the disease, or if they have a reasonable expectation that the patient will benefit. While prescribing a drug outside of its approved uses is typically legal, drug manufacturers are thought to be breaking the law when they promote alternative uses because they are not fully aware of the consequences of their products.If there are no standard therapy options available or if standard treatment options are ineffective in treating the problem, general practitioners frequently use off-label treatments. Off-label drug use allows doctors the freedom to utilize novel therapeutic approaches based on the most recent research, butthere is no assurance of their scientific validity due to a lack of examination of safety and efficacy. Therefore, a doctor must consider a drug's scientific validity and medical support when recommending it for off-label use.[5]

The necessity of off-label use

The patient's circumstance frequently necessitates a new strategy or new treatment when the best therapeutic option isunsuccessful, and this eventually leads to off-label

applications. Furthermore, off-label use can give patients early access to potentially beneficial drugs. In summary, the advantages of off-label prescribing include quicker patient access to drugs as medical knowledge develops and lower costs for novel treatments. When conventional treatments don't work or when patients are diverse, it might be helpful. Additionally, it permits experimentation and chance discovery. However, if there is uncertainty over the scientific validity of off-label use, the patient could be exposed to unknown health hazards or get inadequate treatment.[5,6]

Approved sources for off-label data

There are numerous additional sources for this information, notwithstanding the FDA's ban on businesses promoting theirproducts for off-label usage. The following is a discussion ofacceptable sources for off-label information:

References to compendia and pharmacological information

Organizations or businesses that are unaffiliated with manufacturers create compendia and reference books on drugs. Both labeled and off-label usage are frequently included in these references. If off-label drug uses are listed in significant compendia like the U.S. Pharmacopoeia Drug Information (USP DI) or the American Hospital Formulary Service Drug Information (AHFS DI), Medicare, Medicaid, and many private insurers will pay for them. Manufacturers can profit from compendia listings since the presence of their goods in these sources can increase sales.[6]

Journal publications

The clinical trials required for regulatory approval are carried out by drug and medical device companies, who subsequently make the results available through marketing, advertising, and publication in the medical literature. In order to find new applications for sold medicines and technologies, company researchers and independent researchers then carry out clinical investigations and submit the findings for publication. If FDA guidelines are followed, businesses are permitted to freely disseminate copies of these papers that include applications for unapproved products.[6]

Medical and postgraduate training

continuing medical education is only one type of medical and graduate education that follows FDA guidelines to determine independence. Because off-label applications are frequently included in educational programs, it is crucial to draw a distinction between independent and promotional, company-sponsored activities.Even though educational events may be seen as autonomous, businesses routinely hire and educate influential academic physicians as speakers or key opinion leaders (KOLs) to provide unrecognized instructional speeches to peers. For Grand Rounds, businesses may also give unlimited grants to academic medical centre departments. The author of publications or posters displayed during a medical education programs that discuss off-label applications may also be a KOL. These discussions are not governed by any regulations because the FDA regards the viewpoints presented by these leaders as being independent, and they are free to discuss both labeled and unlabeled usage.[6,7,10,11] Health liaisons

Companies are allowed by the FDA to answer inquiries on off-label uses from healthcare providers who have not asked for it. These enquiries are typically made by doctors looking for proof to back up an off-label treatment. The company's medical affairs division, for example, must handle these enquiries as it is a separate division from sales and marketing. Responses to these uninvited questions need to be balanced, specific, and well-documented. The company's response materials, which can include journal articles, formulary guidance, or responses to inquiries made through a sales representative, must not be promotional.[8,9,12,13]

Sales personnel

Sales agents are permitted to give copies of peer-reviewed journal papers to medical experts, but they are not allowed to

utilize those articles to advertise their company's goods. A medical liaison who is not a part of sales and marketing must be contacted if the physician has inquiries concerning off- label applications, according to the spokesman. A postcard or phone call to the business to request a packet of material be sent to the doctor is used to refer an off-label query. Reprintsof journal articles may be included in the packet, along with a standard letter outlining published clinical studies on an off-label use.[6]

Web pages

Medical makers, prescribing physicians, and patients all benefit from the ease with which information may be accessed via the Internet. The majority of authorized medications have complete prescribing information available online. In order to prevent regulatory issues, only little information is presented on company websites. Off-label information, however, may be freely disseminated by other websites that are not employees of the company. The FDA suggests that a Web page providing prescribing information should make the black-box warning for a medicine stand out.[8,11,14,20]

How pervasive is the usage of medications off label

Because it offers doctors the opportunity to adopt novel therapeutic choices based on the most recent research, off-label prescribing of medications is common throughout theworld. Despite the fact that doctors are legally permitted torecommend licensed medications for any purpose that isconsistent with the best available scientific evidence andethical medical practice, this is unfortunately frequently donein the absence of sufficient scientific evidence. When the besttherapeutic option is no longer effective, patients frequentlyseek new methods or new therapies, which eventually resultsin off-label applications. The improper use of off-labelmedications, which results in the use of medications without considering risk and benefit, has raised serious concerns regarding efficacy and safety investigation by the regulatoryagency. Unfortunately, more clarification is needed on therules governing the off-label use of medicine, even if theregulatory approval procedure requires enough proof ofefficacy and safety for obtaining clearance for certain uses ofprescription drugs. Expecting pharmaceutical corporations torestrict or prohibit off-label promotion is exceedinglyunrealistic, especially given the financial considerationsinvolved. Off-label use is like a two-edged blade that can beboth very beneficial for some patients and expose them tounlimited experimentation, unknown health concerns, or

useless therapy. Consequently, there is a pressing need for direction to promote appropriate off-label usage of medication by the dissemination of information from the pharmaceutical industry that is both accurate and scientifically sound. In fact, only a small number of nations, including the USA and France, have taken the initiative and developed laws regarding the use of medications outside of their prescribed indications.[7,8] Because it can be linked to significant patient benefit or harm, the phrase "off-label druguse" is divisive. The most prevalent method of using drugs off-label is to prescribe them for a condition (such an illness or a symptom) that has never obtained Food and Drug Administration (FDA) approval. Off-label drug usage in the pediatrics population can also refer to the administration of a commercially available drug in a dosage or form not authorized by the FDA. Children are frequently given medications that are illegal or off-label. For the indications for which the medications may be used, neither efficacy nor safety have been proved in the absence of clinical trials. Off-label usage is done for the benefit of a specific patient. A usethat is "off-label" does not necessarily mean it is wrong, unlawful, contraindicated, or experimental. For a specific health issue for which there is no alleviation from the conventional pharmaceuticals that are primarily intended for its management, an off-label use may give the optimum intervention and standard of care for a patient. Three-quarters of marketed prescription medications have no labeling indications for children, making off-label usage occasionally inevitable. [64,65,6 Studies released in the last ten years have demonstrated the prevalence of off-label drug use in the European Union (EU), particularly in the fields of pediatrics, oncology, neurology, infectious disease, and geriatrics. For instance, it is believed that up to 90% of the treatment given to newborns in intensive care units in hospitals is off-label. Additionally, public health insurance organizations frequently compensate the price of medications supplied off-label.[67] In the U.S.A unauthorized use was reported to be 20% in a 2013 study, although a later investigation found that it might be as high as 50% in certain situations or for certain patient groups.Pharmaceutical companies regularly evaluate whether a drug that has been found to be both safe and effective may also be appropriate for brand-new indications or applications. In fact, new approved indications and uses may result from such use. According to research by economist Alexander Tabarrok, the majority of hospital patients in the US receive at least one medication that is not on the label. The massive amount of resources allotted by federal and state agencies, regulators, and prosecutors to police off-label use, along with the headline-grabbing successes in prosecuting off-label cases, may be the most striking evidence of the prevalence of off-label usage. Pharmaceutical prosecutions in the US continue to mostly be based on investigations into off-label drug advertising.[67]

Illustrations of drugs used off-label

Colchicine

Colchicum Autumnale, often known as meadow saffron or autumn crocus, is the source of the alkaloid known as colchicine.It is used to stop or treat gout flare-ups. Typically, just one or a few joints are affected by the abrupt onset of gout symptoms. The most frequently impacted joints are the big toe, knee, or ankle. Too much uric acid in the blood leads to gout. Uric acid may crystallize into tough lumps in your joints if blood levels are too high. Colchicine relieves pain in the afflicted joint(s) by reducing edema and uric acid crystal accumulation.[21]

Off-label usage

Pustular and palmoplantar psoriasis are two types of psoriasis that colchicine is thought to be beneficial in treating.[22]

Skin disease's pathophysiology

A chronic inflammatory skin condition with no recognized cause, psoriasis. Psoriasis has epidermal hyperplasia, inflammatory infiltrates, and vascular proliferation as its histopathological characteristics. The inflammatory process of psoriasis has several distinctive characteristics, including intraepidermal neutrophil and lymphocyte populations. Chemotactic chemicals may play a role in the migration of leukocytes from the dermis to the epidermis.[22,23]

How does colchicine manage plaque psoriasis?

Leucocyte movement and degranulation are hampered bycolchicine's concentration in leucocytes. To achieve clinicalsuccess in the majority of dermatological patients, a dosageof 1-1.5 mg per day was typically sufficient. To lessen thedanger of systemic adverse effects when using colchicine fora longer period of time, it is preferable to reduce the dailydose to 0.5–1 mg [23,24]

Tranexamic acid

In order to prevent excessive blood loss during surgery, postpartum bleeding, and heavy menstrual bleeding, tranexamic acid, a synthetic derivative of the amino acid lysine, blocks the lysine binding sites on plasminogen molecules in a reversible manner.[25]

Off-label usage

Despite the fact that the US Food and Drug Administration has licensed tranexamic acid for the treatment of menorrhagia and the reduction or prevention of hemorrhage, its potential efficacy in the management of melasma has been continuously documented since the 1980s.[26]

The melasma's pathophysiology

Keratinocytes produce more plasminogen activator as a resultof UV exposure, which increases the conversion of plasminogen to plasmin. Tyrosinase activity is enhanced by plasminogen activator, which boosts the production of melanin. Arachidonic acid and fibroblast growth factor are both produced more abundantly when plasmin is present, which correspondingly promotes neovascularization and melanogenesis.[27]

How does tranexamic acid alleviate melasma?

Tranexamic acid reduces UV radiation-inducedneovascularization and melanogenesis via preventingplasminogen activation. Using a topical treatment oftranexamic acid on guinea pig skinafter exposure to UV lightlowered tyrosinase activity and prevented the development ofanticipated skin hyperpigmentation.[28,29]

A retrospective chart assessment of 561 melasma patients who had oral tranexamic acid treatment at a single centre in Singapore was the largest study on the topic. More than 90%of patients had their melasma previously treated with energy- based therapy and bleaching treatments. 90% of patients who

received oral tranexamic acid over a 4-month period showedimprovement in the severity of their melasma. 7% of patients suffered negative effects, with abdominal bloating and pain (experienced by 2% of patients) being the most frequent ones. It is noteworthy that one patient experienced deep vein thrombosis while undergoing treatment and was later diagnosed with protein S deficiency.[30]

Spinolactone

It is an aldosterone antagonist and a diuretic that saves potassium. is a drug that must be prescribed. Under the trade name Aldactone, it is given to treat a wide range of illnesses, such as edema, heart failure, low potassium levels, hypertension, and hyperaldosteronism.[31]

Off-label usage

As an unapproved treatment for hirsutism, spirolactone has been suggested.[32]

Just what is hirsutism?

Hirsutism is the occurrence of terminal coarse hairs in females with a distribution resembling that of males. It is caused by an increase in androgen levels in females as a result of increased androgen (testosterone) production by the adrenal glands or as a result of an ovarian disorder. Polycystic ovarian syndrome (PCOS) and ovarian tumors are the ovarian sources of hyperandrogenism. Cushing's syndrome, androgen-producing tumors, and congenital adrenal hyperplasia (CAH) are some of the causes of the adrenal glands.[33]

How is hirsutism treated by spironolactone?

Ober and Hennessy noted the first evidence of a spironolactone effect on hirsutism in a patient receiving treatment for hypertension.[34]

Spironolactone affects androgen activity in a number of ways, which may lessen hair growth and other abnormalities brought on by androgens. After reports that spironolactone interfered with testosterone synthesis, it was clinically observed that the drug has antiandrogenic effects in males. It also has an anti-androgen receptor effect. Spironolactone slows the development of existing hair in women by decreasing the pace of testosterone production, increasing its metabolic clearance, and lowering the amount of testosterone in the blood.[35]

Prazosin

Prazosin is a selective orally active α_1-adrenoceptor antagonist that is frequently used to treat congestive heart failure (CHF) and hypertension.[36]

Off-label usage

used as a therapy for nightmares caused by post-traumatic stress disorder (PTSD).[37]

How is post-traumatic stress disorder treated by prazosin?

Insomnia brought on by hyperarousal and recurrent nightmares are two symptoms of post-traumatic stress disorder (PTSD), a mental health condition. Norepinephrine is thought to control a conditioned reaction that causes these symptoms. Prazosin, α_1 antagonist, can lower norepinephrine levels in the brain, hence lessening PTSD-related dreams.

Through this mechanism, prazosin can enhance sleep and lessen PTSD-related nightmares.[38] Raynaud's disease treatment is yet another off-label application of prazosin.[39]

Erythromycin

Erythromycin is a member of the macrolide antibiotics class of medications. By decreasing the production of crucial proteins required for the survival of the bacterium, macrolide antibiotics inhibit the growth of sensitive bacteria or even cause their death. It is utilized to treat or prevent a wide rangeof bacterial infections.[40]

Off-label usage

For the treatment of gastroparesis and other GI hypomotility diseases, it has been used successfully off-label.[41]

A description of gastroparesis.

Chronic gastroparesis is a condition that affects a sizable portion of the population. Typically, the digestive system moves food by powerful muscle contractions. Due to the disruption of this mechanism in gastroparesis, undigested food remains in the abdomen for an extended period of time and causes nausea and the urge to vomit.Patients who are not eating might anticipate discomfort, bloating, and heartburn. Gastroparesis can also produce a lack of appetite, which mayresult in malnutrition.[42]

How does erythromycin handle gastroparesis?

Patients frequently reported experiencing stomach pain aftertaking erythromycin as an antibiotic. Erythromycin activatesmotilin receptors in the GI tract, according to research thatwas finally conducted. GI contractions are induced by motilinreceptors, increasing GI motility. Additionally, thismedication heightens stomach contraction and may enhancegastric emptying.[41]

Phenytoin

It is a drug used to control and treat epilepsy, complex partial seizures, generalized tonic-clonic seizures, and status epilepticus. It is a type of medication known as an anticonvulsant. is still a significant antiepileptic medication. Its main mode of action involves blocking and inhibiting voltage-gated sodium channels in the membrane of neuronal cells.[43]

Off-label usage

It was discovered that phenytoin could help a number of chronic wounds heal more quickly.[44]

How can phenytoin aid wound healing?

Kimball made the initial discovery that certain phenytoin-treated patients had gingival hyperplasia in 1939, which sparked research into the drug's possible role in wound healing.In 1958, Shapiro conducted the first controlled clinical experiment and discovered that oral phenytoin pretreatment resulted in reduced swelling, less discomfort, and quicker healing in periodontal patients with surgical wounds than in controls.Phenytoin was subsequently discovered to accelerate dental extraction socket healing and boost the tensile strength of experimental skin and corneal wounds.[45,46,47,48,49]

Mechanism of action

Clinical, animal, and in vitro studies indicate that phenytoin may be involved in the healing process on a number of levels, including promoting the deposition of collagen and other connective tissue components, enhancing the formation of granulation tissue, decreasing collagenase activity (by reducing its production or secretion or both), decreasing bacterial contamination, and reducing wound exudates.[50,51,52]Open wounds treated with phenytoin exhibit decreased polymorphonuclear and eosinophil cell infiltration, neovascularization, and collagenization in biopsy samples.[53, 54]

Tamsulosin

Its medication is a member of the class of drugs known as alpha-blockers. It is used to treat males with benign prostate enlargement, or symptoms of an enlarged prostate.[55]

Off-label usage

To aid in the passage of a distal urethra stone, off-label use in patients.[56]

The mechanism of action

Tamsulosin may be used to increase stone expulsion rates, according to studies. Inhibiting smooth muscle contraction in the ureter is thought to be how beta-blockers work, making it easier for the stone to move into the bladder.[57]

Propranolol

is a non-cardio selective beta-blocker that is used to treat angina pectoris, hypertension, pheochromocytoma, and cardiac arrhythmias.[58]

Off-label usage

It is employed to treat thyroid storm.

Thyroid storm: what is it?

A uncommon endocrinological emergency, thyrotoxic crisis or thyroid storm is a severe form of hyperthyroidism. The pathophysiology is intricate and includes a heightened response to T3 and a sudden rise in free hormone levels caused by a reduction in protein carrier capacity.[59,60]

How is thyroid storm treated with propranolol?

lowering the blood's amount of circulating T3, as well as preventing the hormone's side effects by blocking -adrenergic receptors. Due to its added capability of preventing the peripheral conversion of dormant T4 to active form T3, propranolol has traditionally been favoured.[59]

Gabapentin

is structurally connected to the GABA (gamma-aminobutyric acid) neurotransmitter. It is permitted to stop and manage seizures.

Off-label usage

Diabetic Peripheral Neuropathy (DPN) is treated with it:

DPN is nerve damage brought on by persistently elevated blood sugar. The 2 subunit of voltage-gated calcium channels is a therapeutic target shared by gabapentin and GABA due to their structural similarity. However, the GABA release in spinal cord circuits that alter pain perception may be the causeof the analgesic effects.(61)

Indomethacin

Non-steroidal anti-inflammatory medication (NSAID) indomethacin has antipyretic and analgesic effects. It inhibits cyclooxygenase (COX) in a nonselective manner as its mode of action. Neonatal closure of the patent ductus arteriosus (PDA) may be achieved without surgery by administering indomethacin intravenously (IV) in an off-label manner.(61)

Oncology off-label use

Off-label treatment is widely used in fields including oncology, pediatrics, and rare disorders, usually because there aren't many other pharmaceuticals that work as well. Off-label prescriptions for anticancer medications may have a positive clinical outcome or have no impact, either with or without side effects. Due to the fact that patients getting off- label treatments typically have severe diseases with few chances of recovery, the potential for clinical benefit is considered to be minimal. However, for some cancer types, off-label use might be seen as the norm and can be linked to curative intent, such as with etoposide for Ewing's sarcoma or high-dose carboplatin for pediatric malignancies and germ- cell malignant disease that has already received treatment. The many different forms of neoplasm are not covered by the labeling of anticancer drugs. Chemotherapy is used off-label to treat rare tumors or those with an unclear primary location. Clinical advantages have been linked to administration methods other than those that have been approved. Cisplatin intra-peritoneally injected for ovarian cancer with optimally debulked disease is one example.

In the USA, the usage of oncology medications off-label hasbeen linked to the sluggish spread of knowledge about severe adverse drug responses. The off-label use of thalidomide, which was not at the time of the report approved for the treatment of cancer, led to one major side-effect that was reported between 2000 and 2002. This use was not disclosed in the package insert since it was against US Food and Drug Administration (FDA) policy.(78)

Risks and Benefits

Benefits of off -label use

The usage of medications off-label provides various advantages for patients and healthcare providers. When authorized therapeutic alternatives fail, it can sometimes help doctors treat patients and provide patients earlier access to life-saving drugs. Convincing data on a drug's efficacy and safety in specific circumstances, such as rare illnesses or "orphan" ailments (such as Tourette syndrome), is another frequent justification for administering a drug outside of its approved indications. For various ethical, logistical, or legal reasons, children, pregnant women, and elderly people are frequently excused from clinical trials, hence a large range of drugs are not authorized or particularly designed for these groups. Therefore, off-label prescription is used in pediatric, geriatric, and obstetrics when there are no other treatment options for a certain patient population. Off-label usage is crucial for discovering new applications for already-approved medications, as well as for ensuring that patients receive the best care possible. Nearly 57% of pharmacological therapy breakthroughs were uncovered through off-label usage in modern medicine.(63,75,71)

It allows for the discovery of new indications, especially in cases where the recommended course of treatment has failed. It can also do away with the time-consuming and expensive process of receiving official agency approval for drugs, allowing for earlier access to medications and the adoption of novel practices based on new research (allowing doctors to gather data prior to official approval). Additionally, there are specific situations where off-label medication is the only option. Pediatrics is the most glaring example of this. The majority of medications used in pediatric populations lack authorized indications since there are so few clinical studies conducted on pediatric populations. Another illustration is the absence of authorized medicines for some uncommon diseases caused by the inability to conduct efficient clinical trials; in this case, the sole option for therapy may be using medications that have already been licensed for use in other disorders. But in clinical practice, off-label prescribing for common illnesses frequently happens.(62,63,68,71)

Off-label usage risks

The absence of a risk-benefit analysis and the pharmaceutical industry's lack of a systematic evaluation are the key drawbacks.Patient safety may be put at risk by the use of off-label medications. The absence of controlled research and observations makes it impossible to monitor adverse effects that may be caused by a variety of individual characteristics, including age, co-morbidities, medication-disease interactions, and multiple drug use. Since adverse medication reactions associated with off-label prescription usage render doctors more susceptible to potential legal penalties, there is a need for heightened accountability for patients' well-being. Other possible issues with off-label prescribing may include the pharmaceutical industry (e.g., manufacturers are not permitted to promote off-label pharmaceuticals), the healthcare system (e.g., difficulty in recovering medical costs), or both.(75)

Heart valve damage from the use of fenfluramine and phentermine (fen-phen) for weight loss is one of the adverse effects (AEs) connected with the use of medicines for particular off-label applications. Researchers examined the rate of adverse events (AEs) for on-label usage, off-label use linked to "strong scientific evidence," and off-label use without such evidence using a Canadian primary care database that included all prescriptions, the rationale for each prescription, and AEs. In comparison to on-label prescriptions, they discovered higher adverse events (AEs). On the other hand, AE rates for off-label usage supported by solid scientific research were comparable to those for on-label uses. Off-label usage were mostly associated with an elevated risk of adverse events (AEs) that lacked solid scientific support.(69)(70)

Since companies can only be held accountable for issues that develop when their medication is used within its recognized

indications, drug makers, unlike doctors, have limited legal culpability with relation to off-label prescribing. Off-label prescribing may also prevent the pharmaceutical industry from performing clinical studies for novel or alternative indications, which would undermine public faith in the process of medication review. Off-label prescribing raises a number of challenges, one of which is the ineffective pharmacovigilance brought on by low levels of reporting, which might mask safety risks. It should be kept in mind thatmedications with a strong safety profile for a particular usage, prescribed for the researched population, and having authorized indications, may not be safe when used inappropriately and/or in patient populations that have not been thoroughly studied.[68]

Numerous pediatric patients with rare illnesses use drugs off-label since there isn't enough research on them in this population. Off-label treatment for infants, children, adolescents, and neonates—especially for young patients with rare diseases—remains a serious public health issue. Most medications have little to no information on the labels for pediatric use for children with rare diseases. Since children present unique considerations in clinical trials, pediatric drug testing has been limited or even outlawed due to ethical and therapeutic concerns.[74]

Ethical and legal consideration

Ethical consideration

If a doctor decides it is suitable and useful for the patient, they may prescribe FDA-approved drugs for uses not listed on the label. Any potential side effects should be discussed with the patient by the doctor. The possible advantages of using the medicine outside of the recommended dosage range should be acknowledged by both parties. If the medication turns out to be useless or hazardous, the doctor should also be preparedto adjust the dosage or the medication altogether. Drug use that is not prescribed is legal. This is permitted for doctors and surgeons to perform. Off-label use is frequently seen as legal unless it violates moral principles or other safety laws. Off-label drug use is ethical and acceptable as long as it is supported by reliable data and evidence. Many over-the- counter and prescription medications are successfully used off-label. Off-label prescriptions are not always a bad thing. When patients have exhausted all other recognized options, itmay be helpful.[72,73]

Legal point to consider

Many nations allow the prescription of medications off-label.Sometimes there are no precisely suited medications for a certain situation, or the current range of medications is quickly used up without adequately aiding the patient. The treating physician is caught in the following challenging predicament: He does not want to leave the patient without a cure due to his professional obligations (and is occasionally even prohibited from doing so if he wishes to avoid an omission offence). However, if a doctor decides to deliver unproven medications, they take on all the risks that the regulatory drug approval process and medical malpractice law (which is centered on the "standard" of medicine) shouldordinarily guard against for the patients' safety.[71,77,78]

DISCUSSION

Drugs are frequently prescribed outside of their approved indications, and this practice has been noted as a potential major factor in avoidable adverse drug events (ADEs). Off-label drug use is the practice of prescription medications in a way that is at odds with the prescribing guidelines provided by regulatory bodies. Off-label drug usage can be categorized into a number of distinct subcategories, including use for an unapproved indication, use in a particular group, via an unauthorized route of administration, and use of a dose that is not disclosed on the FDA-approved label.[62] Off-label drug use is the use of medications off-label based on scant or nonexistent scientific evidence. For instance, administering a medication for a therapeutic indication before the findings of the clinical trial are available. Compassionate drug use differs from using medications off-label.[79] Compassionate drug use, also known as extended access, makes investigational therapies available to patients with chronic, seriously life-threatening, or fatal illnesses who lack access to appropriate licensed medications or who are ineligible for clinical trials. Off-label medication in cancer may be useful as it offers patients who have no other options, such as in areas where there were no approved treatments or for patients who have used up normal lines of treatment, evidence-based treatment options.[71,76] Off-label drug usage is associated with a number of safety and ethical concerns, despite the fact that it may occasionally be therapeutically warranted. In some therapeutic situations when a favorable benefit-risk ratio has not yet been completely established, off-label prescribing may endanger patient safety. This is mostly because regulators, those who create guidelines, and even healthcare politicians do not routinely evaluate off-label prescription uses. Use of off-label medications based on no evidence carries a risk of toxicity. When thoroughly examined, several frequently used off-label drug uses have also been discovered to be either hazardous or inefficient. A review of 150 million prescriptions written off-label found that 73% of them lacked solid scientific support.[77,79]

It is difficult to quantify off-label use and its effects because there is rarely a clear connection between prescribed medications and their indication. Evidence supports needing these components in electronic prescriptions, and recent approaches for supporting the documenting of treatment indication, justifications for stopping treatment orders, and ADEs have been created. These new capabilities offer a rare chance to track and methodically assess off-label use and its impact on ADEs.

The outcomes of such monitoring can be very helpful in guiding activities targeted at limiting off-label use and enhancing the function of drug regulatory authorities.

According to studies conducted in the US, off-label use may account for 150 million prescriptions annually, or 20% of all prescriptions. Inappropriate off-label drug usage has a significant financial impact on the healthcare system and poses serious safety issues, particularly when a drug is extensively used despite the fact that regulatory bodies have not established its benefit-risk ratio. Additionally, multiple studies from around the world have shown that off-label

prescribing is a common occurrence in many fields of medicine, including oncology.(76,80)According to a 2002 study conducted in France, 13 of 32 anticancer medications were used off-label. The medications most often used off-label were docetaxel (29%), oxaliplatin (24%), fludarabine (8%) and carboplatin (8%). According to a 2004 Australian research at the Peter MacCallum Cancer Centre, 22% of all prescriptions for acute hospitalized oncology patients were for medications that were not approved by the FDA. 10% of these prescriptions were written off-label due to altered dosage, 9% for an unapproved indication, and 3% for an alternative mode of administration. According to a sizable study carried out by M.D. Anderson Cancer Centre researchers utilizing data from Surveillance, Epidemiology and End Results (SEER), a third of patients with metastatic breast cancer had at some time in their treatment taken off- label medicine. (80,81)

CONCLUSION

While the use of drugs off-label in clinical settings is prevalent. It entails the use of drugs for conditions for which they have not been licensed, in unapproved age ranges, with modified dosage schedules, or with unusual modes of administration. Oncologists, pediatricians, and neonatologists frequently prescribe medicines that are not approved by the FDA. Off-label drug usage is legal, widely accepted by the medical community, and is not inherently against accepted healthcare standards. The need for a register is critical given the global prevalence of off-label drug usage. It permits medical professionals to treat patients, including those in whom an approved course of treatment has failed and in whom the use of an off-label medication may be the only effective course of action.

REFERENCES

1. QasemOzaybiPhM. Guidelines for off-label drugs: conceptandgoodclinicalpractice. Page8.9.10.11; 2021.
2. Waller DG. Off-labelandunlicensedprescribingforchildren: have we made any progress?BrJ ClinPharmacol. 2007;64(1):1-2. doi: 10.1111/j.1365-2125.2007.02987.x, PMID 17577389.
3. Crs report – Prepared For Members And Committees Of Congress – Available February23,2021.Https://Crsreports.Congress.Gov.
4. Radley DC, Finkelstein SN, Stafford RS. Off-labelprescribingamongoffice-basedphysicians. Arch Intern Med.2006;166(9):1021-6. doi: 10.1001/archinte.166.9.1021, PMID 16682577.
5. DuttaG, KumarT, DuttaS, KumarR, PrakashSharmaR,BanerjeeS. Off-labelprescribing. IntJPharmSciRevRes.Sep-Oct2020;64(2):Article No.20. Field RI. The FDA'snewguidanceforoff-labelpromotion Is Only a Start. P T.2008;33(4):220-49. PMID 19750166.
6. VentolaCL, MS. Off-labeldrug.Magazine. 2009;34(8, Jun29) Informations. P&T.
7. Fugh-Berman A, Melnick D. Off-labelpromotion, on-targetsales. International Journal Of Pharmaceutical Sciences Review And Research Plos Med. PLoS Med.2008;5(10):E210. doi: 10.1371/journal.pmed.0050210, PMID 18959472.
8. Rumore M. Legal aspectsofdruginformationpractice. In: Malone P, Kier K, StanoVich J, editors. Drug information: A guideforpharmacists.3rded.New York: Mcgraw-Hill Professional; 2006. p. 448.
9. Government Accountability Office (GAO). Prescription drugs: FDA'soversightofthepromotionofdrugsforoff-labeluses. Items/D08835.Pdf.Jul2008. Available At: Www. Gao. Gov/New.
10. Hearing on confirmationofgovernorKathleenSebeliustobeSecretary of Health and Human Services;Apr2, 2009. Gov/Hearings/Testimony/2009 Test/ 040209qfrs%20for%20 submissions. Pdf. Available from:Http://Finance.Senate. [accessedMay31, 2009].

    Accreditation Council For Continuing Medical Education (ACCME). Annual reportdata2007, August28. Available from:http://Www.Accme; 2008.
11. MelloMM, Studdert DM, Brennan TA. Shifting terrainintheregulationofoff-labelpromotionofpharmaceuticals. N Engl J Med.2009;360(15):1557-66. doi: 10.1056/NEJMhle0807695, PMID 19357413.
12. FDA. Reprint practicesforofflabelmarketing;2009. HTM. Available from:http://Www.Fda.Gov/Regulatoryinformation/Guidances/Ucm125126. [accessedMay31, 2009].
13. O'Reilly J, Dalal A. Off labeloroutofbounds? Prescriber andmarketerliabilityforunapprovedusesofFDA-approveddrugs. Ann Health Law.2003;12(2):295-324. PMID 12856461.
14. Arnold MFDA. Okaysdistributionofjournalarticlesonoff-labeluses. MedMark Media.
15. Gazarian M, Kelly M, Mcphee JR, Graudins LV, Ward RL, Campbell TJ. Off-labeluseofmedicines: consensusrecommendationsforevaluatingappropriateness. Med J Aust.2006;185(10):544-8. doi: 10.5694/j.1326-5377.2006.tb00689.x, PMID 17115966.
16. Radley DC, Finkelstein SN, Stafford RS. Off-labelprescribingamongoffice-basedphysicians. Arch Intern Med.2006;166(9):1021-6. doi: 10.1001/archinte.166.9.1021, PMID 16682577.
17. Bavdekar SB, Gogtay NJ. Unlicensed andoff-labeldruguseinchildren. J Postgrad Med.2005;51(4):249-52. PMID 16388164.
18. Emmerich J, Dumarcet N, Lorence A. France'snewframeworkforregulatingoff-labeldruguse. N Engl J Med.2012;367(14):1279-81. doi: 10.1056/NEJMp1208347, PMID 23034018.
19. Field RI. The FDA'snewguidanceforoff-labelpromotion Is Only a Start. P T.2008;33(4):220-49. PMID 19750166.
20. Leung YY, Yao Hui LL, Kraus VB. Colchicine—updateonmechanismsofactionandtherapeuticuses. Semin Arthritis Rheum.2015Dec;45(3):341-50. doi: 10.1016/j.semarthrit.2015.06.013, PMID 26228647.

21. Sardana K, Sinha S, Sachdeva S. Colchicineindermatology: Rediscovering an Old Drug with Novel Uses.Indian Dermatol Online J. Sep-Oct2020;11(5):693-700. doi: 10.4103/idoj.IDOJ_475_20, PMID 33235833.
22. siba Praychaudhuri1 , wen-yue jiang1.Et Al. Upregulation ofRANTESinpsoriatickeratinocytes: A possiblepathogenicmechanismforpsoriasis. ActaDermVenereol (Stockh).1999;79(9)^11.
23. Kieran P, Jonathan J. Colchicineindermatology: A review. AustralasJ Dermatol. doi: 10.1111/Ajd.12795.2018.
24. Dunn CJ, Goa KL. Tranexamic acid: areviewofitsuseinsurgeryandotherindications. Drugs. 1999Jun;57(6):1005-32. doi: 10.2165/00003495-199957060-00017, PMID 10400410.
25. Higashi N. Treatment ofMelasmaWith Oraltranexamic acid.Skin Res. 1988;30:676-80.
26. Sundbeck A, Karlsson L, Lilja J, Peterson HI. Inhibition oftumourvascularizationbytranexamic acid. Experimental studiesonpossiblemechanisms. Anticancer Res. 1981;1(5):299-304. PMID 6179454.
27. Maeda K, Naganuma M. Topical Trans-4-Aminomethylcyclohexanecarboxylic acidpreventsultravioletradiation-inducedpigmentation. J PhotochemPhotobiol B. 1998;47(2-3):136-41. doi: 10.1016/s1011-1344(98)00212-7, PMID 10093913.
28. Li D, Shi Y, Li M, Liu J, Feng X. Tranexamic acidcantreatultravioletradiation-inducedpigmentationinguineapigs. Eur J Dermatol. 2010;20(3):289-92. doi: 10.1684/ejd.2010.0912, PMID 20400389.
29. Li D, Shi Y, Li M, Liu J, Feng X. Tranexamic acidcantreatultravioletradiation-inducedpigmentationinguineapigs. Eur J Dermatol. 2010;20(3):289-92. doi: 10.1684/ejd.2010.0912, PMID 20400389.
30. Carone L, Oxberry SG, Twycross R, Charlesworth S, Mihalyo M, Wilcock A. Spironolactone. J Pain Symptom Manage.2017Feb;53(2):288-92. doi: 10.1016/j.jpainsymman.2016.12.320, PMID 28024992.
31. Vargas-Mora P, Morgado-Carrasco D.Spironolactoneindermatology: usesinacne, HidradenitisSuppurativa, femalepatternhairloss, andhirsutism. ActasDermo Sifiliogr. 2020;111(8):639-49. doi: 10.1016/j.adengl.2020.03.015.
32. Sachdeva S. Hirsutism: evaluationandtreatment. Indian J Dermatol.2010;55(1):3-7. doi: 10.4103/0019-5154.60342, PMID 20418968.
33. Ober KP, Hennessy JF. Spironolactonetherapyforhirsutismin A hyperandrogenicwoman. Ann Intern Med.1978Nov;89(5 Pt 1):643-4. doi: 10.7326/0003-4819-89-5-643, PMID 717935.
34. Cumming DC. Use ofspironolactoneintreatmentofhirsutism. Cleve Clin J Med.1990May;57(3):285-7. doi: 10.3949/ccjm.57.3.285, PMID 2357784.
35. Aärynen M, Mäkelä M, Hämeenaho P, MattilaMJ.Prazosinenhancestheantihypertensiveeffectsofbeta-blockers duringisometricanddynamicexercise. Ann ClinRes. 1981;13(2):71-6. PMID 7015988.
36. Kung S, Espinel Z, Lapid MI. Treatment ofnightmareswithprazosin: A systematicreview. Mayo Clin Proc.2012Sep;87(9):890-900. doi: 10.1016/j.mayocp.2012.05.015, PMID 22883741.
37. Hudson SM, Whiteside TE, Lorenz RA, Wargo KA. Prazosinforthetreatmentofnightmaresrelatedtoposttraumaticstressdisorder: areviewoftheliterature. Prim Care Companion CNS Disord. 2012;14(2). doi: 10.4088/PCC.11r01222, PMID 22943034.
38. Basquez R, Pippin MM. Prazosin. In: Statpearls. Treasure Island, (FL): Statpearls Publishing; 2022Jun21. p. 2022Jan–.
40. Brittain DC. Erythromycin. Med Clin North Am.1987Nov;71(6):1147-54. doi: 10.1016/s0025-7125(16)30802-1, PMID 3320616.
41. Maganti K, Onyemere K, Jones MP. Oral erythromycinandsymptomaticreliefofgastroparesis: A systematicreview. Am J Gastroenterol. 2003;98(2):259-63. doi: 10.1111/j.1572-0241.2003.07167.x, PMID 12591038.
42. Camilleri M, Parkman HP, Shafi MA, Abell TL, Gerson L, American College of Gastroenterology. Clinical guideline: managementofgastroparesis. Am J Gastroenterol. 2013;108(1):18-37; quiz 38. doi: 10.1038/ajg.2012.373, PM