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Unlicensed and off-label medication uses in dermatology: a systematic review of literatures

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UNLICENSED AND OFF-LABEL MEDICATION USES IN DERMATOLOGY: A SYSTEMATIC REVIEW OF LITERATURES

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Department of General Practice

RCSI

A dissertation submitted in partial fulfilment of the requirement for the Masters in Health Care Ethics and Law

Date of Submission: 25th July 2015
Supervisor: Dr David Smith
Student Number: 13119664
Word Count: 18,360

July 2015
Candidate Thesis Declaration

I declare that this thesis, which I submit to RCSI for examination in consideration of the award of a higher degree, MSc in Healthcare Ethics and Law, is my own personal effort. Where any of the content presented is the result of input or data from a related collaborative research programme this is duly acknowledged in the text such that it is possible to ascertain how much of the work is my own. I have not already obtained a degree in RCSI or elsewhere on the basis of this work. Furthermore, I took reasonable care to ensure that the work is original, and, to the best of my knowledge, does not breach copyright law, and has not been taken from other sources except where such work has been cited and acknowledged within the text.

Signed ______________________________________________________________________

Student Number  13119664 ______________________________________________________________________

Date  25th July 2015 ______________________________________________________________________
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<thead>
<tr>
<th>Acronym</th>
<th>Full Form</th>
</tr>
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<tbody>
<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
</tr>
<tr>
<td>USA</td>
<td>United States of America</td>
</tr>
<tr>
<td>TRIP</td>
<td>Turning Research into Practice</td>
</tr>
<tr>
<td>SD</td>
<td>Standard Deviation</td>
</tr>
<tr>
<td>IQR</td>
<td>Interquartile Range</td>
</tr>
<tr>
<td>FDCA</td>
<td>Food, Drug and Cosmetic Act</td>
</tr>
<tr>
<td>ICH</td>
<td>International Conference on Harmonization</td>
</tr>
<tr>
<td>EU</td>
<td>Europe</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
</tr>
<tr>
<td>EMA</td>
<td>European Medical Agency</td>
</tr>
<tr>
<td>EAACI</td>
<td>European Academy of Allergology and Clinical Immunology</td>
</tr>
<tr>
<td>WAO</td>
<td>World Allergy Organization</td>
</tr>
<tr>
<td>OLDU</td>
<td>Off-Label Drug Use</td>
</tr>
<tr>
<td>NDA</td>
<td>New Drug Application</td>
</tr>
<tr>
<td>COPD</td>
<td>Chronic Obstructive Pulmonary Disease</td>
</tr>
<tr>
<td>IND</td>
<td>Investigational New Drug</td>
</tr>
<tr>
<td>IRB</td>
<td>Institutional Review Board</td>
</tr>
<tr>
<td>PDUFA</td>
<td>Prescription Drug User Fee Act</td>
</tr>
<tr>
<td>CDER</td>
<td>Center for Drug Evaluation and Research</td>
</tr>
<tr>
<td>GP</td>
<td>General Practitioner</td>
</tr>
<tr>
<td>AKs</td>
<td>Actinic Keratosis</td>
</tr>
<tr>
<td>LP</td>
<td>Lichen planus</td>
</tr>
<tr>
<td>ADRs</td>
<td>Adverse Drug Reactions</td>
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</tbody>
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Abstract

Background: It is a common practice for physicians to treat dermatologic conditions with medications that are not indicated for the specific condition being treated. These "off-label" prescriptions are often for drugs that have both well accepted the therapeutic value in the medical community and proven efficacy on the basis of results of clinical trials.

Objective: The aim of this study is to determine the main risk factors of most unlicensed and off-label medications used in treatment of dermatological diseases worldwide and to make a detailed examination of ethical and legal trends, patterns, preventive methods, possible solutions and recommendations associated with using unlicensed and off-label drugs in dermatology.

Methods: A systemic review of the relevant available studies on unlicensed and off-label medication uses in dermatology worldwide was performed.

Results: Ten epidemiological studies regarding the use of unlicensed drugs and off-label drugs in dermatology worldwide were identified. The selected studies were between the year 1994 and 2014.

Conclusion: Off-label medications seem to be commonly prescribed in clinical practice in dermatology and differs between countries, inpatient and outpatient settings and age. However, prescribing off-label medications to patients who expect to receive an effective treatment will likely lead to foreseeable ethical and legal difficulties. Some of the key ethical issues include the impact on the patient autonomous decision, informed consent and nature of the relationship between dermatologists and drugs companies. Legally, concerns surrounding the clinical implications, litigation for professional misconduct and FDA policies on off-label uses. A management guideline for off-label drug use is urgently needed.

Keywords: Unlicensed drugs, off-label drugs, dermatology, prescriptions, ethics, legal issues and legislation.
Chapter 1.0

Introduction:

1.1 Background to the Study:

"Off-label" means the medication is being used in a manner not specified by the Food and Drug Administration (FDA) as an approved packaging label. This label is a written report that provides detailed instructions regarding the approved uses and doses, which are based on the results of clinical studies that the drug maker submitted to the FDA, "said Kelli Miller, the Cleveland Clinic Men's Health Advisor".

"Many people may be surprised to know that the FDA regulates drug approval, not drug prescribing, and doctors are free to prescribe a drug for any [reason they think is medically appropriate]," says G. Caleb Alexander, MD, MS, a medical ethics advocate and assistant professor of medicine at the University of Chicago Medical Center.

Despite the prominence of off-label drug use, experts say few patients are aware that they are receiving a drug off-label and doctors are not required to tell a patient that a drug is being used off-label. When a doctor writes a prescription to treat an ailment, the patient probably assumes that the drug has been approved for that use by the Food and Drug Administration (FDA). When a doctor prescribes a drug for an unapproved use, it is called an “off-label” prescription. The term refers to the fact that all drugs have “labeling” detailed written descriptions of their intended use based on studies submitted to the FDA.

Dermatologists, like other physicians, face a dilemma when attempting to use only drugs with regulatory body approved indications. Neither industry or regulators want to be accused of experimenting on children, pregnant females or old people! In pediatrics, only about 20% of all drugs marketed in the US have been labeled for use by infants and children (Jaffe, S., 1994). Such an exclusion results in widespread off-label use. One study found that in 36% of 707 admissions, children received one or more courses of an unlicensed or off-label treatment (Turner S. et al., 1998). In 731 pregnant patients, 23% took more than one drug for off-label indications (Rayburn W. F. and Turnbull G. L., 1995).

It is a common practice for dermatologists to treat dermatologic conditions with medications that are not indicated for the specific condition being treated. These "off-label" prescriptions are often for drugs that have both well accepted
therapeutic value in the medical community and proven efficacy on the basis of results of clinical trials (Sugarman, J.H. et al., 2002). Off-label prescribing isn't necessarily bad. It can be beneficial, especially when patients have exhausted all other approved options, as may be the case with rare diseases or cancer.

Topical steroids are an excellent example of a class of drugs that is used in a broad range of clinical disorders, frequently without a particular indication other than managing general inflammation.

1.2 Problem Statement:

In this study, it is argued that the therapeutic use of off-label medications should not be permitted in the clinical practice. The use of off-label medications in the clinical practice without a full disclosure raises many complex ethical and legal concerns. Some of the key ethical issues to be highlighted include the impact on an autonomous decision of the patient and the arguments for and against the informed consent for off-label use. Also, concerns surrounding the clinical implications, the challenged position of FDA, and the reasons for FDA policies for off-label use. By continuing to prescribe off-label drugs deceptively, dermatologists may not only jeopardize the trust of their patients but may also be faced with increasing litigation for professional misconduct.

1.3 Purpose of the Study:

(1) To determine the risk factors for using unlicensed and off-label medications in Dermatology (2) To study the ethical and legal considerations when using unlicensed and off-label medications in Dermatology (3) To compare the results of studies performed in different settings worldwide and identify common therapeutics areas to allow for focused intervention because off-label drug use can be a measure of the lack of knowledge concerning dermatological treatments.

1.4 Research Question:

How common and what are the ethical and legal issues of using unlicensed and off-label drugs in dermatology worldwide?
1.5 Significance of the Study:

To determine the main risk factors of most unlicensed and off-label medications used in treatment of dermatological diseases worldwide and to make a detailed examination of ethical and legal trends, patterns, preventive methods, possible solutions and recommendations associated with using unlicensed and off-label drugs in dermatology.

1.6 Institutional Framework:

Royal College of Surgeons University in Ireland.

Chapter 2.0
Methodology:

2.1 Material and methods:

In March 2015, a comprehensive and highly sensitive electronic literature search strategy of the large biomedical databases was conducted including Pubmed, Medline, EMBASE, Cochrane Library, CINAHL, Scopus, TRIP (Turning Research into Practice), Web of Knowledge (Science & Social Science), Justis and Hastings Center with the following search terms: unlicensed drugs, off-label drugs, dermatology, prescriptions, ethics, legal issues and legislation. A hand search was conducted in abstracts from relevant conferences from major dermatological societies.

The search was limited to (i) Human data; (ii) Articles written in English and (iii) Articles published after the first year included on the searching databases. All types of epidemiological studies regarding unlicensed and off-label medication use in dermatology were included. Reviews and case reports were excluded.

Two independent reviewers examined the title and abstract of the articles obtained in the first search to recognize relevant studies and extracted data. Full texts of all studies meeting the inclusion criteria were reviewed, and their bibliographic references were checked for additional sources. The articles upon whose relevance both reviewers agreed were included in the analysis. The variables assessed were as follows: the type of study, sample size, instruments used, statistical analysis and results.
2.2 Methodological Limitations:

**Lack of available and reliable data**: a lack of data or reliable data will likely lead to limit the scope of analysis, the size of sample or it can be a significant obstacle to finding a trend and a meaningful relationship.

**Lack of prior research studies on the topic**: citing prior research studies forms the basis of the literature review and helps lay a foundation for understanding the research problem that are investigated. This limitation can serve as an important opportunity to describe the need for further researches.

**Measure used to collect the data**: sometimes it is the case that, after completing my interpretation of the findings, I discover that the way in which I had gathered data inhibited my ability to conduct a thorough analysis of the results.

2.3 Limitations of the Researcher:

**Access**: if a study depends on having access to database, organizations, or documents and, for whatever reason, access is denied or otherwise limited, it can affect the results of the study and the reasons for this need to be described in the study.

**Time limitation**: the time available to investigate a research problem is constrained by the due date of the research submission.

**Cultural and other types of bias**: we all have biases, whether we are conscious of them or not. Bias is when a person, place, or thing is viewed or shown in a consistently inaccurate way. It is usually negative though one can have a positive bias as well. So, if the author detects bias in prior research, he/she must be acknowledged and explain what measures were taken to avoid perpetuating prejudice.
Chapter 3.0

Results:

Ten epidemiological studies regarding the use of unlicensed drugs and off-label drugs in dermatology was identified and summarized in Table 1. The selected studies were between the year 1994 and 2014.

Of the ten studies, 3 included pediatric patients with dermatologic diseases. Six studies were performed in the USA while only four studies occurred in Europe countries.

Table 3.1: Studies related to ethically and legally implications of off-label drugs in dermatology.

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Title</th>
</tr>
</thead>
<tbody>
<tr>
<td>Torres</td>
<td>1994</td>
<td>The use of FDA-approved medications for unlabeled (off-label) uses. The legal and ethical implications</td>
</tr>
<tr>
<td>Sugarman</td>
<td>2002</td>
<td>Off-label prescribing in the treatment of dermatologic disease</td>
</tr>
<tr>
<td>Picard</td>
<td>2003</td>
<td>Assessment off-label prescribing in Dermatology</td>
</tr>
<tr>
<td>Blondon</td>
<td>2008</td>
<td>Off-label prescribing</td>
</tr>
<tr>
<td>Parikh</td>
<td>2014</td>
<td>Common use of prescription off-label acne therapy in children younger than 12 years old</td>
</tr>
<tr>
<td>Kelly</td>
<td>2012</td>
<td>Ethics in pediatric dermatology</td>
</tr>
<tr>
<td>Silva</td>
<td>2014</td>
<td>Off-label prescribing for allergic diseases in children</td>
</tr>
<tr>
<td>Cristopher</td>
<td>2012</td>
<td>Ten common questions and their answers about off-label drug use</td>
</tr>
<tr>
<td>Danes</td>
<td>2014</td>
<td>Outcomes of off-label drug use in hospitals: a multicentric prospective study</td>
</tr>
<tr>
<td>Largent</td>
<td>2009</td>
<td>Going off-label without venturing off-course: evidence and ethical off-label prescribing</td>
</tr>
</tbody>
</table>

Altogether, these studies promote the concept of Off-label drug use can be motivated by several factors. First, a medication may not have been studied and approved for a particular population (e.g., pediatric, geriatric, or pregnant
Second, a life-threatening or terminal medical condition may motivate a health care professional to give any treatment that is logical and available, whether approved by the FDA or not. Third, if one medication from a class of drugs has FDA approval, physicians commonly use other medications in the same category without specific FDA approval for that use for the same indication. Besides, if the pathologic or physiologic features of 2 conditions are similar, a physician may use a medication approved for 1 of these conditions for both (e.g., eczema and psoriasis).

Picard et al. (2003) assessed off-label prescribing in Dermatology because of the official policy of the French National Health Insurance system is to deny reimbursement for drugs prescribed for off-label indications. The objectives of their study were 1) to quantify the use of off-label prescriptions by physicians from a hospital department of dermatology in France; 2) to characterize these off-label prescriptions; 3) to assess data from the literature on the appropriateness of these off-label prescriptions. They depended on the symptom or the disease that was treated and the type of prescription were recorded on standard forms for each patient consulting between February 1 and April 1, 2001.

They found eighty-six percent of prescriptions were labeled, 14% were off-labeled. Inflammatory and hypersensitivity dermatoses were the most frequent indications of off-label prescriptions (26%). Treatments which most frequently corresponded to off-label prescriptions were topical corticosteroids and methotrexate. Examination of the literature showed that 70% of the off-label prescriptions were not based on strong data from evidence-based-medicine. Many off-label prescriptions were made by the most graduate physicians.

Their study showed a considerable number of off-label prescriptions in dermatology. These prescriptions were often related to rare diseases that were managed by senior dermatologists. These off-label prescriptions were rarely in agreement with data from evidence-based-medicine.

Sugarman et al. stated that it is a common practice for physicians to treat dermatologic conditions with medications that are not indicated for the specific condition being treated. These "off-label" prescriptions are often for drugs that have both well accepted the therapeutic value in the medical community and proven efficacy on the basis of results of clinical trials. The purpose of his study was to quantify the use of off-label prescriptions for a dermatologic disease by a representative sample of physicians in the United States. Data from the 1990-
1997 National Ambulatory Medical Care Survey, performed by the National Center for Health Statistics were used to assess medications prescribed at office visits for dermatologic disease. They identified the most common diagnoses listed at office visits in which the primary and only diagnosis listed was dermatologic. For the leading ten dermatologic conditions for which medications are indicated, we categorized each primary drug mention by indication. He and his colleagues found that the range of off-label prescribing varied from 17% to 73%, with a weighted mean (+/- SD) of 32% +/- 18%. The conditions most frequently managed with off-label prescriptions were acne rosacea (73%) and actinic keratosis (52%), whereas those with the fewest off-label prescriptions were atopic dermatitis (17%) and psoriasis (16%). The use of off-label prescriptions by dermatologists in the diseases studied ranged from 7% to 73% with a weighted mean (+/- SD) of 24% (+/- 24%), whereas the range for non-dermatologists was 18% to 96% with a weighted mean (+/- SD) of 34% (+/- 18%).

They concluded that Off-label prescribing was common in the management of dermatologic conditions. Also, it is currently within the standard of care to use off-label prescriptions in the treatment of dermatologic disease.

In a study by Danes et al., a multi-centric prospective cohort study was carried out on 226 patients in five tertiary hospitals from May 2011 to May 2012. Information on clinical characteristics of patients, drugs, outcomes and costs was collected. Patients were followed up for 6 months, and information was assessed by reviewing clinical records and interviewing physicians. The study aimed to assess the clinical evidence, outcome and cost of off-label use of medicines in the hospital setting.

The median (interquartile range (IQR)) age of patients was 46 (33-62) years; 59% were women. Patients had received a median of three previous treatments, and a lack of response (or suboptimal) was the primary reason for off-label use (72.1%). A total of 232 off-label medicines were administered for 102 different indications. The most frequent medicines were rituximab (49; 21.1 %), botulinum toxin (25; 10.7 %) and omalizumab (14; 6.0 %). In 117 (51.8 %) cases, the level of clinical evidence for their use was low. A partial clinical response was observed in 82 patients (36.3 %), complete response in 71 (31.4 %) and stabilization in 11 (4.9 %). A total of 58 (26.5 %) patients had adverse effects, which in 11 (4.9 %) were severe. The median (IQR) cost per patient was 2,943.07 Euro (541.9-5,872.54).
The authors concluded that there was a high variability of off-label medicines and indications. Although the clinical evidence of off-label medicines was often low, clinical response was observed in many patients with previous multiple treatment failures, but at the expense of some adverse effects and a high cost. Registers of patients would be helpful for clinical decisions although clinical trials are needed.

Blondon et al. (2008) explored that off-label prescribing and unlicensed drug use are common in all fields of medicine and may be encountered in therapeutic guidelines. The term does not imply improper nor illegal use, and may provide the only available treatment for "orphan" conditions, or for certain populations (children, pregnant women, very old patients). Off-label drug use should be based on sound scientific evidence of efficacy and safety. In Switzerland, patients need to be informed that health insurance coverage is not guaranteed with off-label use. The prescribing physician bears the responsibility of off-label use with the possibility of unanticipated risks, and should, therefore be prepared for possible malpractice suits.

Largent et al. (2009) commented on several previous articles have addressed the appropriateness of off-label prescribing and the attendant ethical and professional obligations. Though useful, these accounts have distinctive limitations. They treat the phenomenon of off-label prescribing as monolithic and require rigorous informed consent for all situations; they address issues related to off-label prescribing at a particular institutional level, such as the hospital formulary, limiting their applicability to diverse practice environments; or they address off-label prescribing at a regulatory level, which does not attend to immediate ethical concerns. Practicing physicians need a comprehensive and workable ethical framework that prioritizes scrutiny of off-label prescribing and links the certainty of net benefit to physician responsibilities. These issues have gained even greater importance following the recent issuance by the FDA of revised “Good Reprint Practices.”

This formal guidance permits pharmaceutical companies to encourage off-label use by distributing peer reviewed articles relating to off-label use of their drugs. Besides, a November 2008 rules change made Medicare coverage automatic for a wider array of off-label uses of cancer drugs. New medications reaching the market, aggressive marketing of off-label uses to patients as well as to physicians, patient expectations that doctors will do "something," and concerns
regarding rising health care costs underscore the importance of practical
guidance for physicians.

They concluded that off-label use is an important area of practice in which
evidence gaps should trigger more reflection and scrutiny. Four characteristics
of off-label use signal to physicians the need for a higher level of control: new
drugs, novel off-label uses, drugs with known serious adverse effects, and high-
cost drugs. By classifying off-label uses as supported, suppositional, or
investigational, this conceptual framework grounds recommendations for
prescribing practices in a judgment of the strength of the evidence for net health
benefit. This elevates the role of evidence in the otherwise unregulated realm of
off-label prescribing and will help physicians in exercising their responsibility for
applying evidence in practice in a rigorous fashion.

Torres (1994) stated that physicians increasingly use Food and Drug
Administration (FDA)-approved drugs (medication) for unlabeled (off-label)
indications. The ethical and legal implications of these actions are not always
clear.

One prescribes a drug in the hope that medication will benefit the person to
whom it is given. Every drug has the potential to cause effects on the body that
can be beneficial or adverse. Adverse reactions can range in seriousness from
relatively mild to fatal.1 One estimate showed that adverse drug reactions
handle 1.0% to 3.5% of admissions to medical wards. One government
estimate showed that 130 000 US hospital-based deaths per year were caused
by adverse drug reactions. These adverse reactions can occur with proper use
(idiosyncratic) or because of improper drug use. As a result, no drug can be
considered absolutely safe.

In his article, he examined the common law and federal statutory regulations
concerning this issue and also explore some of the ethical and financial matters
involved.

To assure safety to US consumers, Congress established the Federal Food,
Drug and Cosmetic Act (FDCA), requiring new drug products to demonstrate
safety and effectiveness for their indications. The FDA administers the FDCA
and must determine whether a drug is safe and efficient. The FDA regulations
as they relate to the FDCA have led to requirements for relatively long and
exhaustive animal and human testing with difficult testing procedures. This
process keeps most dangerous and useless drugs off the market but results in
approximately 4000 drugs being rejected for every one that makes it. In practical terms, the cost of discovering and developing a new drug in the USA can exceed $75 million, and the time required to advance a drug from an investigational status to approval by the FDA could consume up to 10 years. This in turn, has resulted in some US physicians using FDA-approved purposes. “Whatever the initial cause, prescriptions are written for unlabeled purposes because of discussions by doctors and reports in the medical literature and thus some unlabeled uses become widespread before the new uses are approved by the FDA. This use of FDA-approved drugs for unlabeled (off-label) purposes raises many legal and ethical questions. Physicians need to be knowledgeable in this area.

On the other hand, Diana Silva, Ignacio Ansotegui and Mário Morais-Almeida (2014) discussed Off-label prescribing for allergic diseases in children. They recognized that a high percentage of prescriptions performed for allergy treatment in daily clinical practice were off label. The clinicians struggle on a daily basis with the responsibility to balance risk-benefits of an off-label prescription while involving the patients and their families in this decision. It is crucial to increasing awareness of this reality not only for the clinician but also to the global organizations and competent authorities. New measures for surveillance of off-label use should be established, namely through population databases implementation. There is a need for new proposal to correct the inconsistency between the priorities for pediatric drug research, frequently dependent on commercial motivations, in order to comply with the true needs of the children, especially on the respiratory and allergy fields.

The majority of drugs prescribed have not been tested for children and safety and efficacy of children’s medicines are frequently supported by the low quality of evidence. In Europe, the percentage of authorized medicines for children is 33.3%. This is explained by the lack of clinical research in this population, caused by ethical, scientific and technical issues, but also commercial priorities. Therefore, most of the therapies prescribed to children are on an off-label or unlicensed basis.

Global legislation and regulatory efforts have been done to overpass these limitations aiming to produce proper research in the pediatric population, promoted by an International Conference on Harmonization (ICH) guidelines for clinical investigation of medicinal products in the pediatric population. Since 1997, the Food and Drug Administration (FDA) in the United States of America (US) produced several regulation/legislation initiatives (Pediatric Rule
Regulation, 1998; Best Pharmaceutical for Children Act, 2002 and Pediatric Research Equity Act, 2003). In Europe (EU), followed by US experiences, new regulations were implemented since January 2007. In both continents the measures were taken enclosed financial incentives to the industry, the addition of 6 months extra patent protection and an additional two years market exclusivity for orphan medicines. Furthermore, World Health Organization (WHO) adopted in 2007 the WHA60.20 Resolution “Better Medicines for Children” to undertake activities in the interest of improving pediatric medicines research, regulation and rational. One of the most important was the establishment of the Model List of Essential Medicines for Children, now in its 4th version. However, major discrepancies between drug prescription patterns in children and the drugs granted pediatric exclusivity still exists. Looking back to the last 5 years of the Pediatric Regulation from the European Medical Agency (EMA) [Regulation(EC) N°1901/2006], 600 pediatric investigation plans (PIP) were performed, of those 453 referred to not yet authorized drugs, while the remaining related to new indications. However, no specific therapeutic area was addressed more than the other, and as far as Pneumology and Allergology are considered, they only accounted for 4% of PIP. At the same time, 30% of the prescribed drugs for children are for the respiratory system. This suggests that pediatric studies still do not address the real need in pediatric drug development despite an overall increase of medicines now available for children. Most of the drugs available on the market, especially those considered for the treatment of allergic diseases, are still not specifically tested in children, particularly in the younger ones.

In a joint initiative, the European Academy of Allergology and Clinical Immunology (EAACI), the EU-funded network of excellence, the Global Allergy and Asthma European Network (GA2LEN), the European Dermatology Forum (EDF) and the World Allergy Organization (WAO) published a guideline for urticaria management. In it was recommended as the first line treatment for urticaria the use of oral anti-histamines in an up-dosing step up therapy until up to 4 times the dose. These new recommendations were also advised for children, adjusting the dose accordingly to the weight. Recent randomized, double-blind, placebo-controlled trials in adults support the efficacy and safety of this up-dosing use, namely in cold contact urticaria. Nevertheless, due to the absence of controlled trials in children, these changes were not updated in the SPC of the anti-histamines in the market and as stated above only a few of them were actually studied for their long term effects in children. This explains why a large portion of the off-label type of use when considering anti-histamines is due to a different dose prescription. For chronic disease, it is also important not only efficacy and safety but also compliance with the treatment. Children
pediatric formulations, namely under six years of age, are usually liquid and it is necessary to make them stable, sterile, pleasant and long lasting. Furthermore, as children grow, drug doses should be adapted to weight and, to avoid dosing errors, the means to deliver accurate doses of these liquid formulations need to be available. In atopic dermatitis, antihistamines also are considered as a potential benefit to reducing pruritus, and although no evidence exists to support their role in the treatment they can be useful in reducing this disturbing symptom in children.

Accordingly to the most recently published guidelines for atopic dermatitis the main treatment is skin hydration, topical anti-inflammatory medications and antipruritic therapy. For anti-inflammatory medication, topical corticosteroids or topical calcineurin inhibitors are used. For topical corticosteroids, numerous substances are available, grouped by potency. Potent and very potent corticosteroids (Group III and IV) are more likely to cause systemic or local side effects (like adrenal suppression, skin atrophy or striae) than group I (mild) and II (moderate strength); therefore the first should be avoided for treatment in infants, whose higher surface area to body weight ratio and age-dependent maturation of the skin barrier function leaves them vulnerable to overdosing. According to the FDA, use of these products is also limited by age and duration of treatment. Still and especially from birth to 4 years old, topical corticosteroids were prescribed off-label in 13% of all prescriptions, of those 58% due to high dosage use. Recent guidelines recommend that for mild disease activity, a small amount of topical corticosteroids twice to thrice weekly until reaching a mean monthly dose of 15 grams in infants, 30 g in children and up to 60 to 90 g in adolescents and adults.

Nowadays new topical anti-inflammatory alternatives include calcineurin inhibitors and fourth generation corticosteroids. These fourth generation corticosteroids, like methylprednisolone aceponate, seem to have a favorable benefit-risk-ratio in this age group. Regarding topical immunomodulators, calcineurin inhibitors, like tacrolimus and pimecrolimus, as they don’t cause skin atrophy, are favored for long-term management and to be used in delicate body areas, such as the eyelid region, the perioral skin, genital area, the axilla or the inguinal fold. As a result of the immunosuppressant activity of these drugs, there are concerns about their potential to promote skin infections and malignancies, particularly lymphomas, following long-term treatment. These drugs are only approved for children with more than two years of age by FDA and EMA. Due to the high prevalence of atopic dermatitis in children, which begins in over 60% of cases during the first year of life, usually affects more sensitive skin areas and have a higher body surface/volume ratio that enhances
the risk of systemic exposure to corticosteroids, it was seen an increase of use of topical calcineurin inhibitors. Off-label use, particularly in infants in the US, reached a high prevalence of prescriptions in 2004, approximately 525,000 (14% of yearly prescriptions) for pimecrolimus and 69,000 (7%) for tacrolimus. This led FDA to include a black box warning in 2005, changed to a box warning in 2006, on the labels of topical tacrolimus and pimecrolimus. Still, a further discussion has occurred and even with large epidemiological data, at the current time, FDA maintains that may be “a possibility of an association”. However, guidelines recommend clinicians to use tacrolimus ointment, especially for eczema on the face, eyelid, and skin folds that are unresponsive to low-potency topical steroids in children older than two years. Other systemic drugs for atopic dermatitis treatment also recommended off-label in children and adolescents is cyclosporine, however only reserved for the most severe and refractory to classical treatment and usually demanding specialized care.

While Parikh and his colleagues (2014) wrote about the common use of prescription off-label acne therapy in children younger than 12 years old in the USA. Acne is occurring more frequently in younger age groups, but most available treatments are considered off-label in small children. As the epidemiology of acne has changed to include younger children over the past 20 years, neither regulators, pharmaceutical companies, nor clinicians have understood the need or value of obtaining regulatory sanctions for problems physicians have managed using clinical judgment. The objective of the study was to analyze the frequency of off-label acne treatment according to age and other demographic factors. They searched the National Ambulatory Medical Care Survey from 1993 to 2010 for visits in children younger than 12 years of age for the diagnosis of International Classification of Diseases, Ninth Revision, code 706.1. They tabulated leading acne treatments and assessed factors associated with off-label prescribing. Off-label but appropriate acne treatments were used in 29% of acne visits for children younger than 12 years of age. Dermatologists were more likely than pediatricians to prescribe off-label treatment (p < 0.001). The most frequently used off-label treatments were topical retinoids, followed by oral antibiotics. There was no significant trend in the rate of off-label prescribing over time (p = 0.40). Off-label treatment is well within the standard of care for young children with acne. More data on the use of topical retinoids in small children will improve our understanding of their use, which may help optimize treatment outcomes for children with acne.

Kelly and his colleagues (2012) wrote about ethics in pediatric dermatology and raised the concept of the patient-parent-physician relationship is central to
studying medical ethics in pediatric dermatology. The rights of children in medical decision making are ambiguous, and parents and physicians will often override the autonomy of a child when a particular treatment is deemed to be in the child's best interest. The use of physical restraint to enforce a treatment should be justified, and a reasonable attempt should be made to ensure the cooperation of the child, if possible. Medical photography is central to the practice of pediatric dermatology in that it allows for serial observation of cutaneous lesions over time. Established guidelines and standards should be followed. They identified that pediatric Dermatologists frequently prescribe medications off-label; if following established professional standards, and prescribing with real intention, off-label prescribing can be appropriate and rational.

Christopher W., Christopher B. and William L. (2012) from Mayo Clinic, USA tried to answer the common ten questions about off-label drug use. Their article introduced and answered ten questions regarding off-label drug use (OLDU) in an effort to clarify the practice's meaning, a breadth of application, acceptance, and liabilities. OLDU is a polarizing term because it can be associated with great benefit or harm to patients. In addition, OLDU, along with allegations of pharmaceutical company promotion of OLDU, has been the cause of major lawsuits and historically large out-of-court legal settlements. Therefore, all health care professionals have likely heard the term OLDU used, yet they propose that many have an under-appreciation of its definition, prevalence, and implications.

Chapter 4.0
Discussion:

The term off-label drug use (OLDU) is used extensively in the medical literature, continuing medical education exercises, and the media but many health care professionals have an under-appreciation of its definition, prevalence, and implications. This article introduces and determines the main risk factors of most unlicensed and off-label medications used in treatment of dermatological diseases worldwide and to make a detailed examination of ethical and legal trends, patterns, preventive methods, possible solutions and recommendations associated with using unlicensed and off-label drugs in dermatology.
Off-label drug use involves prescribing medications for indications, or using a dosage or dosage form, which have not been approved by the US Food and Drug Administration. Since the Food and Drug Administration does not regulate the practice of medicine, OLDU has become common. It occurs in every specialty of medicine, but it may be more common in areas of medicine in which the patient population is less likely to be included in clinical trials (e.g., pediatric, pregnant, or psychiatric patients) or for external use like in dermatology. 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. Besides, health care professionals should educate themselves about OLDU to weigh the risks and benefits and provide the best possible care for their patients.

Chapter 5.0

The Stages of Drug Development, Review and Prescribing

5.1 The Stages of Drug Development and Review:

The path a drug travels from a lab to a medicine cabinet is usually long and every drug takes a unique route, this explains why a limited number of medications are approved on-label by FDA.

Common problems include unexpected safety issues that crop up or failure to demonstrate a drug's effectiveness. A sponsor may need to conduct additional studies--perhaps studies of more people, different types of persons, or for a longer period of time. Manufacturing issues are also among the reasons that approval may be delayed or denied. Drugs must be manufactured in accordance with standards called good manufacturing practices, and the FDA inspects manufacturing facilities before a drug can be approved. If a facility is not ready for inspection, approval can be delayed. Any manufacturing deficiencies found a need to be corrected before approval.

Investigational New Drug Application (IND)--The pharmaceutical industry sometimes seeks advice from the FDA prior to submission of an IND.

1- Animal tested

Sponsors--companies, research institutions, and other organizations that take responsibility for developing a drug. They must show the FDA results of preclinical testing in laboratory animals and what they propose to do for human
trials. At this stage, the FDA decides whether it is reasonably safe for the company to move forward with testing the drug in humans.

2- **IND Application**

Clinical Trials--Drug studies in humans can begin only after an IND is reviewed by the FDA and a local institutional review board (IRB). The board is a panel of scientists and non-scientists in hospitals and research institutions that oversee clinical research.

IRBs approve the clinical trial protocols, which describe the type of people who may participate in the clinical trial, the schedule of tests and procedures, the medications and dosages to be studied, the length of the study, the study's objectives and other details. IRBs make sure the study is acceptable, that participants have given consent and are fully informed of their risks and that researchers take appropriate steps to protect patients from harm.

3- **Phase 1 Clinical Trial**

Phase 1 studies are usually conducted in healthy volunteers. The goal here is to determine what the drug's most frequent side effects are and, often, how the drug is metabolized and excreted. The number of subjects typically ranges from 20 to 80.

4- **Phase 2 Clinical Trial**

Phase 2 studies begin if Phase 1 studies do not reveal unacceptable toxicity. While the emphasis in Phase 1 is on safety, the emphasis in Phase 2 is on effectiveness. This phase aims to obtain preliminary data on whether the drug works in people who have a certain disease or condition. For controlled trials, patients receiving the drug are compared with similar patients receiving a different treatment--usually an inactive substance (placebo), or a different drug. Safety continues to be evaluated, and short-term side effects are studied. Typically, the number of subjects in Phase 2 studies ranges from a few dozen to about 300.

5- **Phase 3 Clinical Trial**

At the end of Phase 2, the FDA and sponsors try to come to an agreement on how large-scale studies in Phase 3 should be done. How often the FDA meets with a sponsor varies, but this is one of two most common meeting points prior to submission of a new drug application. The other most common time is pre-NDA--right before a new drug application is submitted.
Phase 3 studies begin if evidence of effectiveness is shown in Phase 2. These studies gather more information about safety and efficacy, studying different populations and different dosages and using the drug in combination with other drugs. The number of subjects usually ranges from several hundred to about 3,000 people.

6- **Review Meeting**

Post-market requirement and commitment studies are required of or agreed to by a sponsor, and are conducted after the FDA has approved a product for marketing. The FDA uses post-market requirement and commitment studies to gather additional information about a product's safety, efficacy, or optimal use.

7- **NDA Application**

New Drug Application (NDA) -- This is the formal step a drug sponsor takes to ask that the FDA consider approving a new drug for marketing in the United States. An NDA includes all animal and human data and analyzes of the data, as well as information about how the drug behaves in the body and how it is manufactured.

8- **Application Reviewed**

When an NDA comes in, the FDA has 60 days to decide whether to file it so that it can be reviewed. The FDA can refuse to file an application that is incomplete. For example, some required studies may be missing. In accordance with the Prescription Drug User Fee Act (PDUFA), the FDA's Center for Drug Evaluation and Research (CDER) expects to review and act on at least 90 percent of NDAs for standard drugs no later than 10 months after the applications are received. The review goal is six months for priority drugs.

5.2 **Drug Prescription:**

5.2.1 **Who are allowed to write a medical prescription (on-label or even off-label drug)?** To answer this question, read the following:

A prescriber is a healthcare professional who can write a prescription. This applies to both hospital prescriptions and private prescriptions.

Appropriate practitioners can be: independent prescribers and supplementary prescribers.
5.2.2 Independent Prescribers

Independent Prescribers are healthcare professionals who are responsible for: assessing patient’s health and making clinical decisions about how to manage the condition, including prescribing medication.

They include: doctors, such as GP or a hospital physician, dentists, who may prescribe medication to treat a condition affecting your teeth, nurse, pharmacist (independent prescriber, who can prescribe any medicine for any medical condition within their competence, including some controlled medicines (except diamorphine, cocaine and dipipanone for the treatment of addiction)) and optometrist (independent prescriber, who can prescribe any medicine for conditions that affect the eye and surrounding tissue, but cannot prescribe any controlled medicines independently).

5.2.3 Supplementary prescribers

Supplementary prescribers are responsible for continuing health care after an independent prescriber has assessed a patient’s health. They work with the independent prescriber to fulfill a clinical management plan agreed between the prescribers and the patient.

Supplementary prescribers include: nurses/midwives, pharmacists, podiatrists (foot care specialists), physiotherapists (healthcare professionals who use physical techniques, such as massage and manipulation, to promote healing), diagnostic and therapeutic radiographers (specialists in using medical imaging techniques, such as X-rays), optometrists (healthcare professionals who examine eyes, test sight, prescribe and dispense glasses and contact lenses)

A supplementary prescriber can prescribe any medicine, including controlled medicines, for any condition within their competence under the agreed clinical management plan. For example, GP (an independent prescriber) may assess a condition such as chronic obstructive pulmonary disease (COPD) and refer you to a specialist physiotherapist (a supplementary prescriber) to manage your long-term care. The physiotherapist will be able to prescribe medicines, such as inhalers, under a clinical management plan.
Chapter 6.0

Some examples of using off-label drug in Dermatology:

Off-label medications seem to be commonly prescribed in clinical practice in dermatology and differs between countries, inpatient and outpatient settings and age. To know how using off-label drug is very common in dermatology, these are some examples:

In view of their unique mechanism of action, topical retinoids are prescribed widely in dermatology for both indicated purposes and several worthwhile, evidence-based off-label uses. For seasoned clinicians, prescribing medications off-label can be efficacious and even practical. A recent study evaluating off-label prescribing in treating dermatologic disease concluded that it is currently within the standard of care to use off-label prescriptions in treating dermatologic disease (Sugarman, Fleischer, & Feldman, 2002). However, practitioners who prescribe, dispense, or administer medications for an off-label use should have a full understanding of the rationale for such use, as well as any potential legal liabilities (Keltz, 2003)

Clinicians should consider using a topical retinoid for first-line management for acne treatment (Wolf, 2002). It reverses thickening of the stratum corneum and the abnormal desquamation of keratinocytes (Verschoore et al., 1993). Acne therapy with retinoids can be frustrating in the beginning. An exacerbation of acne often occurs in the first 2 to 4 weeks of therapy as the follicular epithelium is loosening. Fortunately, by the end of the 2nd month, a significant improvement with the acne (Prystowsky, 2001) and remission of irritation is typically noted. To enhance compliance, the patient should be aware of these expected sequelae.

Topical retinoids are often used off-label for treating actinic keratosis (AKs/pre-cancers) and actinic lentigines (freckles) in view of the ability to decrease melanogenesis, its antiproliferative effect, antipromoter effect, and prodifferentiation effect (Goldfarb, 2000). Although the actual number of solar lentigines may not change with adapalene, improvement of discrete pigmentation and significant color reduction occurs (Goldfarb, 2000). Topical tretinoin decreases the number of AKs on the face by approximately 50% when used as monotherapy over a minimum of 6 months (Prystowsky, 2001). Topical tretinoin effectively treats photodamage. Human studies have found tretinoin to be noncarcinogenic and can prevent the formation of UV-induced lesions (Baumann, 2003). Since topical tretinoin's ability to normalize the differentiation of dysplastic epithelium in AKs, it can be considered for chemoprevention in
patients at high risk of basal or squamous cell carcinomas (Prystowsky, 2001). Retinoids provide an alternative for patients with significant photodamage who have no objections to off-label usage, who might be at risk for AKs, and who are looking for a gentle therapy (Goldfarb, 2000).

Transplant recipients are a unique subset of people for whom the sequelae of sun damage are even more hazardous. Within 5 years of immunosuppression, 40% of transplant recipients experience premalignant skin tumors such as AKs and Bowen’s disease, as well as skin cancers such as squamous cell carcinoma (SCC) and basal cell carcinomas (Stockfleth, Ulrich, Meyer, & Christophers, 2002). Early, preventative treatment could halt the development of invasive SCC (Euvrard, 2000). Topical retinoids can provide an often-favorable alternative to cryotherapy, and other destructive regimens, in persons with multiple lesions (Stockfleth et al., 2002).

Chemopreventative treatment with retinoids has been studied in patients with oropharyngeal carcinoma. The mechanism of action of vitamin A modulates growth and differentiation of cells, and vitamin A deficiency enhances susceptibility to carcinogenesis. Side effects of topical use have been minimal. Suppression of oral leukoplakias has been noted with the direct application of retinoic acid. Treatment may be justified in those patients with recurrent and persistent lesions that may otherwise progress (Gorsky & Epstein, 2002).

Rosacea is a common, multifactorial, multiphasic, inflammatory skin disease in which chronic flushing and blushing results in permanently dilated blood vessels (telangiectasias). Although there is no known cure, rosacea can be managed and controlled with medication (Bergfeld, 1999). Many first-line treatments have been refractory to this condition. In a comparison study regarding the efficacy of topical tretinoin and low-dose oral isotretinoin in rosacea, low-dose oral isotretinoin and topical tretinoin cream appear to be beneficial in treating severe or recalcitrant rosacea (Ertl, Levine, & Klingman, 1994). Systemic medications are not without risk. If possible, the risk of systemic side effects should be minimized. Recent clinical research suggests that topical tretinoin minimizes the manifestations of papular-pustular rosacea within a relatively short treatment duration (Bergfeld, 1999). Topical retinoids have often been considered controversial as a treatment for rosacea because of the associated increased redness, burning, and peeling of the skin. This irritation, however, has been typically temporary. According to a recent literature review, in addition to the traditional avoidance of triggers along with topical and oral antibiotic therapy, current effective treatment now also includes both topical and oral retinoid therapy, topical vitamin C therapy, and cosmetic surgery (Cohen & Tiemstra, 2002).
Human papillomavirus (HPV) infections are widespread and cause a plethora of benign clinical lesions on the skin and mucous membranes (Fitzpatrick et al., 1997). Topical retinoic acid has shown moderate, favorable results for treating verruca plantaris and verruca plana (Verschoore, 1993). Topical tretinoin is often beneficial when treating facial verruca. As dermatology practitioners, we have noticed that treatment of facial verruca with tretinoin is less irritative and is comparatively efficacious to imiquimod (Aldara).

Increased epidermal proliferation and new collagen formation contribute to the improvement of hypertrophic scars, keloids, and acne scars (Verschoore, 1993). In an open-label, multicenter, prospective study, topical tretinoin 0.1% significantly improved the clinical appearance of pregnancy-induced stretch marks (Rangel, Arias, Garcia, & Lopez-Padilla, 2001). Striae originating from weight gain or endocrine-related disorders could likewise benefit from the use of topical retinoid therapy.

Lichen planus (LP) is an acute or chronic inflammatory dermatosis involving skin and/or mucous membranes. Topical retinoic acid (tretinoin) is an effective maintenance therapy for cutaneous lichen planus and can contribute to preventing recurrence (Verschoore, 1993). This is most likely due to the increased epidermal proliferation and collagen-forming activities of topical retinoids. The rationale for using tazarotene in oral lichen planus (OLP) is its regulatory action on the growth and differentiation of keratinocytes and on inflammation (Petruzzi et al., 2002). Compared to control, topical tazarotene showed a significant reduction of lesions and remote transitory side effects (burning sensations and taste abnormalities). Topical tazarotene may provide a valuable therapeutic tool in treating hyperkeratotic oral lichen planus (Petruzzi et al., 2002).

Melasma is an acquired light or dark brown hyperpigmentation that rapidly evolves. It is limited to sun-exposed areas, most often on the face. Genetic predisposition, solar UV radiation, hormones, and several drugs have been identified as notable factors in the pathogenesis of melasma. Treatment consists of sun protection, 4% hydroquinone cream twice daily, with adjunctive tretinoin 0.05% to 0.1% cream at bedtime. Sunbathing is contraindicated since this can result in the reversal of months of topical therapy. Tretinoin is reasonably well tolerated and increases the efficacy of hydroquinone (Pathak, Fitzpatrick, & Kraus, 1986). Patients with dermal melasma do not respond well to hydroquinone and tretinoin. The best therapy results are obtained in those presenting with epidermal or mixed melasma (Pathak et al., 1986). Wood's lamp examination is helpful to differentiate melasma involvement in skin
phototypes I to IV and accentuates epidermal melasma, not dermal melasma. It is of no value in skin phototypes V and VI (McMichael, 2003).

Darier’s disease is a rare, noncurable, genodermatosis affecting approximately 1 in 55,000 people (English, 2000). This disease is often associated with disfiguring, symmetrical, generalized pruritic cutaneous eruptions occurring in the seborrheic areas that can be malodorous, often detrimental to the self-esteem and quality of life of these individuals. Retinoids (oral and topical) are effective for treating Darier’s disease; however, the mechanism of action is not known (English, 2000). Oral retinoids are the most effective treatment but are associated with troublesome side effects (Cooper & Burge, 2003). Case studies have reported favorable success regarding the use of tazarotene gel and adapalene gel for this disorder (English, 2000).

Pretreatment of skin with all-trans retinoic acid (tretinoin) can enhance wound healing. Histological effects of tretinoin demonstrate compaction of the stratum corneum, epidermal acanthosis with correction of atypia, an increase in small vessels, and increased cellularity in the upper dermis. Tretinoin dramatically accelerates wound healing in a photodamaged skin (Popp, Klingman, & Stoudemayer, 1995). Pretreatment of skin with topical tretinoin may be beneficial in reducing healing times of patients undergoing electroepilation (Anthony, Miller, & Dinehart, 1991). Pretreatment with topical all-trans retinoic acid (tretinoin) has also reversed impaired wound healing in genetically diabetic mice (Kitano, Yoshimura, Uchida, Sato, & Harii, 2001).

The employment of topical retinoids in wound healing is flourishing. Retinoic acid reverses the inhibitory effects of glucocorticoids on wound healing and expedites the formation of healthy granulation tissue. Pretreatment with tretinoin prior to epidermal injuries such as chemical peeling and dermabrasion accelerates wound healing. Short-contact tretinoin therapy is a novel modality for treating chronic ulcers and stimulating granulation tissue formation (Paquette, Badiavas, & Falanga, 2001). A comparison of tretinoin, adapalene, and collagenase in an experimental model of wound healing concluded that tretinoin and adapalene contributed to the wound healing process resulting in an enhancement of collagen production, angiogenesis, and granulation tissue formation (Basak et al., 2002).

Granular parakeratosis is a rare, acquired dermatosis characterized by keratotic papules, located in intertriginous regions. A recent case report demonstrated rapid clearance of such lesions to the axilla, with topical administration of tretinoin (Brown & Heilman, 2002).
This is a condition that consists of a primary extraskeletal bone formation that arises within the skin. Local application of tretinoin decreases the number of papules over the face in those patients suffering from this condition. Response time varies from a few weeks to 6 months. Tretinoin cream can be considered in treating multiple mililiary osteoma cutis of the face, especially when dealing with small and superficial lesions (Cohen, Chetov, Cagnano, Naimer, & Vardy, 2001).

Patients with alopecia areata can have patchy or confluent hair loss on the scalp and/or body. Treatment options are tailored to the severity of the disease, including either irritants/immunogens or local/systemic immunosuppressives (Olsen, 2003). Combination therapy is often used. Beneficial treatment outcomes, using topical tretinoin for hair growth disorders, have been reported (Hass & Arndt, 1986). Safety and efficacy of 0.05% tretinoin and adjunctive intralesional triamcinolone were evaluated for treating alopecia areata. Topical tretinoin appeared to enhance the hair growth producing effect of the intralesional triamcinolone. Tretinoin helps to normalize cell differentiation, and the familiar retinoid dermatitis may contribute to the stimulation of hair growth by creating an immune response. Topical tretinoin coupled with topical minoxidil has also shown promising results in treating alopecia areata.

Wat H. and Dytoc M. (2014) researched to provide evidence-based clinical guidelines for the off-label use of topical vitamin D in the treatment of dermatologic disease. Topical vitamin D is approved by the US Food and Drug Administration for the treatment of psoriasis but is also used off-label in the management of a variety of cutaneous diseases despite a lack of evidence-based guidelines.

They found that a moderate to strong recommendation was given for the use of topical vitamin D in combination with corticosteroids and phototherapy in vitiligo and as monotherapy for various ichthyoses, morphea, pityriasis alba, prurigo nodularis, and polymorphous light eruption. There is evidence showing that topical vitamin D is ineffective in the treatment of actinic keratosis, seborrheic keratosis, lichen planus, seborrheic dermatitis, alopecia areata, chemotherapy-induced alopecia, and hypertrophic scars.

They concluded from their study that topical vitamin D analogues have a significant role in the off-label treatment of dermatologic disease, but higher quality studies are still required.
Table 6.1: A listing of some drugs and their unlabeled indications:

These listings were compiled from the USPDI8 and AHFS1 Drug Information

<table>
<thead>
<tr>
<th>Drug</th>
<th>Unlabeled Use Relevant to Dermatology</th>
<th>Approved Dermatologic Indications include</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acyclovir</td>
<td>Laser resurfacing, prophylaxis Chemical peel Wire-brush surgery</td>
<td>Herpes genitalis, simplex &amp; zoster prophylaxis Varicella – treatment</td>
</tr>
<tr>
<td>Azelaic acid</td>
<td>Melasma caused by hyperfunctioning melanocytes</td>
<td>Acne vulgaris – mild to moderate</td>
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<tr>
<td>Cimetidine</td>
<td>Urticaria, acute in combination with an antihistamine Warts</td>
<td></td>
</tr>
<tr>
<td>Clindamycin topical</td>
<td>Eczema, infected Folliculitis caused by S. aureus.</td>
<td>Impetigo, localized caused by S. aureus and beta-hemolytic streptococci, including S. pyogenes</td>
</tr>
<tr>
<td>Clofazimine</td>
<td>Has Orphan Drug status for: Leprosy, lepromatous (Hansen’s disease) Leprosy, dapsone resistant</td>
<td></td>
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<tr>
<td>Corticosteroids</td>
<td>Pemphigoid Sarcoid, localized</td>
<td>Many inflammatory diseases are listed as</td>
</tr>
<tr>
<td>Medicine</td>
<td>Conditions</td>
<td>Remarks</td>
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<tr>
<td>-----------------</td>
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<tr>
<td>Cyclosporine</td>
<td>Atopic dermatitis, Pyoderma gangrenosum</td>
<td>Transplant rejection – prophylaxis &amp; treatment</td>
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<td></td>
<td></td>
<td>Psoriasis, chronic severe</td>
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<td>WHEN under the care of a qualified, suitably</td>
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<td>equipped specialist.</td>
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<td></td>
<td>Actinomycotic mycetoma, Cicatricial pemphigoid</td>
<td>Leprosy (Hansen’s disease) in combination with</td>
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<tr>
<td>Dapsone</td>
<td>– desquamative gingival lesions</td>
<td>other agents</td>
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<tr>
<td></td>
<td>Dermatosis, subcorneal pustular Granuloma</td>
<td>Dermatitis herpetiformis</td>
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<td>annulare</td>
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<td></td>
<td>Lupus erythematosus, systemic – certain skin</td>
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<td>lesions</td>
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<td></td>
<td>Pemphigoid lesions with oral manifestations</td>
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<td></td>
<td>Polychondritis, relapsing</td>
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<tr>
<td></td>
<td>Pyoderma gangrenosum</td>
<td></td>
</tr>
<tr>
<td>Estrogen +</td>
<td>Acne in females</td>
<td>Acne in females (approved in Canada)</td>
</tr>
<tr>
<td>Cyproterone</td>
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<tr>
<td>Estrogen +</td>
<td>Hirsutism</td>
<td>Acne in females also needing contraception</td>
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<tr>
<td>Progestin</td>
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<tr>
<td>Isotretinoin</td>
<td>Acne, less severe than nodular</td>
<td>Acne vulgaris – severe recalcitrant nodular</td>
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<td>Folliculitis Fordyce disease</td>
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<td>Severe rosacea including nodulocystic rosacea</td>
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<td>and</td>
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<tr>
<td>Drug</td>
<td>Conditions</td>
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<tr>
<td>Methotrexate</td>
<td>Dermatomyositis, systemic (polymyositis) Sarcoid Vasculitis</td>
<td></td>
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<tr>
<td></td>
<td>Mycosis fungoides, advanced Numerous cancerous conditions Psoriasis, severe, resistant, recalcitrant, disabling</td>
<td></td>
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<tr>
<td>Mupirocin</td>
<td>Eczema, infected Folliculitis, localized caused by S. aureus Skin infections, minor</td>
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<td>Impetigo, localized caused by S. aureus and beta-hemolytic streptococci, including S. pyogenes</td>
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<tr>
<td>Nitroglycerin</td>
<td>Anal fissures ?? Hemorrhoids ??</td>
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<tr>
<td>Sulfasalazine</td>
<td>Psoriasis</td>
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<tr>
<td>Thalidomide</td>
<td>Has Orphan Drug classification for: Aphthous ulcers, in the terminally immunocompromised Graft v’s host disease Kaposi’s sarcoma Leprosy, reactional lepromatous Lupus erythematosus, cutaneous</td>
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<tr>
<td></td>
<td>Erythema nodosum leprosum</td>
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<tr>
<td>Mycobacterial infection</td>
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| Tretinoin (retinoic acid, vitamin A acid) | Actinic keratoses hands & arms  
Disorders of keratinization such as keratosis follicularis  
Icthyosis congenita & vulgaris Melasma  
Post-inflammatory facial hyperpigmentation  
Verruca plana. | Acne vulgaris  
Hyperpigmentation, mottled, facial due to photoaging  
Skin roughness, facial, due to photoaging  
Wrinkling, fine facial, due to photoaging |
| Trimethoprim | Acne  
Pneumonia, Pneumocystis carinii (in the US) | Pneumonia, Pneumocystis carinii in Canada but not in the US. |

6.1 Adverse drug reactions and off-label (unlicensed) medicines:

Bellis et al. tested a hypothesis that off-label and unlicensed drug (OLUL) status is a risk factor for adverse drug reactions (ADRs). Off-label and unlicensed (OLUL) prescribing has been prevalent in pediatric practice. They used data from a prospective cohort study of adverse drug reactions (ADRs) among pediatric inpatients. A nested case–control study was conducted within a prospective cohort study. They concluded that off-label and unlicensed medicines are more likely to be implicated in an adverse drug reactions (ADR) than authorized medicines. The number of drugs administered is a risk factor for ADRs highlighting the need to use the lowest number of medicines, at the lowest dose for the shortest period, with continual vigilance by prescribers, in order to reduce the risk of ADRs.
Chapter 7.0

Ethical Issues

7.1 Full informed consent:

Informed consent is the process by which the treating health care provider discloses appropriate information to a competent patient so that the patient may make a voluntary choice to accept or refuse treatment. (Appelbaum, 2007). It originates from the legal and ethical right the patient has to direct what happens to her body and from the ethical duty of the physician to involve the patient in her health care.

The most important goal of informed consent is that the patient has an opportunity to be an informed participant in her health care decisions. It is generally accepted that informed consent includes a discussion of the following elements:

- The nature of the decision/procedure
- Reasonable alternatives to the proposed intervention
- The relevant risks, benefits, and uncertainties related to each alternative
- Assessment of patient understanding
- The acceptance of the intervention by the patient

In order for the patient's consent to be valid, she must be considered competent to make the decision at hand and her consent must be voluntary. It is easy for coercive situations to arise in medicine. Patients often feel powerless and vulnerable. To encourage voluntariness, the physician can make clear to the patient that he/she is participating in a decision-making process, not merely signing a form. With this understanding, the informed consent process should be seen as an invitation for the patient to participate in health care decisions. The physician is also generally obligated to provide a recommendation and share his reasoning process with the patient. Comprehension on the part of the patient is equally as important as the information provided. Consequently, the discussion should be carried on in layperson's terms and the patient's understanding should be assessed along the way.

Basic or simple consent entails letting the patient know what a physician would like to do; giving basic information about the procedure and ensuring that the patient assents or consents to the intervention. Assent refers to a patient’s willing acceptance of treatment, intervention or clinical care. Basic consent is
appropriate, for example, when drawing blood in a patient who has given blood before. Sometimes consent to the procedure is implied (e.g. the patient came in to have blood drawn), but an explanation of the elements of the procedure remain necessary. Decisions that merit this sort of basic informed consent process require a low level of patient involvement because there is a high-level of community consensus that the treatment being offered is the only or best option and/or there is low risk involved in the management. If a patient does not consent under the paradigm of basic consent, then a fuller informed consent discussion is warranted.

7.1.1 Information for patients about the license for their medicines:

General Medical Council (GMC) in UK determines what sorts of information must be given to patients (or their parents or carers) about the medicines that are proposed to prescribe to allow patients to make an informed decision.

Some medicines are routinely used outside the terms of their license. In emergencies or where there is no realistic alternative treatment and such information is likely to cause distress, it may not be practical or necessary to draw attention to the license. In other cases, where prescribing unlicensed medicines is supported by authoritative clinical guidance, it may be sufficient to describe in general terms why the medicine is not licensed for the proposed use or patient population. Doctors must always answer questions from patients (or their parents or carers) about medicines fully and honestly.

If doctors intend to prescribe unlicensed medicines where that is not routine or if there are suitably licensed alternatives available, doctors should explain this to the patient, and their reasons for doing so.

Doctors should be careful about using medical devices for purposes for which they were not intended.

7.1.2 Which sorts of interventions require informed consent?

All health care interventions require some kind of consent by the patient, following a discussion of the procedure with a health care provider. Patients fill out a general consent form when they are admitted or receive treatment from a health care institution. Most medical institutions have policies that state which health interventions require a signed consent form. For example, surgery, anesthesia, and other invasive procedures are usually in this category. These
signed forms are the culmination of a dialogue required to foster the patient's informed participation in the clinical decision.

For a broad range of decisions, explicit written consent is neither required nor needed, but some meaningful discussion is always needed. For instance, a man contemplating having a tumor marker S100 screen for malignant Melanoma (skin cancer) should know the relevant arguments for and against this screening test, discussed in lay terms.

Does the use of off-label drugs require a higher standard of informed consent?

7.1.3 How much information is considered "adequate"?

How does the patient know when provided enough information about a proposed intervention? Most of the literature and law in this area suggest one of three approaches:

Reasonable physician standard: what would a typical physician say about this intervention? This standard allows the physician to determine what information is appropriate to disclose. However, this standard is often inadequate, since most research shows that the typical physician tells the patient very little. This standard is also generally considered inconsistent with the goals of informed consent, as the focus is on the doctor rather than on what the patient needs to know.

Reasonable patient standard: what would the average patient need to know in order to be an informed participant in the decision? This standard focuses on considering what a typical patient would need to know in order to understand the decision at hand.

Subjective standard: what would this particular patient need to know and understand in order to make an informed decision? This standard is the most challenging to incorporate into practice since it requires tailoring information to each patient.

Most states have legislation or legal cases that determine the required standard for informed consent. The best approach to the question of how much information is enough is one that meets both your professional obligation to provide the best care and respects the patient as a person, with the right to a voice in health care decisions.
7.1.4 Exceptions to fully informed consent:

If the patient does not have decision-making capacity, such as a person with dementia, in which case a proxy, or surrogate decision-maker, must be found.

A lack of decision-making capacity with inadequate time to find an appropriate proxy without harming the patient, such as a life-threatening emergency where the patient is not conscious

When a competent patient designates a trusted loved one to make treatment decisions for him or her. In some cultures, family members make treatment decisions on behalf of their loved ones. Provided the patient consents to this arrangement and is assured that any questions about his/her medical care will be answered, the physician may seek consent from a family member instead of the patient. In some jurisdictions like Ireland nobody can consent on behalf of another person over the age of 18 (Appelbaum, 2007).

In most cases, it is clear whether or not patients have the capacity to make their own decisions. Occasionally, it is not so clear. Patients are under an unusual amount of stress during illness and can experience anxiety, fear, and depression. The stress associated with illness should not necessarily preclude one from participating in one's own care. However, precautions should be taken to ensure the patient does have the capacity to make good decisions. There are several different standards of decision-making capabilities. Generally the physician should assess the patient's ability to:

- Understand his or her situation,
- Understand the risks associated with the decision at hand, and
- Communicate a decision based on that understanding.

When this is unclear, a psychiatric consultation can be helpful. Of course, just because a patient refuses a treatment does not in itself mean the patient is incompetent. Competent patients have the right to refuse treatment, even those treatments that may be life-saving. Treatment refusal may, however, be an indication that it is necessary to pause to discuss further the patient's beliefs and to understand about the decision.

A patient's decision-making capacity is variable as their medications or underlying disease processes ebb and flow. Doctors should do what they can to catch a patient in a lucid state - even lightening up on the medications if necessary and safe - in order to include her in the decision-making process. Delirious patients have waxing and waning abilities to understand information.
However, if a careful assessment is done and documented at each contact, and during lucid periods the patient consistently and persistently makes the same decision over time, this may constitute adequate decisional capacity for the question at hand.

If the patient is determined to be incapacitated/incompetent to make health care decisions, a surrogate decision maker must speak for her. There is a specific hierarchy of appropriate decision makers defined by state law (DNR Orders during Anesthesia and Urgent Procedures, Washington State Medical Association). (What laws are you referring to) If no appropriate surrogate decision maker is available, the physicians are expected to act in the best interest of the patient until a surrogate is found or appointed. In rare circumstances, when no surrogate can be identified, a guardian ad litem may have to be appointed by the court. Confer with social work and risk management if doctors have trouble finding a legal surrogate for the patient.

7.1.5 Informed consent for children:

Children do not have the decision-making capacity to provide informed consent. Since consent, by definition, is given for an intervention for oneself, parents cannot provide informed consent on behalf of their children. Instead, they can provide informed permission for treatment. For older children and adolescents, assent should always be sought in addition to the authorization of legal surrogates. Adolescents and mature minors are legally and ethically authorized to provide informed consent if they are emancipated, and in many states, including Washington, they may provide consent for matters regarding sexual and reproductive health, mental health, and substance abuse.

The primary responsibility of the physician is the well-being of the child. Therefore, if the parental decision places the child at risk of harm, then further action may be indicated. When there are differences in opinion between the parents and physicians that cannot be resolved ethics consultation may be pursued, and legal avenues may be pursued when all other means have failed. Children should be included in decision-making at a developmentally appropriate level and assent should be sought when possible.
7.1.6 Informed consent in emergency situations:

The patient's consent should only be "presumed," rather than obtained, in emergency situations when the patient is unconscious or incompetent and no surrogate decision maker is available and the emergency interventions will prevent death or disability. In general, the patient's presence in the hospital ward, ICU or clinic does not represent implied consent to all treatment and procedures. The patient's wishes and values may be quite different from the values of the physician. While the principle of respect for person obligates you to do your best to include the patient in the health care decisions that affect patient's life and body, the principle of beneficence may require physician to act on the patient's behalf when patient's life is at stake.

7.2 Patient Autonomy

Once a drug has been approved by the FDA for one purpose, a physician can prescribe that drug for any purpose. The practice of prescribing a drug for a purpose other than that for which it is approved is known as "off-label" use. Off-label use is legal and does not necessarily mean that the drug is being used inappropriately (Gazarian, M., et al., 2006). In fact, many physicians prescribe a drug off-label because they believe it is the best treatment for a particular condition even though it has not yet been formally tested for use in that status (Meadows, W.A. and Hollowell, B.D., 2008). Off-label use becomes an ethical, not a legal, issue when the principle of informed consent is introduced.

The concept of informed consent as it is currently understood arose in response to the many medical research abuses of the middle half of the twentieth century from the mid 1930s through the mid 1970s in Nazi Germany and the United States. Simply put, informed consent demands that patients give their consent to any treatment or research protocol that a clinician proposes. The "informed" part of the term forces us to ask: how much information must patients receive in order to be able to give "informed" consent? (Zain, M., 2012).

Informed consent is a principle that is observed to ensure that patient autonomy is preserved, requiring that competent patients be made aware of and understand enough about the intended benefits and possible risks of proposed treatment to make an informed decision (Veatch, R.C., 1997). This consent can be implied by the patient's lack of protest, and, in the case of many routine medical interventions. The FDA requires explicit written consent for drugs being used experimentally or as a part of research, but no explicit consent is required.
for any off-label drug use if it can be argued that, like any other treatment, the drug is being used in the patient’s best interests (Committee on Drugs, 2002).

On the other hand, some people argue that off-label use is not be requiring an informed consent. One may wonder why, even though the ethical and legal principles of informed consent and shared decision-making are not being upheld, off-label use has become so prevalent in the daily practice of medicine. The lack of scientific support for most drug use of this type should serve to heighten these concerns. Some contend, however, that there are logical reasons not to inform patients of a drug’s off-label status and instances in which off-label use is actually beneficial (Zain, M., 2012).

The most commonly used defense of off-label drug use is that acquiring FDA approval for all uses is not economically feasible. This is especially true in pediatric care, in which three-fourths of prescription drugs are used off-label (Gazarian, M., et al., 2006). It is not cost-effective for pharmaceutical companies to get drugs reapproved for children or for other uses (Committee on Drugs, 2002). Once a drug is determined to be safe and efficient for one use, the pharmaceutical industry relies on the off-label market to expand its sales potential.

7.3 Relationship between doctors and drugs companies:

A majority of physicians don’t consider it unethical to accept such gifts as reception of pens, pen-stand, pads, calendars, drug samples, company funded lunch or dinner etc at which company's products are favorably mentioned. However, acceptance of expensive gifts of recreational value rather than professional activities is unethical according to them. Also, they concur not to support medical products of drug companies whose medical representatives furnish biased or self-serving information regarding their products. Even among those doctors who claim that they only prescribe medicines that are most beneficial to their patients irrespective of the fact that they are constantly visited and pressurized by pharmaceutical companies to prescribe their brands only - a substantial body of evidence suggests otherwise. Because when a gift is given, it imposes on a doctor a scene of indebtedness. As an upright man instructed in the art of healing, he may feel inclined to reciprocate resulting in shoddy prescriptions.

As a consequence of the relationship between doctors and drug companies, the credibility of the medical profession in the eyes of the patients and the public is ever on the decline. If a patient gets to know that the doctor is prescribing drug
or medical advice on the basis of commercial influence he may lose trust and confidence in the doctor (which are the precursors to any successful treatment). In such a scenario, patients are more likely than doctors to believe that gifts may influence prescribing behavior that is morally inappropriate according to them.

Medicine is a noble profession. The primary aim of the medical profession is to render service to humanity. Financial gain is a subordinate consideration. However, it has been observed globally that health care practitioners in conjunction with pharmaceutical companies are prescribing and thereby promoting unnecessary drugs just for the sake of monetary gains. This article reviews the salient aspects of the relationship between doctors and drugs companies and its future consequences.

The interaction between doctors and medical representatives is almost as old as the medical profession itself. The basic role of a medical representative is to apprise the doctor about his company's products including the drugs. There is nothing wrong in that as long as the ultimate beneficiary of this information is the patient. After all, continued professional development is an essential component of a good health care system. Even the Medical Council of India expects that every registered medical practitioner should try to upgrade his knowledge and skill for the betterment of his patients.

Unfortunately, there is often a conflict between the interests of the patient and those of the doctors as far as the drug promotion is concerned. WHO defines drugs promotion as all informational and persuasive activities by manufacturers, distributors to induce /influence the sale and use of medicinal drugs. Drug promotion has an important bearing on the rational use of a drug; on drug -price control mechanism; on equity of drug distribution - all making it a central public health issue. Often, drug promotion strategies adopted by various pharmaceutical companies are too attractive to be resisted by a doctor. This, in turn, places the interest of the doctors ahead that of the patients. Doctors, who are frequently in contact with medical representatives, are more likely to prescribe newer and expensive drugs of their favorite pharmaceutical companies to achieve their selfish end i.e. to receive more and more financial gain from the companies as cutbacks. In our country, the doctors are held in high esteem by the gullible patients. They are considered second to 'Gods' by most patients. Therefore, doctors may prescribe expensive drugs of their favorite pharmaceutical companies with scant regard for the expense borne by the poor patients. Interaction between drug companies and doctors are pervasive. Relationships of doctors with drug companies begin when they are just medical students attending the various clinical OPD’s and wards, continue
during internship and residency training, and persist throughout their professional careers.

7.3.1 The Nature and Effect of the Relationships:

The drug companies interact with doctors in order to promote their medical products. They reach out to almost all concerned doctors to attain their goals. The doctors are compensated adequately in the form of gifts and other incentives to drug companies. Consequentially, both the parties are benefited from this interaction with potential consequences for patients. Few doctors may be morally so stout that they continue to prescribe those medicines that appear to be most beneficial as well as economical to their patients despite being in contact with so many drug companies. The aggressive marketing strategies by the companies just act as tools of information for them. However, the prescribing behavior of a vast majority of the medical community is palpably influenced by pharmaceutical companies. Many physicians believe that their interactions with drug companies have educational value for themselves and also provide benefits for patients, because physicians are kept informed about available therapeutic agents and the poor patients can be given free drug samples provided by different companies. Some physicians contend that they themselves are invulnerable to any bias as a result of interaction with drug companies.

There is a growing consensus among doctors that prescribing more expensive brands of reputed companies of which the quality is assured is far better than prescribing cheaper brands of unknown quality. This may be one of the reasons behind such shoddy prescriptions. However, this cannot be generalized. It is an open secret that the professional associations depend solely on pharmaceutical companies to sponsor their medical programs, CME's, Conferences, Annual Meeting, Workshops, “etc”. Many junior, as well as senior physicians, seek sponsorships or financial aids from these companies to attend national as well as International Conferences. Even pleasure-trips within the country and abroad for a few heavyweight doctors and their immediate family members are arranged and funded by some pharmaceutical companies. The doctors, in turn, tend to reciprocate by prescribing medical products of these firms in blatant disregard to patient’s welfare. In one study, it was found that there are many different ways by which drug companies relate directly or indirectly to doctors. These range from the seemingly trivial (e.g., the ubiquitous dispensing of gifts such as pens and writing pads with drug names inscribed) to the much more fascinating gifts (e.g., the ghost writing of articles for teaching faculty, the

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payment of large sums in cash to prominent physicians who extol the virtues of company products and the support of lavish trips and entertainment for doctors who commonly prescribe company products).

It is being realized more now than ever before that the interaction between doctors and drug companies should be contained within acceptable boundaries. It would be impracticable to ask the medical professionals to distance themselves from pharmaceutical companies. The real challenge for the medical profession, drug companies and the government is to formulate mutually acceptable guidelines to avoid certain egregiously unethical medical practice. The ultimate arbiter of this malpractice is, of course the medical profession itself. It is for them to decide whether or not to accept the proffered information and gifts from drug companies. For that, medical students should be exposed to the marketing strategies of pharmaceutical companies and the methods to counter them. During MBBS course, the students should be instructed not to depend on drug companies for their professional advancement. As the doctors posted in rural or remote areas are supposedly not aware of the latest trends in medical practice, they depend on the drug companies for product information. This problem can be obviated if more and more CME's are conducted in those areas by registered medical association so that they can keep pace with emerging medical technology. Professional associations should also strive hard to generate funds so that they can conduct their scientific programs independently. Mushrooming of drug companies is also responsible for this unethical medical practice. Since, one pharmaceutical company in order to surpass another company brings out the same drug at much cheaper price, compromising the quality of the drug. If the retail price and the quality of the drug are regulated and standardized by the Government. The unethical practice of drug companies can be put in check. However, before that we have to understand the dynamics of Indian drug bazaar that involves not only the doctors and the drug companies but also the go-in-betweens like a chemist and medical representatives, “etc”. However then, all said and done, the only pragmatic approach to dealing with this unethical practice is for doctors not to accept anything of financial value from drug companies. Till date apart from the American Medical Association and others, the Indian Medical Association has also expressed its concern over it and made an appeal to the medical community not to accept expensive gifts from pharmaceutical companies.

In summary, Ethical issues surrounding the threat to patient autonomy, informed consent and the impact on the physician-patient relationship and physician-drug company relationship are some of the main ethical concerns to
be raised when using off-label medications in dermatology. Although eliminating off-label use is unfeasible, preventing them from being used deceptively is imperative based on the numerous ethical issues discussed.

Chapter 8.0
Legal Issue:

8.1 Regulations of off-label use in various countries

8.1.1 United States

In the United States, no law prohibits a physician or other healthcare practitioner from prescribing an approved medication for other uses than their specific FDA-approved indications.[citation needed] Pharmaceutical companies are not allowed to promote a drug for any other purpose without formal FDA approval. Marketing information for the drug will list one or more indications, that is, illnesses or medical conditions for which the drug has been shown to be both safe and efficient.

However, once a drug has been approved for sale for one purpose, physicians are free to prescribe it for any other purpose that in their professional judgment is both safe and effective, and are not limited to official, FDA-approved indications. This off-label prescribing is most commonly done with older, generic medications that have found new uses but have not had the formal and often costly applications and studies required by the FDA to formally approve the drug for these new indications. However, there is often extensive medical literature to support the off-label use.

A leading example of how regulatory agencies approach off-label use is provided by the United States Food and Drug Administration (FDA)'s Center for Drug Evaluation and Research, which reviews a company's New Drug Application (NDA) for clinical trial data to see if the results support the drug for a specific use or indication. If satisfied that the drug is safe and effective, the drug's manufacturer and the FDA agree on specific language describing dosage, route of administration, and other information to be included on the drug's label. More detail is included in the drug's package insert.

The FDA approves a drug for prescription use, and continues to regulate the pharmaceutical industry's promotional practices for that drug through the work of the Office of Prescription Drug Promotion (OPDP, formerly the Division of Drug Marketing, Advertisement and Communication (DDMAC). The FDA does
not have the legal authority to regulate the practice of the medicine, and the physician may prescribe a drug off-label. Contrary to popular notion, it is legal in the United States and in many other countries to use drugs off-label, including controlled substances such as opiates. Actiq, for example, is commonly prescribed off-label even though it is a Schedule II controlled substance. While it would be legal for a physician to decide independently to prescribe a drug such as Actiq off-label, it is illegal for the company to promote off-label uses to prescribers. In fact, Cephalon, the maker of Actiq, was fined for illegal promotion of the drug in September 2008. Under the Food, Drug, and Cosmetic Act (FDCA) at U.S.C. 21 §§301-97, manufacturers are prohibited from directly marketing a drug for a use other than the FDA-approved indication. However, in December of 2012, the United States Second Circuit Court found that promotion of off-label uses by a company sales representative was considered to be protected speech per the First Amendment. In addition, The Food and Drug Administration Modernization Act of 1997 created an exception to the prohibition of off-label marketing, allowing manufacturers to provide medical practitioners with publications on off-label uses of a drug, in response to an unsolicited request. In 2004, the federal government and whistleblower David Franklin reached a $430 million settlement in Franklin v. Parke-Davis to resolve claims that Warner-Lambert engaged in off-label promotion of Neurontin in violation of the FDCA and the False Claims Act. At the time, the settlement was one of the largest recoveries against a pharmaceutical company in U.S. history, and the first off-label promotion settlement in U.S. history.

8.1.2 United Kingdom

Physicians in the United Kingdom can prescribe medications off-label. According to the British General Medical Council, off-label prescriptions must better serve patient needs than alternatives and must be supported by evidence or experience to demonstrate safety and efficacy.

8.1.2.1 Prescribing guidance: the guidelines on prescribing medicines by GMC

General Medical Council (GMC) in the UK (2013) puts guidelines to regulate prescribing medications:

1. In Good medical practice:
Doctors must keep up to date with, and follow, the law, our guidance and other regulations relevant to their work. Doctors must recognize and work within the limits of their competence. In providing clinical care, doctors must:

a. Prescribe drugs or treatment, including repeat prescriptions, only when doctors have adequate knowledge of the patient’s health and are satisfied that the drugs or treatment serve the patient’s needs.

b. Provide effective treatments based on the best available evidence

c. Check the care or treatment provided for each patient is compatible with any other treatments the patient is receiving, including (where possible) self-prescribed over-the-counter medications.

Doctors must make a good use of the resources available to the patients. Documents that doctors make (including clinical records) to formally record their work must be clear, accurate and legible. Doctors should make records at the same time as the events are recording or as soon as possible afterwards.

Clinical records should include:

a. Relevant clinical findings.

b. The decisions made, actions agreed and who is making the decisions and agreeing the actions.

c. The information given to patients.

d. Any drugs prescribed or other investigation or treatment requested.

e. Who is making the record and when?

2. This guidance provides more detailed advice on how to comply with these principles when prescribing and managing medicines and medical devices, including appliances.

3. Doctors are responsible for the prescriptions they sign and their decisions and actions when they supply and administer drugs and devices or authorize or instruct others to do so. Doctors must be prepared to explain and justify their decisions and actions when prescribing, administering and managing medicines.

4. 'Prescribing' is used to describe many related activities, including prescribing medicines, devices and dressings on the NHS and advising patients on the purchase of over the counter medicines and other remedies. It may also be
used to describe written information provided for patients (information
prescriptions) or advice given. While some of this guidance is particularly
relevant to prescription only medicines, doctors should follow it in relation to the
other activities undertook, so far as it is relevant and applicable. This guidance
applies to medical devices as well as to medicines.

5. Serious or persistent failure to follow this guidance will put doctors
registration at risk.

8.1.2.2 General Medical Council (GMC) regulations for prescribing
unlicensed medicines

Healthcare professionals should usually prescribe licensed medicines in
accordance with the terms of their license. However, healthcare professionals
may prescribe unlicensed medicines, on the basis of an assessment of the
individual patient, that it is necessary to do so to meet the particular needs of
the patient.

Prescribing unlicensed medicines may be required where:

a. No suitably licensed medicine that will meet the patient’s need. Examples
   include (but are not limited to) where:

   i) There is no licensed medicine applicable to the particular patient. For
      example, if the patient is a child and a medicine licensed only for adult patients
      would meet the needs of the child; or

   ii) A medicine licensed to treat a condition or symptom in children would
       nonetheless not meet the specifically assessed needs of the particular child
       patient, but a medicine licensed for the same condition or symptom in adults
       would do so; or

   iii) The dosage specified for a licensed medicine would not meet the patient’s
       need; or

   iv) The patient needs a medicine in a formulation that is not specified in an
       applicable license, or

b. A suitably licensed medicine that would meet the patient’s need is not
   available. This may arise where, for example, there is a temporary shortage in
   supply; or

   c. The prescribing forms are part of a properly approved research project.
When prescribing an unlicensed medicine, doctors must:

a. Be satisfied that there is sufficient evidence or experience of using the medicine to demonstrate its safety and efficacy

b. Take responsibility for prescribing the medicine and for overseeing the patient’s care, monitoring and any follow-up treatment or ensure that arrangements are made for another suitable doctor to do so.

c. Make a clear, accurate and legible record of all medicines prescribed where not following a common practice and reasons for prescribing an unlicensed medicine.

8.2 Do Physicians Expose Themselves to Legal Vulnerability for Including OLDUs in Their Clinical Practices, Particularly if the Patient Experiences an Adverse Reaction Related to an OLDU?

Physicians have been involved in legal claims due to an adverse reaction related to a medication prescribed for an off-label use. The legal theories used in these lawsuits include the unregulated use of a research drug, failure to provide adequate informed consent for an OLDU and medical negligence. In developing legal precedents for off-label therapies, the courts have typically treated medicines and devices as coequals. As such, many of the tribunals' views on OLDU have evolved from decisions regarding off-label uses of medical devices.

8.3 Research vs. Practice

The FDA makes it clear that it does not regulate the practice of medicine and that the Federal Food, Drug, and Cosmetic Act of 1938 will not play a role in creating physician liability for OLDU. However, the FDA requires stringent review before drugs and medical devices be involved in research to ensure that steps are taken to protect properly human study participants. When not classified as tools involved in research, medications can be prescribed and medical devices can be used in an off-label manner without FDA regulatory oversight. Regarding this point, during its evaluation of possible harm arising from placement of an orthopedic spine medical device, an Ohio appellate court stated that “the off-label use of a medical device is merely a matter of medical judgment and, as such, subjects a physician to professional liability for exercising professional medical judgment, but off-label use of a medical device
is not barred by the U.S. Food and Drug Administration”. By way of legal precedent and similar FDA regulatory processes, the same standard would apply to OLDU.

Drawing a clear line of demarcation between a drug's use in research vs. practice can often be difficult. Prescribing a drug in a new and yet untested manner does not alone brand it as an interest of research. The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research has attempted to define whether a drug's use might be classified as a practice or research tool, and their definitions follow. The goal of medical practice is to “provide diagnosis, preventative treatment or therapy”. Research, on the other hand, is “designed to test a hypothesis, permit conclusions to be drawn, and thereby to develop or contribute to generalizable knowledge”. When not deemed research, legal claims brought solely on the basis of failure to gain adequate FDA approval before prescribing an off-label drug will likely be struck down. However, physicians may not be sheltered from other forms of liability theories.

8.4 Medical Malpractice:

8.4.1 Medical Malpractice: Informed Consent

No court decision to date has mandated that a physician must disclose, through an informed consent process, the off-label use of a drug. Two arguments are often voiced by those who oppose any routine requirement for disclosure: (1) disclosure may unduly frighten patients and (2) the extensive burden placed on physicians to constantly review and communicate medication risk and benefit information may divert attention away from other more important patient care issues.

Perhaps the most cited modern legal case involving the medical informed consent process is Canterbury v Spence. The Canterbury Court held that “the test for determining whether a particular peril must be divulged is its materiality to the patient's decision”. A material risk is one in which “a reasonable person, in what the physician knows or should know to be the patient's position, would be likely to attach significance to the risk or cluster of risks in deciding whether or not to forego the proposed therapy”.

Many courts have not considered OLDU to be an independent material issue requiring disclosure during the consent process. A 1996 Ohio court held that off-label use of medical devices was a “matter of medical judgment”. According
to the court, physicians may be subject to professional liability for medical negligence involving OLDU but will not be held liable for nondisclosure.

The results of a 2006 nationwide poll on the public's view of OLDU may precipitate concerns for future court challenges not fully appreciated by previous legal opinion. Half of the poll's respondents falsely believed that a drug could be prescribed only for its primary FDA-approved use. An almost similar percentage felt that physicians should be prohibited from prescribing drugs for off-label use. Nearly two-thirds of those responding felt that except for use in clinical trials, OLDU should be completely banned. This is a remarkable aggregate response given that a considerable fraction of those responding negatively to OLDU had likely benefited from the practice at some point in their lives (although they were probably unaware).

Although many courts do not require physicians to disclose OLDU, patients may have a different belief and concern regarding their use. Whether these matters will develop into a greater expectation for adequate disclosure remains unknown. Some physicians have suggested that providing patients with information about OLDU may afford greater protection from future liability suits.

8.4.2 Medical Malpractice: Negligence

Medical malpractice is a broad term that includes the action of negligence. In fact, 4 elements of tort law dealing with negligence must be proved before liability can be found to exist: (1) the prescribing physician must have a duty to the patient, (2) that duty must be breached, (3) there must be some injury requiring compensation, and (4) there must be a causal link between the breech and that injury.

A physician's duty of care is defined as the same degree of care provided by other physicians practicing under similar circumstances. Use of off-label medication alone does not result in liability under negligence standards. When a patient believes that he or she was harmed by an off-label use of a drug, it must be established that the prescribing physician deviated from the standard of practice.38 Because the FDA prohibits manufacturers from sponsoring physician education for off-label use of their medications, physicians may find it difficult to establish how others in their field are using medications outside their FDA-approved uses. As peer-reviewed published evidence focusing on a drug's off-label use grows over time, new standards of practice involving the off-label use of a drug begin to develop.
To help determine whether the standards of practice are being met when prescribing medications for OLDU, physicians should first ask themselves several questions: (1) Does the native drug have FDA approval? (2) Has the off-label use been subjected to substantial peer review? (3) Is the off-label use medically necessary for treatment? (4) Is the use of the medication non-experimental? To mitigate the risk of liability, physicians should always prescribe off-label drugs in “good faith, in the best interest of the patient, and without fraudulent intent”. This 3-pronged approach to prescribing medications will also ensure that the tenets of the FDA's requirement are met; specifically, physicians prescribing medications for off-label use should “be well informed about the product, to base its use on firm scientific rationale and on sound medical evidence, and to maintain records of the product’s use and effects”.

8.5 Practical implications:

FDA-approved drugs for off-label indications, and unlabeled drug uses, have played a significant role in the way in which we treat skin disease. A good example is the use of thalidomide to treat the cutaneous manifestations of erythema nodosum leprosum, first reported in 1965, recommended by the WHO in 1988 and finally approved by the FDA in September 1997 (Thalidomide. Skin Therapy Letter 1997).

If the unlabeled use of a drug is for treatment rather than research, this constitutes innovative therapy and appears to be within the physician’s ethical and legal prerogative supported by FDA regulations, common law, and ethical cannons (Torres, A., 1994). Although the off-label use of a drug is not necessarily an improper use of the drug, there is no regulatory body approved information on risk/benefit available. In this situation, the prescriber has to utilize consultation with colleagues, plus information gained from the package insert and a review of the medical literature (Shapiro, S.A., 1979). The ethical and legal implications of this situation are not always clear. Although no specific informed consent appears to be required, unlabeled drug use best serves the patient and protects the physician from liability when it is accompanied by informed consent that adequately informs the patient of the innovative nature of the therapy together with the greater uncertainty of risk (Torres, A., 1994). As recent well-known cases have shown, extra care must be taken to ensure that the physician and the patient are both well-informed of the risks and benefits, so their collaboration can result in the best possible clinical outcome (Reardon, F., 1997).
Ultimately, regardless of the legality of unlabeled drug use, if an approved drug is used for unlabeled purposes, a physician should carefully weigh the risk/benefit of the utilization of the drug before, during and after treatment (Torres, A., 1994).

8.6 The Reasons for FDA policies on off-label use:

The current situation permits a company to promote the labeled use of a new drug. Permitting sponsors to promote off-label uses would diminish or eliminate the company’s incentive to carry out clinical trials and obtain definitive data. Such activity could result in harm to the patient, or fail to show that the drug is effective. If there is a deliberate attempt to diminish the use of evidence-based medicine in arriving at safety and efficacy decisions concerning a drug, the regulatory process will be eroded (Woodcock, J., 1997). Pharmaceutical companies could get approval for a drug for some narrow use and then heavily promote it for much broader uses that had not been adequately tested (The dangers of off-label drug promotion, Public Citizen Internet URL). What if preliminary findings are not subsequently borne out by further study or are refuted by other studies?

Decisions on efficacy should be based on significant results, obtained from well designed and administered clinical trials, published in peer-reviewed journals. Peer judgment and review are essential for balanced results.

In summary, legal issues including unclear regulations in many countries, FDA policies, medical malpractice and reasonable patient standards add increasing complexity. Although eliminating off-label use is unfeasible, preventing them from being used deceptively is imperative based on the numerous legal issues discussed.
Chapter 9.0

Recommendations:

9.1 Recommendations for patients:

■ When your doctor prescribes a drug - any drug – (includes: tablet, capsule, syrup, ointment, cream, gel, solution, lotion and shampoo), ask if it’s an approved use or an “off-label” use.

■ If your doctor does not know, that’s not reassuring. Ask the pharmacist the same question.

■ If the drug is being prescribed off-label, ask what the drug has been approved for.

■ If you get an off-label prescription, ask your doctor whether the scientific evidence really supports this use.

■ Go online and research the drug. Try to find the “label” — that is, the official printed information that specifies what the drug is approved to treat. The best place to start is the FDA’s Web site search engine for drugs at http://www.accessdata.fda.gov/scripts/cder/drugsatfda/.

■ Check other trusted Internet sites. If reassured, good. If further concerns are raised, talk with your doctor again.

■ A drug that is often used off-label is not necessarily a signal that the off-label use is useful and beneficial.

■ Don’t accept from a doctor or pharmacist the statement, “everyone prescribes this off-label. It is OK. What is his or her specific reason for prescribing the drug?”

9.2 Recommendations for prescribers:

■ Be satisfied that an alternative, licensed medicine would not meet the patient’s needs before prescribing an unlicensed medicine.

■ Be satisfied that such use would better serve the patient’s needs than an appropriately licensed alternative before prescribing a medicine off-label.

■ Before prescribing an unlicensed medicine or using a medicine off-label, prescribers should:
■ Be satisfied that there are a sufficient evidence base and/or experience of using the medicine to show its safety and efficacy.

■ Take responsibility for prescribing the medicine and for overseeing the patient’s care, including monitoring and follow-up.

■ Record the medicine prescribed where common practice is not being followed and the reasons for prescribing this medicine. Prescribers may wish to record that they have discussed the issue with the patient.

9.3 Best practice for communication includes:

Physicians give patients, or those authorizing treatment on their behalf, sufficient information about the proposed treatment, including known severe or common adverse reactions, to enable them to make an informed decision.

Where current practice supports the use of a medicine outside the terms of its license, it may not be necessary to draw attention to the license when seeking consent. However, it is good practice to give as much information as patients require or which they may see as relevant.

Explain the reasons for prescribing a medicine off-label or prescribing an unlicensed medicine where there is little evidence to support its use, or where the use of a medicine is innovative.

Healthcare professionals have a responsibility to help monitor the safety of drugs in clinical use through submission of suspected adverse drug reactions. Such reporting is equally important for unlicensed medicines or those used off-label as for those that are licensed.
Chapter 10

Conclusion:

Despite the controversy over the therapeutic use of off-label prescribing medications without a full disclosure, off-label medications seem to be commonly prescribed in clinical practice in dermatology and venereology fields. However, prescribing off-label medications to patients who expect to receive an effective treatment will likely lead to foreseeable ethical and legal difficulties. Ethical issues surrounding the threat to patient autonomy, informed consent and the impact on the physician-patient relationship and physician-drug company relationship are some of the main ethical concerns to be raised. In addition, legal issues including unclear regulations in many countries, FDA policies and reasonable patient standards add increasing complexity. Although eliminating off-label use is unfeasible, preventing them from being used deceptively is imperative based on the numerous ethical and legal issues discussed.

Off-label use in children is common and differs between countries, inpatient and outpatient settings and age. Allergy medicines are on the top of the most prescribed off-label drugs in children in dermatology, nevertheless this has not been accompanied by new research on their safety and efficacy in children, especially with those drugs already in market. In this narrative review, it was recognized that a high percentage of drugs prescription in an allergist daily clinical practice are off-label. It is fundamental to increase awareness of this reality, as it is the responsibility of the clinician to balance risk-benefits of the prescription. Parents/guardians should be informed and involved in the decision in order to prevent misunderstandings, increase compliance and awareness to adverse effects in the pursuance of a good clinical outcome. There is a need for new studies with a better design to access long-term safety and efficacy of respiratory and allergy to market drugs in children, primarily in those under two years of age. New ways should be found by the competent authorities to promote more research accordingly to the patients’ needs.

The issue of going off-label involves both the doctor and the patient. The patient needs to understand that the doctor is prescribing the drug for a non-approved, or off-label use, and he or she needs to understand the risks and consequences of that particular regimen as well as the benefits.

In addition, informed consent must be obtained. My suggestion is to get written consent to document the fact that an informed consent discussion occurred and
that the patient is aware of the risks and benefits of this proposed off-label and unlicensed drug use.

Certainly, I would be extremely reluctant to suggest that medications be used off-label for minors because the potential consequences are significant if something goes wrong.

I urge any doctor who wishes to prescribe for an off-label use to be extremely confident that the drug is appropriate for that use and be willing to face the consequences if his or her judgment is in error. I urge dermatologists to take a very cautious approach to using any medication off label. It’s highly unlikely that I would do it myself. It would have to be an extremely rare case where no other approved therapy would work.

One of the primary reasons for my reluctance is the liability issue. If the patient has an adverse reaction to this particular medication, even if a dermatologist obtains informed consent, the dermatologist may be found liable. Additionally, the action could be viewed as reckless or wanton. That could lead to significantly greater financial responsibility on the part of the prescribing doctor.

I cannot, and will not, recommend that dermatologists prescribe medications outside of their indications. If you do go off-label, another issue is the possibility that your malpractice insurance may not protect you. It protects you from acts or omissions in the practice of your profession that may not include going off-label.

A management guideline for off-label drug use is urgently needed, with which we can guide medical institutions to establish the management regulations of off-label drug use. Clinical research should be promoted actively, and pharmaceutical enterprises should be encouraged to provide completely drug information. Academic organizations should be invited to join in for best professional drug use.
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