Title
Comparative effectiveness research in photodynamic therapy for oral lichen planus

Author
AlGhamdi, Mohammed Abdulkhalig

Publication Date
2016

Peer reviewed|Thesis/dissertation

UNIVERSITY OF CALIFORNIA,
Los Angeles

Comparative Effectiveness Research in Photodynamic Therapy for Oral Lichen Planus

A thesis submitted in partial satisfaction
of the requirement for the degree Master of Science
in Oral Biology

by

Mohammed Abdulkhalig I. AlGhamdi

2016

ABSTRACT OF THE THESIS

Comparative Effectiveness Research in Photodynamic Therapy for Oral Lichen Planus

by

Mohammed Abdulkhalig I. AlGhamdi

Master of Science in Oral Biology

University of California,

Los Angeles

2016

Professor Francesco Chiappelli, Chair

Introduction:

Since there is a lack in knowing the etiology of OLP “Oral Lichen Planus”, there is still a gap in the understanding and subsequently correct management of OLP.

OLP is a chronic immunologic mucocutaneous disease affecting on average 0.5-3% of the population with a significant female predilection, and a potential risk of developing into a carcinoma at advanced stages.

Still used widely among practitioners, steroids appear to remain the most reliable treatment modality among other options including the newer photodynamic therapy “PDT”.

PDT is a minimally invasive procedure, kills damaged cells by the use of oxygen, chemistry and light. Among its many advantages, this modality doesn’t usually result in systemic involvement

as in the case of steroids; and it's done in a series of appointments to monitor results and stage the need for additional therapy accordingly.

The importance of this research stems out of the awareness of an existing gap in the knowledge, and the importance of the lesion by itself with its malignant potential.

The aims of this research are to investigate whether or not PDT poses a better treatment option for OLP in adult patients than topical steroids, and out of the two concentrations of the most frequently prescribed topical corticosteroid, which one is more effective than the other.

Methods:

The search strategy included search engines and hand searching to obtain systematic reviews and randomized clinical trials relevant to the search question. Independent readers validated the quality of the evidence prior to conducting the acceptable sampling analysis.

Results:

For the main hypothesis, the bibliome consisted of four clinical trials, of which only one was yielded by the acceptance sampling process.

For the correlatory hypothesis, the bibliome consisted of one clinical trial, which was retained following the acceptable sampling step.

Qualitative assessment was performed on the findings of both search results and a qualitative consensus was made based on the best available evidence detected.

Conclusion:

Laser phototherapy is more effective for treatment of atrophic-erosive oral lichen planus than topical steroids. There is no significant difference between the two concentrations of topical Clobetasol of 0.025% and 0.05% in the treatment of OLP.

Key words: Oral lichen planus, photodynamic therapy, steroids, evidence-based dentistry, CER, Clobetasol.

The thesis of Mohammed Abdulkhalig I. AlGhamdi is approved.

Russell E. Christensen

Carl A. Maida

Francesco Chiappelli, Committee Chair

University of California, Los Angeles
2016

Dedication

Thanks to Allah, The Greatest, The most Merciful on his countless blessings and his permission to start and finish this work

This work is dedicated to every soul with love for science

TABLE OF CONTENTS

Contents

LIST OF TABLES AND DIAGRAMS

Acknowledgment

This work would not have been completed if it was not for the brilliant guidance of Professor Chiappelli, and the distinguished committee members, Dr. Carl Maida and Dr. Russell Christensen.

My gratitude is also extended to Dr. Andre Barkhordarian for his valuable input, and all the members of Dr. Chiappelli's lab at UCLA.

Last but not least, I'm forever grateful for the unparalleled, unlimited and unconditional love and support of my parents, family and friends.

C h a p t e r 1

Background

Lichen Planus (LP), is a chronic inflammatory systemic disease of the skin, mucosal membranes, and nails, and its name derives from the observed resultant clinical signs due to evident white lacy lines, which resemble moss-like plants (Sharma *et al*., 2012). The etymology of the term lichen planus is derived from the Greek term "Leichen", meaning tree moss, and the Latin term planus, meaning flat or even.

1.1 Cutaneous Lichen Planus

Cutaneous lichen planus (CLP) includes manifestations on the skin or nails. While lichen planus can appear on any areas of the skin, the most common areas of affliction are the inner wrists, forearms, and the ankles. The appearance of dermal lichen planus usually presents itself as red to purplish. It is often itchy, flat-topped; round or it has irregularly shaped bumps, which develop over several weeks.

When an outbreak of lichen planus occurs on the scalp, it may cause redness, irritation, and, in some cases, hair loss (Gorouhi *et al*., 2013; Eisen, 1999).

1.2 Mucosal Lichen Planus

While mucosal lichen planus (MLP) is a chronic inflammatory condition, which most commonly affects the oral mucosa, it can also affect the genitals, esophagus, larynx, and conjunctiva (Eisen, 1999). When afflicting the genitalia, lichen planus typically presents itself as bright red patches or sores (Machin *et al.*, 2010).

1.3 Oral Lichen Planus

Oral manifestations of the disease were first scientifically described by the Vienna School of Dermatology co-founder, Dr. Ferdinand Ritter von Hebra in 1860.

However, it was British Physician Sir Erasmus Wilson who originally used the term Lichen Planus in the 1869 Journal of Cutaneous Medicine, and he observed the condition in fifty patients that he was treating at that time, where three out of the fifty patients had accompanying oral presentations. He noted what seemed to be a correlation of emotional and psychological components to the physical symptoms of their disorder (Wilson, 1869).

Oral lichen planus (OLP), is a chronic inflammatory mucocutaneous condition affecting the mouth, and or other areas of the body such as the genitalia and larynx where approximately 15% of OLP patients develop skin lesions. Skin lesions are infrequently associated with erosive OLP. It has varying reported prevalence rates that could fall within the range of 0.5%- 3% of the population (Kalmar, 2007; Eversole, 2002; Wang *et al.*, 2015; Mostafa and Tarakji, 2015; Lodi *et al.*, 2005; Zakrzewska *et al.*, 2005). Although the disorder has been most often reported to occur in middle-aged patients, it has been reported to affect pediatric patients as well; however, these instances are statistically rare. Women are classically reported to be affected more with the condition than men, in a rate of about 1.4:1, though this notion is not being much researched nor focused upon in the newer published studies (Carbone *et al*., 2009; Lavanya *et al.*, 2011).

More epidemiology is presented in tables 1-4.

Dr. J.O. Andreasen originally classified OLP in 1968 based on its clinical presentations into six categories, which included both erosive and non-erosive, with most of the lesions appearing on the buccal mucosa, gingiva, tongue, palate, and lips (Andreasen, 1968).

Later attempts to classify the clinical presentations resulted in narrowing them down to four: reticular, papular, atrophic and erosive; and another classification was based on the lesions being either white or red in appearance (Wang *et al.*, 2015). Given the bases of these classification systems, unless verified by a histological biopsy or accompanied by symptoms, they are merely a visual reference for clinicians and not determinants for treatment.

Andreasen's (Andreasen, 1968) depiction of OLP clinical presentations is:

1. Reticular OLP: the most frequently seen clinical presentation. Denoted by white lacy lines "Wickham's striae". It could occur on any oral mucosal surface, mostly on buccal mucosa and tongue. It is often asymptomatic and unobservable to affected individuals. It is only observable when patients feel a change in texture with their tongue or if it is detected by their clinicians during a routine examination.
2. Plaque-like OLP: as denoted by its name, is defined by various sizes of thick plaques occurring on the infected tissues. It is most often observed on the tongue and has the appearance of a bald area. While it could resemble leukoplakia in appearance, its symptoms are not readily treated even by steroids.
3. Papular OLP: small papules measuring approximately 0.5- 2 mm in size. These white dots are small and can be easily overlooked if there is not a significant number of them present**.**
4. Bullous OLP: rare presentation consists of fragile, thin-walled bullae ranging from 4mm – 2 cm in diameter. It is often discovered only after the vesicles have ruptured, commonly due to eating and talking, leaving painful erythematous zones. Unlike the aforementioned asymptomatic OLP presentations, this one is often considered erosive since it causes discomfort and pain when these bullae rupture.

5. Atrophic OLP: an erosive form of OLP, is often called the erythematous form as it is denoted by reddened patches, often on the gingiva. Oftentimes, patients complain of a burning sensation with irritation. As with other classifications, this presentation of OLP can simultaneously appear with other forms.
6. Ulcerative OLP: another erosive form of OLP, characterized by the presence of ulcers. There may be only one ulcer or several, and this clinical presentation can occur with any of the other OLP forms. It is painful and can interfere with patients' daily activities such as eating, talking, and brushing their teeth. This form has a higher report of malignancy and can affect any tissue, including those of the tonsils and esophagus.

There is a risk of OLP progression into a malignancy, more specifically the risk of erosive clinical presentations' of OLP progression to a squamous cell carcinoma (SCC).
Due to the longstanding chronic inflammatory nature of OLP, the threat of malignant progression is valid. OLP is identified by the World Health Organization working group as a potentially malignant disorder.

Given that, certain genetic predispositions theoretically can be implicated in the progression of OLP lesions into malignant stages in some OLP-affected patients. This makes controlling inflammation of high importance to prevent potential carcinogenesis related to such chronic inflammatory states. More elaboration on this point follows in page 10.

Up to date, the topic of malignant transformation is still unresolved, contributing to the highly variable range (0.4%- 8%) of reporting SCC in OLP-affected patients (Lodi *et al.*, 2005; Van der Meij *et al.*, 1999; Fitzpatrick *et al.*, 2014; Kassem *et al.*, 2012). The OLP erosive clinical presentations potentially have higher rates of malignant transformation, and they are also associated with diabetes mellitus and hypertension in a triad known as the Grinspan syndrome (Yang *et al*., 2016; Eversole, 2002; Aljabre 1994).

Although no known treatment is curative, active symptoms of OLP can go into remission for a significant amount of time (Ismail *et al*., 2007). Spontaneous remission rates are very low, if not rare, and estimated to be of 6.5% in a study on 214 patients with a mean follow-up of 7.5 years (Silverman *et al.,* 1991; Carbone *et al*., 2009).

There are several testing methods to confirm a diagnosis of OLP and/or distinguish it from other conditions that could possibly cause similar signs and symptoms, such as candidiasis, allergic mucositis, radiation mucositis or lupus erythematosus (Scully *et al.*, 2000; Lavanya *et al.*, 2011; Eversole, 2002). Tissue biopsies for histological examinations can be used to confirm the diagnosis, exclude other diseases that may mimic OLP, or identify possible areas of dysplasia within the lesions.

The histological diagnosis of OLP is often based on the criteria of World Health Organization (WHO) Collaborating Center for Oral Precancerous Lesions (Kramer *et al.*, 1978). Some of the main looked at histological criteria include:

- Liquefaction degeneration of basal layer
- Dense lymphocytic infiltrate within the connective tissue resembling a band
- “Saw tooth” appearance of the rete pegs

A culture can also be utilized to distinguish OLP from a secondary fungal, bacteria, or viral infection.

Direct immunofluorescence could also be used, in which a single antibody is chemically linked to a fluorophore, which recognizes the target molecule, binds to it, and allows it to be detected by microscopy. This test is especially helpful in distinguishing erosive OLP from other afflictions such as: pemphigus vulgaris, benign mucous membrane pemphigoid, dermatitis herpetiformis, and linear immunoglobulin A (IgA) disease (Lavanya *et al.*, 2011). Additionally, blood tests can be done to diagnose other conditions, such as hepatitis C, that can be associated with OLP (Scully *et al.*, 2000).

OLP symptoms can be exacerbated by several "trigger" mechanisms, which are associated with the occurrence of the oral lesions. Research attempts have been made in the past to establish a stronger link than an association relationship between these triggers and the disorder and prove the etiology of the disorder. The main associations include:

1) Drug consumption and dental materials: the intake of certain pharmaceuticals has been implicated in the appearance of OLP lesions, including the use of NASID's, antibiotics, beta-blockers (Carrozzo, Gandolfo, 1999). The use of some identified dental materials has also been linked to OLP lesions as in the case of dental amalgam fillings and gold crowns. It's believed that these factors are responsible for more of an OLP-like mucositis (Eversole 2002; Kurago, 2016).

2) Viral infections: some of the researched viruses that were linked to OLP include herpes simplex virus-1, cytomegalovirus, human herpesvirus-6, hepatitis B virus, Epstein-Barr virus and human papillomavirus. No significant correlations could be made.

Association to hepatitis C virus was the most researched among them all, yet the exact mechanism of OLP development in HCV patients is not clear.

There seems to be an increased regional prevalence of the HCV association with OLP in countries of Southern Europe, Japan, USA, among all other countries of the world. Meanwhile, countries with highest prevalence of HCV infections report negative or nonsignificant prevalence of OLP.

3) Stress: there is an interplay between the emotional status of patients and OLP, where inadequate compensating reactions may lead to development of the disorder. There is a correlation between OLP exacerbations and episodes of anxiety, and it's reportedly common for OLP patients to suffer from anxiety and depression. No cause-effect relationship has been demonstrated yet between the onset of OLP and stress, suggesting stress plays more of a secondary role in OLP pathogenesis. The activation of the immune system would also be manifested in behavior.

Psychological support as a complementary strategy should be considered especially in patients with unsatisfactory responses to treatment (Dillenburg *et al*., 2014; Ader, 1996).

4) Dysregulated T-cell mediated immunity:

The strongest theory prominent today for OLP etiology is that it is T-cell mediated.

T cells with alpha-beta T-cell receptors, including $CD4^+$ "helper" and $CD8^+$ "cytotoxic" T cells, are typically found within OLP lesions within both the epithelium and lamina propria infiltrates. According to this postulated theory, $CD8^+$ T cells trigger apoptosis of the basal cells of the oral epithelium.

An early event in the disease mechanism involves keratinocyte antigen expression or unmasking of an antigen that may be a self-peptide or a heat shock protein. Following this, T cells (mostly $CD8^+$ cells) migrate into the epithelium either due to random encounter of antigen during routine surveillance or a chemokine-mediated migration toward basal keratinocytes. These migrated $CD8^+$ T cells are activated directly by antigen binding to major histocompatibility complex (MHC-1) on keratinocyte or through activated $CD4^+$ lymphocytes. In addition, the number of Langerhans cells in OLP lesions are increased along with upregulation of MHC-II expression; subsequent antigen presentation to $CD4^+$ cells and Interleukin 12 (IL-12) activates $CD4^+$ T helper cells which activate $CD8^+$ T cells through receptor interaction, interferon gamma (INF – γ) and IL-2. The specific mechanism of cytotoxicity directed at keratinocytes in OLP is still unclear, though is suggested that the activated $CD8^+$ T cells kill the basal keratinocytes through tumor necrosis factor (TNF-α), Fas–FasL mediated or granzyme B activated apoptosis. Th1 cells produce interferon gamma (IFN-γ), and IFN- γ+ cells were identified in OLP. Natural killer (NK) cells also can produce IFN-γ, and cells with NK cell markers ($CD56^{dim}$ $CD16^+$) have been identified in OLP lesions (Lavanya *et al.*, 2011; Kurago, 2016).

Under the current inability to offer a cure for OLP, the focus of clinicians is limited to providing patients with active OLP treatment to reduce their symptoms, manage active flares and monitor them for the possibility of developing potential malignancies (Scully *et al.*, 2000). Maintaining a clean oral cavity and optimizing the oral hygiene practices are essential for OLP treatment, since inflammation due to dental plaque and calculus can increase both symptoms and extension of the lesions (Di Stasio *et al.*, 2014).

Treatment for OLP is empirical and can include, but is not limited to: immunosuppressants including polycyclic compounds "e.g., topical and systemic steroids", calcineurin inhibitors "e.g. tacrolimus, cyclosporine", antirhuematic agents "e.g., azathioprine", retinoids "e.g., topical as tretinoin, or systemic as etretinate", photochemotherapy, photodynamic therapy, humanized monoclonal antibodies and low dose - low molecular weight heparin (Scully *et al*., 2000).

Of these treatments, steroids are the most commonly used as they inhibit the activation of T cells and the secretion of Th1 cytokines. At the same time, they stimulate the secretion of IL-10, a Th2 cytokine that interferes with Th1 cytokine activities (Kurago, 2016).

Steroids can modulate inflammation and immune response by a number of mechanisms listed in table (5).

Most often, antifungals such as miconazole or nystatin are added along with steroids to prevent the occurrence of secondary fungal infections like candidiasis.

The decision to whether use a topical or systemic steroid to treat OLP lesions is primarily based on the extent of these lesions. Small, confined lesions that are less in number are often treated first with topical steroids. OLP lesions that are large in size, with less defined borders and that are more aggressive are often treated with systemic steroids. Also, when topical steroids are unsuccessful in

the treatment of recalcitrant OLP symptoms, systemic steroids such as prednisone are often used as second line treatment (Liu *et al.*, 2013).

While steroids in general often constitute a first-line choice for OLP treatment, there is still no clear agreed-upon algorithm for concerned physicians to follow. This in return gives room for subjective factors to come into play, affecting the course and final outcome of the therapy. Such factors may include individual physician's clinical judgment, personal experience and preference for a specific drug.

As some physicians are traditionally conservative in their approach, they might choose to start the therapy with moderately potent steroids of milder doses. On the contrary, some of their peers have a different philosophy to tackle the same pathology, directing them to choose the most potent option at first for a shorter duration of therapy, which is followed by a tapering off phase of a less potent steroid. While both schools of practice can result in successful results, a valid concern is still present to whether resorting to each of these former school of thoughts would result in perspective unforeseen side effects.

While the former conservative approach could lend more time for the chronic inflammation to develop, the latter radical approach comes with its potential share of overwhelming the immune system and increasing the magnitude of unwarranted side effects.

All of the aforementioned reasons vindicate that some physicians currently prescribe their own concoctions, which represent the extract of their best accumulative knowledge. Many forms of topical steroids exist for the treatment of OLP; gel, ointment, adhesive, paste and mouthwash. However, one great disadvantage to the use of topical steroids is the limited amount of direct contact time with the lesion, thus shortening the active ingredient's effective treatment time (Thongprasom *et al.*, 2008).

Although steroids have been proven to be effective in OLP treatment, they are also associated with some side effects such as weight gain, Cushingoid features, osteoporosis, increased mood swings and nervousness, cataracts, glaucoma, and a lower resistance to infection (Stanbury *et al*., 1998; Liu *et al*., 2013).

The risk of experiencing side effects consequential to steroidal therapy is dependent on factors that include:

1) Category, form of steroid and dosage: tablets cause more side effects than injections or inhalers.
2) Length of treatment: likelihood of developing side effects increases as duration of steroid therapy exceeds three weeks.
3) Patient's age: children and elderly are generally more prone to the development of side effects.

1.3.1 Mechanism of Action of Topical Corticosteroids

When the steroid molecule is transported to the nucleus of the cell and upon interacting with its DNA, the cell makes lipocortin proteins, which, in turn, cease the production of arachidonic acid (Barnes, 2006). Without arachidonic acid, many inflammatory chemicals such as prostaglandins, leukotrienes, and platelet-activating factor are not produced and inflammation is reduced (Barnes, 2006; Kragballe, 1989). By constricting capillaries, steroids decrease redness and swelling (Liu *et al.,* 2013; Barnes, 2006). Additionally, steroids impair white blood cells' ability to identify foreign cells, and thus they limit the immunological response (Kragballe, 1989; Liu *et al*., 2013).

1.3.2 Examples of Most Used Topical Steroids for Treatment of OLP

Clobetasol

Clobetasol propionate, in the form of cream or ointment, is a topical super-potent halogenated corticosteroid used to treat OLP (Scully *et al*., 2000). In comparison with the other corticosteroids, clobetasol propionate is probably one of the most potent topical steroids (Carbone *et al*., 2009; Chamani *et al*., 2015). Clobetasol works by suppressing mitosis and increasing the synthesis of proteins, all of which decrease inflammation and cause vasoconstriction (Radwan-Oczko, 2013).

Fluocinolone Acetonide

A topical corticosteroid of medium potency used among OLP treatments. It is prescribed in cream, gel or ointment form (Scully *et al*., 2000). Fluocinolone acetonide works by inhibiting cell proliferation, thus suppressing the immune system and, thereby reducing inflammation (Barnes, 2006).

Triamcinolone Acetonide

A topical corticosteroid of medium potency, which comes in paste, cream, ointment, or suspension "for intralesional administration" (Scully *et al*., 2000). It acts by binding to cytosolic glucocorticoid receptors and altering gene expression, which results in aids in the production of anti-inflammatory proteins and inhibits inflammatory mediators which reduces inflammation and autoimmune reactions (Barnes, 2006).

1.3.3 Mechanism of Action of Systemic Corticosteroids

When taken in an amount which exceeds the body's regular level, systemic corticosteroids reduce inflammation by mimicking the effects of hormones naturally produced by the body through the adrenal glands (Barnes, 2006). Additionally, as with topical steroids, systemic corticosteroids also inhibit the immune system's ability to attack its own tissues (Coutinho & Chapman, 2011). However, the potential clinical implications of glucocorticoid-mediated stimulatory effects on the innate inflammatory response are still largely unknown and speculative (Yeager *et al.*, 2004).

1.3.4 Examples of Most Used Systemic Steroids for Treatment of OLP

Prednisone

A systemic synthetic glucocorticoid with a short plasma half-life (Liu *et al*., 2013; Scully *et al*., 2000). It provides anti-inflammatory and immunomodulating properties by entering the cell nucleus and binding to and activating specific nuclear receptors, which alters the gene expression and inhibits the production of inflammatory cytokines (Coutinho and Chapman, 2011).

Prednisolone

A systemic synthetic glucocorticoid that decreases inflammation by suppressing the migration of polymorphonuclear leukocytes and reducing capillary permeability (Lavanya *et al*., 2011).

Calcineurin inhibitors, such as cyclosporine, tacrolimus, and pimecrolimus have also been used to treat OLP. This class of drugs does not contain steroids, and thus it is usually reserved for cases of steroid resistance because they directly target T-cell activation and proliferation (Kurago, 2016). While cyclosporine is an immunosuppressant commonly prescribed for transplant recipients to reduce their chances of organ transplant rejection, its ability to suppress T-cell activity has also been used to treat OLP when used in its mouthwash or topical base form (Lavanya *et al*., 2011).

Another calcineurin inhibitor, tacrolimus, offers a deeper penetration to the oral mucosa than cyclosporine. The Food and Drug Administration (FDA) has stated that tacrolimus may be a carcinogen and should be only utilized for short-term treatment (Lavanya *et al*., 2014).

Pimecrolimus is a semi-synthetic product of ascomycin, which in its 1% topical form has also been used to treat OLP ((Thongprasom *et al*., 2013; Lavanya *et al*., 2011). However, it has also been given a "Black Box" warning by the FDA as its use theoretically increases the risk of squamous cell carcinoma and lymphoma in patients.

In addition to corticosteroids and calcineurin inhibitors, retinoids which also offer the ability to modify the immune response, have also been used to treat OLP. Examples
of the topical retinoids used to treat OLP include: tretinoin, isotretinoin, and fenretinide (Lavanya *et al*., 2011). However, retinoids have been known to have the side effects of liver toxicity and abnormalities of serum lipid profiles, which might increase the risk of coronary heart disease.

1.3.5. Other Pharmacological Non-Steroidal Options for OLP Treatment

Other pharmacological treatments have also been used to treat active OLP symptoms.

For example, the antibacterial agent used to treat leprosy, dapsone, has been used to treat OLP. However, within the first six weeks of treatment, patients have reported experiencing unwanted side effects such as fever, jaundice, and rash; such resultant side effects are often treated with corticosteroids (Scully *et al*., 2000).

Mycophenolic acid, originally used to treat psoriasis, has also been used to treat OLP, but this treatment requires long-term usage to be effective and can be a costly medication for patients.

Another psoriasis treatment, efalizumab, might offer potential treatment for patients suffering from OLP (Lavanya *et al*., 2014).

It is interesting to note the use of a low dose heparin might offer a non-steroidal pharmacological treatment for patients with OLP. Both efalizumab and a low dose of heparin are injected subcutaneously (Scully *et al*., 2000; Lavanya *et al*., 2014).

1.3.6 Alternative Therapies

Although the common pharmacological modalities used to treat OLP have demonstrated success, the concern regarding the potential development of adverse side effects in patients has steered research efforts to explore nonpharmacological options (Thongprasom *et al*., 2013).

Among these options are herbal medicine, photo chemotherapy, and photodynamic therapy (Scully *et al*., 2000).

One non-traditional method used to treat OLP is the herbal medicine, turmeric. It is an herb that has long been used as a natural medicine by many diverse civilizations. Specifically, the curcuminoids in turmeric has been shown to have anti-inflammatory effects and, as OLP is an inflammatory disease, turmeric offers current adjunctive palliation and a potential future treatment modality for OLP (Thongprasom *et al*., 2013; Singh *et al*., 2013).

1.3.6.1 Phototherapy

Exposure to light has been used as a therapeutic modality for many centuries.

This was exemplified by the ancient Greeks who believed "heliotherapy" was a health restorative, and the Chinese who thought conditions such as rickets could be cured by exposure to the sun.

Light, when used as a treatment for various pathologies, is known as phototherapy. While phototherapy involves the application of ultraviolet light, the treatment may involve exposure to lasers, ultraviolet B (UVB), or ultraviolet A (UVA), which is a long wave ultraviolet radiation.

1.3.6.2 Photochemotherapy (PUVA)

This modality was first introduced for oral lesions by Jansén *et al*. in 1987. Mouth PUVA utilizes a photosensitizing psoralen drug (P), and exposure to a UVA radiation of a wavelength between 300- 400 nm. Upon absorption of the light energy, the psoralen molecules get activated and suppress DNA synthesis (Bulat *et al*., 2011).

Among the most frequently used photosensitizers are 8-MOP (methoxsalen) for peroral administration and trioxsalen (4,5, 8-trimethylpsoralen, TMP) for dermatological disorders (Shenoi & Prabhu 2014; Kuusilehto *et al*., 1997).

Use of PUVA is usually reserved for more serious conditions, and it has more systemic side effects and complications than photodynamic therapy (Wolff, 1990; Van Weelden *et al*., 1990).

2. Photodynamic Therapy (PDT)

Part of the current alternative therapies for OLP treatment, it was first utilized as a treatment modality in the 1960s. However, it was Thomas Dougherty, founder of the International Photodynamic Association, who brought the use of PDT to the forefront in 1986.

PDT is a procedure based on the activation of molecules of various chemical agents, photosensitizers, by light emitting radiation using selected wavelengths.

Initially, it involves the application of photosensitizing agent to a target area. Subsequently, the target area is irradiated with light of an appropriate wavelength, which causes the photosensitizing agent to react. Following activation, cytotoxic free radicals are released, resulting in the destruction of targeted cells (Gursoy *et al*., 2012).

Interestingly, although the photosensitizing agent and light in the PDT are each individually non-toxic, when combined, they produce an effect that can destroy microorganisms such as bacteria, viruses, fungi, protozoa and microorganisms (Mohanty *et al*., 2013). The three main variables in PDT are photosensitizers, oxygenation of tissues, and the light source utilized (Konopka & Goslinski, 2007).

2.1 Photosensitizers

Numerous natural and synthetic photoactive compounds possess photosensitizing potential, including quinones (cercosporin) and degradation products of chlorophyll. The main photosensitizing agents used in clinics belong to porphyrin-chlorine group and dyes like methylene-blue and toluidine-blue. Photosensitizers should be non-toxic and only display local toxicity after being activated by illumination. (Konopka & Goslinski, 2007).
An ideal photosensitizer is one that fulfills certain requirements listed in table (6).

The photosensitizers used in PDT may be either topical or systemic in nature and the method of treatment is dependent on the agent (Gursoy *et al*., 2012). PDT photosensitizers may be given to the patient through intravenous injection, oral ingestion, or topical application (Konopka & Goslinski, 2007).

2.2 PDT Systemic Photosensitizers

PDT systemic photosensitizers are non-metallic oligomeric porphyrins (Gursoy *et al*., 2012; Konopka & Goslinski, 2007). The two primary photosensitizers used are a hematoporphyrin derivative (HPDs), a porfimer sodium, known as (Photofrin); and meta-tetrahydroxyphenylchlorin (mTHPC, Foscan®). The former is regarded as a first generation photosensitizer, whereas the latter is a second-generation photosensitizer. These photosensitizers are usually activated by light at 630-655 nm (Kvaal & Warloe, 2007; Mohanty *et al*., 2013).

While lower wavelength light will offer greater light absorption, the actual tissue penetration of the light lessens (Gursoy *et al*., 2012).

2.3 PDT Topical Photosensitizers

While there are other topical PDT photosensitizers currently being researched, the main photosensitizer used topically is 5-aminolevulinic acid (5-ALA). Other topical photosensitizers include Photolon (chlorine e6), methylene blue and toluidine blue dyes.

5-aminolevulinic acid can be applied topically, orally or systemically; and it is the only agent that can be applied topically. It provides some advantages, among which is the complete lack of systemic photosensitivity. It has disadvantages too, manifested mainly in the shallow penetration depth of around 1– 2 mm (Kvaal & Warloe, 2007; Gursoy *et al*., 2012).

Photolon or Fotolon is sodium salt of chlorin e_6 and its derivatives and is administered in form of injections (Ali-Seyed *et al*., 2011).

Methylene blue and toluidine blue are cationic phenothiazine dyes that have maximum wavelength absorption of 656 nm and 625 nm, respectively (wainwright, 2005).

2.4 PDT Light Source

Light is responsible for activation of the previously mentioned photosynthesizers.

The light source used in PDT is a specific wavelength visible light of low power (Mohanty *et al*., 2013; Konopka & Goslinski, 2007). Since human tissues transmit light on the red spectrum effectively; most photosensitizers are activated by red light at 630 nm – 700 nm (Gursoy *et al*., 2012; Konopka & Goslinski. 2007). Depth of light penetration can be of 0.5 cm at 630 nm wavelength, up to 1.5 cm at around 700 nm (Salva, 2002; Kübler *et al*., 2005). The therapeutic window of PDT light sources' wavelengths falls between 600 nm to 1200 nm (Mohanty *et al*., 2013; Gursoy *et al*., 2012).

The total dose of light, the dose rates at which light is delivered and the depth of penetration are main variables looked at when selecting a light source. These variables are dependent on the type of photosensitizer used in the process and the type of tissue being treated.

In the past, light sources like argon-pumped dye laser and Nd/YAG were used. Currently, the diode laser systems, which offer portability, ease of use, and cost effectiveness are the predominant field's standard. The concept of laser biostimulation, enables lasers to change cell function in a non-thermal and non-destructive manner that will be discussed further under "PDT Reaction" (Agha-Hosseini *et al*., 2012).

LED, a non-laser light source that offers its advantages of easy handling and affordability has been also used in PDT.

Other light sources, such as xenon arc, quartz halogen and tungsten filament are used to treat large affected areas (Konopka & Goslinski, 2007).

2.5 PDT Reaction

While the exact mechanism of action underlying PDT is still unclear, there are theories to how it works (Kvaal *et al*., 2013; Yang *et al*., 2016; Ozog 2016 *et al*., 2016). Photosensitizers transition from a low energy level "ground state" to a higher energy level "triplet state" upon exposure to a light source of an appropriate wavelength. It is only at this triplet state where the effect of the reaction would be noticed, by the following mechanisms:

1) The activated photosensitizer produces free radicals and highly reactive oxygen species through electron/hydrogen transfers or removal by reacting with biomolecules.

2) The activated photosensitizer produces singlet oxygen by reacting with molecular oxygen. Singlet oxygen is a highly reactive, electronically excited state of oxygen (Gursoy *et al*., 2012).

These mechanisms result ultimately in cellular death of the affected tissue cells. It has been indicated that there is no direct correlation between DNA damage and cellular death, although DNA is targeted by the above-mentioned oxidative events (Jori *et al*., 2006).

2.6 Advantages of PDT

Unlike its pharmacological counterparts, PDT offers several advantages (Gursoy *et al*., 2012; Kvaal *et al*., 2013):

1) Enables physicians to selectively target its toxicity to specific areas.
2) Minimal invasiveness.
3) Low risk of complication.

4) Negligible risk of accumulative toxicity.
5) Rare side effects of low intensity.
6) No buildup of resistance toward the modality.

2.7 Uses of PDT

A wide array of diseases and conditions are being treated with PDT, among which are skin diseases, tumors, premalignant conditions, mucosal hypertrophy, periodontitis and oral lesions.

2.8 Limitations of PDT

Other than the fact that the exact mechanism of action of PDT is still unclear, there are other shortcomings of the modality. Large lesions are less likely to be affected by this modality for reasons that include less depth of penetration and light passage. Also PDT is not applicable in cases where skin photosensitivity lasts for weeks.

2.9 Side Effects of PDT

Could vary depending on many factors such as the photosensitizer used, skin sensitivity to light after treatment, and the time interval between photosensitizer administration and the application of light.

Main side effects of PDT include residual systemic photosensitization, which might get activated by daylight; therefore patients are instructed to avoid bright light for a certain amount of time. Also pain and swelling could be experienced by some patients after the PDT application. Scarring of tissues close to the area being treated is also likely (Gursoy *et al*., 2012).

3. Evidence Based Dentistry (EBD)

It is a patient-centered approach driven by a relevant clinical question driven to making treatment decisions. The concept of evidence based medicine and dentistry has been endorsed in their respective fields since at least the 1990's (Chiappelli, 2014). It was promoted to reduce the reliance on clinical experiences and anecdotal or low quality evidence for delivering healthcare (Goldstein, 2002).

Evidence based medicine and dentistry have been defined as being based on conscientious, explicit, and judicious use of the best evidence available from well-designed studies, clinical expertise, along with patient needs and expectations when forming clinical decisions (Chiappelli, 2014; Goldstein, 2002). A concern for the soundness and generalizability of the evidence is a priority for the translational evidence-based researcher (Bauer *et al*., 2006).

Evidence-based health care (EBHC) seeks to deliver the best available health-care modality for a specific patient in a specific setting. EBHC seeks to determine the best treatment modality that provides efficacy, cost effectiveness, optimal benefit, and minimalization of risk to the patient (Chiappelli, 2014).

It should be noted EBHC is distinct in that it utilized the systematic process of research synthesis which involves (Chiappelli, 2014):

1) Embracing all the available evidence
2) Ranking the level of that evidence
3) Obtaining an overarching analysis of the evidence at hand

The American Dental Association (ADA) defines evidence-based dentistry (EBD) as "an approach to oral healthcare that requires the judicious integration of systematic assessments of clinically relevant scientific evidence, relating to the patient's oral and medical condition and history, with the dentist's clinical expertise and the patient's treatment needs and preferences".

If we have the best available evidence ever but if it clashes with the patient's preferences or values, it is deemed worthless. Also the expertise of the clinician is needed to balance the evidence with what would be best for the individual patient. The importance of evidence-based practice stems from the fact of the utmost importance and the ever growing crucial need for it. Stakeholders could waste so much valuable time in hope to find the reliable and correct information among the continually building and tremendous number of published papers that are out there. PubMed alone contains over 23 million citations and nearly 2,000-4,000 new articles are added every day. There is no way anyone could ever keep up with the current pace of medical literature.

Another reason to do EBP is that patients are counting on clinicians and researchers to provide them with the best care. 30%-40% of patients do not receive care according to scientific evidence, 20%-25% of care has been medically unnecessary and potentially harmful (Chou *et al.*, 2011), and it can take 17 years for evidence to be implemented into practice (Morris *et al.*, 2011).

Scientific evidence is obtained from studies which can come in various designs, such as systematic reviews and meta-analyses, randomized controlled clinical trials, nonrandomized controlled clinical trials, cohort studies, case-control studies, cross-over studies, and expert opinions (Burns *et al*., 2011).

In expert opinions, professionals draw upon the knowledge and skills acquired through a study and utilize their experience as the basis in the formulation of their expert opinion (West *et al*., 2002).

A systematic review as defined by Altman and Oxman is "a review that attempts to collate all empirical evidence that fits pre-specified eligibility criteria to answer a specific research question using explicit, systematic methods to minimize bias, thus providing more reliable findings from which conclusions can be drawn and decisions made" (Higgins *et al*., 2011).
Systematic reviews gather available data addressing a certain topic in an organized and systematic method, evaluated the data, and provide a summary. Such reviews of well-designed studies provide valuable scientific evidence and in the Journal of the Canadian Academy of Child and Adolescent Psychiatry, Uman described the composition of systematic reviews to be comprised of the following eight steps (Uman, 2011):

1. Formulation of a question the review will address.
2. Defining of the inclusion/exclusion criteria.
3. Designing a literature search strategy.
4. Choosing the candidate studies.
5. Data extraction of the included studies.
6. Data assessment for quality.
7. Analysis of data and results.
8. Publication.

Additionally, The Cochrane Collaboration offers other guidelines for systematic reviews.

Participants in randomized controlled clinical trial (RCT's) are randomly assigned into one of two groups, a control or an experimental group. The study is conducted with the outcome variable being studied as the only expected difference between the two groups.

A nonrandomized controlled clinical trial is an experiment that evaluates the effect(s) of one (or more) therapeutic interventions in a group of subjects (West *et al*., 2002).

While RCTs are preferable, nonrandomized RCT's are the next best evidence and are often conducted when randomization is not feasible or ethical.

Cohort studies involve the observance rather than the experimental manipulation of outcomes. These are followed by case control studies which are studies comparing patients who have a condition, with those who do not (Burns, 2011). In crossover studies, each patient receives different treatments during different time periods and, as the name reflects, the patient is "crossing over" from one treatment to another during the course of the trial.

An illustration of different study designs is presented in diagram (1).

EBD consists of an investigational component and a clinical mode. Seeking to provide the patient with the best treatment modality involves the employment of certain protocols. Comparative effectiveness and efficacy research and analysis for practice (CEERAP) are protocols used to enable the clinician to identify the best available evidence for a given treatment modality, aiding the patient greater empowerment in their decision-making and facilitate the physician/patient relationship and dialogue.

CEERAP integrates with patient-centered outcomes research (PCOR) to formulate evidence-based decisions for patient-centered treatment in clinical practice.

Comparative effectiveness research (CER), a particular domain of CEERAP, includes the conduct and synthesis of research by comparing the benefits and harms of different interventions and strategies to prevent, diagnose, treat, and monitor health conditions in real world settings (Chiappelli, 2014).

CER was defined by the Institute of Medicine (IoM) as "the generation and synthesis of evidence that compares the benefits and harms of alternative methods to prevent, diagnose, treat, and monitor or improve the delivery of care. The purpose of CER is to assist consumers, clinicians, purchasers, and policy makers to make informed decisions that will improve health care at both the individual and population levels".

Central to the individualized patient centered research (PCOR) is the research question.

The PICOTS format is an effective standard approach for focusing the research question (Chiappelli, 2014).

Using PICOTS, the research question addresses the following:

- (P) = the patient's characteristics
- (I) = the independent variables
- (C) = the modality that is in comparison
- (O) = the outcome variable of interest
- (T) = within the planned timeline
- (S) = the projected clinical or experimental setting

The process of research synthesis entails:

1. Topic Selection
2. Research Question Formulation
3. Designing/Execution of Literature Search
4. Publications Selection, Quality Assessment and Data Abstraction
5. Results Synthesis

Once the research question has been formulated, a search strategy is employed. Initially, key words are selected and ultimately used to find relevant data. Inclusion and exclusion criteria are then applied to the data and bibliome is created. The bibliome is further critically appraised and the data ranked in quality, with the lowest ranked ones getting eventually eliminated. The research is synthesized into homogenous data from the accepted bibliome and an overarching statistical analysis is conducted. This results in a compilation of the best available evidence in the formulation of a scientific review (Chiappelli, 2014).

The purpose of PCOR and CER is to assist patients, providers, and others to make informed decisions. To accomplish this, researchers must begin to engage the full range of stakeholders in all stages of research.

In patient-centered models, stakeholder engagement strategies should include:

1) Evidence prioritization: prioritizing topics to be addressed and the crafting of focused PICOTS questions.
2) Evidence Generation.
3) Evidence Synthesis: systematic review of research (i.e., research synthesis).
4) Evidence Integration: integrating different fields (e.g., clinical, behavioral, economical) in the related protocols to the research (i.e. translational inference).

5) Evidence Dissemination: distributing the outcomes of the research process to all stakeholders.
6) Evidence Utilization: adoption and implementation of the findings of research in policies and for their practical use in specific clinical and world settings (i.e., translational effectiveness).
7) Evidence Feedback: feedback offered by stakeholders in regard to their participation (Chiappelli, 2014).

C h a p t e r 2

Methodology

Objectives of this Systematic Review

A clinical inquiry arose after encountering OLP affected patients and noticing the various kinds of complications they experience throughout the course of seeking medical assistance.

A primary thought was developed to explore more about the relatively newer modality of photodynamic therapy and how would it compare with the current convention on corticosteroids being the golden standard for the treatment of those OLP patients. Given that the exact etiology of OLP is still unknown, setting PDT as the intervention was ideal since it is neutral in targeting OLP-affected tissues regardless of the etiology or biological pathway. OLP treatment can be specific depending on the etiology that is still unknown, and this review addresses that gap in knowledge.

A continuation of the primary thought was in regards to the case of steroids being proven the most effective for those patients, then what kind of steroid is that and in what concentration?

These thoughts were translated into hypotheses as will be discussed further, a main hypothesis and a correlatory hypothesis, pertaining to each of the two thoughts mentioned in the previous paragraph respectively. This research synthesis systemically tests these two hypotheses.

1.Main Hypothesis

PDT, in comparison to steroids, results in better clinical improvement of OLP in effected adult patients age 20 years and older with zero dysplasia; as monitored for at least a month of in-office PDT in a clinical or hospital setting.

This hypothesis was translated into the following PICOTS question:

P: Male and female adult patients (age > 20 years), with OLP and no dysplasia.

I: Photodynamic therapy.

C: Topical corticosteroid-based medications.

O: Clinical improvement.

T: At least one month of in-office PDT.

S: General dental clinics or hospital environment.

In this systematic review, the following definitions were adopted:

1) The intervention (PDT) was defined as "a procedure based on the activation of molecules of various chemical agents called photosensitizers by light emitting radiation using a selected wavelength. The activating light is most often generated by lasers or in some cases by arc lamps or fluorescent light sources. And the photosensitizers exclude any psoralen derivatives".
2) The outcome (clinical improvement) was defined as "a reduction in lesion size and or resolution of symptoms".

1.1 Search Strategy Design for the Main Hypothesis

The search was conducted using six search engines. The searching process for relevant studies was performed using keywords obtained from the key questions, which are derived from the main PICOTS question.

The key questions were:

- KQ1: Does PDT improve intermediate results?
- KQ2: Does PDT improve health outcomes?
- KQ3: What are the wavelength, light dose, and photosensitizer agent that result in the best OLP treatment outcome?
- KQ4: What are the adverse effects of treating OLP with PDT?
- KQ5: What is the strength of evidence that intermediate outcomes are associated with improvements in the final health outcomes?

From these key questions, keywords emerged. Subsequently, MeSH words were derived from these keywords and used for running the literature search on the search engines.

The keywords were:

- Photodynamic Therapy
- Photodynamic Treatment
- PDT
- Phototherapy
- Steroids
- Corticosteroids
- Oral Lichen Planus
- OLP

1.2 Search Engines Used for the Main Hypothesis

Search was terminated on 10/28/2016. The search engines used in the search process were:

PubMed

The search strategy used:

("photodynamic"[text word] OR PDT[text word] OR phototherapy[text word] OR "Phototherapy"[Mesh]) AND ("Lichen Planus, Oral"[Mesh] OR ("lichen planus"[text word] AND (oral[text word] OR mouth[text word] OR mucou*[text word])) OR OLP[text word]) AND English[lang] NOT (animals[mh] NOT humans[mh] AND "Adrenal Cortex Hormones"[Mesh] OR corticosteroid*[text word] OR corticoid*[text word])

Web of Science

“Oral lichen planus” AND (“photodynamic treatment” OR “photodynamic therapy” OR “PDT” OR “phototherapy*”

Scopus

“Oral lichen planus” AND “photodynamic therapy” OR “photodynamic treatment” OR “PDT”

Biosis

Oral lichen planus” AND (“photodynamic treatment” OR “photodynamic therapy” OR “PDT” OR “phototherapy*”

Cochrane Library

#1 MeSH descriptor: [Oral lichen planus] explode all trees

#2 “OLP” (Word variations have been searched)

#3 #1 or #2

#4 “Photodynamic therapy” or “PDT” or “photodynamic treatment” (Word variations have been searched)

#5 MeSH descriptor: [steroid] explode all trees

#6 steroid (word variations have been searched)

#7 #4 or #5 or #6

#8 #3 and #7

ADA-EBD

“Oral lichen planus”

Studies are categorized on this database by the topic. All the relevant search results were retrieved for reviewing and evaluation.

1.3 Determination of the Relevance of the Found Literature to the Main Hypothesis

The search process started by entering the search strategy into the respective six different search engines. This resulted in obtaining an initial sum of 121papers.

After that, systematic steps were followed to further funnel the found sum of papers in accordance with their relevance to the specific aim of this review.

Often, many of these papers get published on more than just one search engine at the same time, so a step of removing potential duplicates followed. This resulted in narrowing down the total number of found papers to 69, on which the inclusion/exclusion criteria were applied and this in turn brought the number of relevant studies down to 8. Four of these eight studies weren't adhering to the PICOTS question of this review and thus were eliminated.

The final result of all the above filtering steps was the attainment of four papers that constituted the bibliome of this part of the systematic review.
The research process is summarized in diagram (2).

1.3.A Relevance to Inclusion Criteria

- Age > 20 years
- English-language papers only
- Both genders and all ethnicities
- All OLP clinical presentations
- All PDT photosensitizing agents
- All PDT light sources
- All PDT light wavelengths
- Studies comparing PDT vs. steroids

1.3.B Relevance to Exclusion Criteria

- Patients age 20 years and less
- Patients with systemic diseases
- Any drug use less than a month before study
- Patients with photosensitivity
- Patients who had lesion/s with dysplasia
- Oral Lichenoid Lesions (OLL's)
- Case-control studies, narrative reviews, expert opinions, animal and laboratory studies
- Patients who received treatment for OLP at least 1 month previous to the beginning of the study
- Studies about steroid and OLP

2.Correlatory Hypothesis

It was based on the observed current clinical practice. Among the choices of topical steroids available for OLP treatment, clobetasol propionate seems to be the most frequently prescribed. This correlatory hypothesis was:

Clobetasol 0.05%, in comparison to Clobetasol 0.025%, results in better clinical improvement of OLP in effected adult patients age 20 years and older with zero dysplasia; as monitored for at least a month of Clobetasol application, measured in a clinical setting.

The correlatory hypothesis was translated into the following PICOTS question:

P: Male and female adult patients (age > 20 years), with OLP and no dysplasia.

I: 0.05% Clobetasol.

C: 0.025% Clobetasol.

O: Clinical improvement.

T: At least one month of in-office PDT.

S: General dental clinics or hospital environment.

The outcome (clinical improvement) was defined as "a reduction in lesion size and or resolution of symptoms".

2.1 Search Strategy Design for the Correlatory Hypothesis

The search was conducted using five different search engines and hand searching. The searching process for relevant studies was performed using keywords obtained from the key questions, which are derived from the main PICOTS question.

The key questions were:

- KQ1: Does steroid improve intermediate results?
- KQ2: Does steroid improve health outcomes?
- KQ3: What is the steroid dose that result in the best OLP treatment outcome?
- KQ4: What are the adverse effects of treating OLP with steroid?
- KQ5: What is the strength of evidence that intermediate outcomes are associated with improvements in the final health outcomes?

From these key questions, keywords emerged. Subsequently, MeSH words were derived from these keywords and used for running the literature search on the search engines.

The keywords were:

- Oral lichen planus
- OLP
- Photodynamic Therapy
- Photodynamic Treatment
- PDT
- Phototherapy
- Steroids
- Corticosteroids
- Clobetasol

2.2 Search Engines Used for the Correlatory Hypothesis

The search was terminated on 10/11/2016. Search engines used in the search process were:

PubMed

("Lichen Planus, Oral"[MeSH] OR "oral lichen planus"[text word] OR OLP[text word]) AND (("Clobetasol"[MeSH] OR clobetasol[text word] OR Clofenazon[text word] OR "Clobetasol Propionate"[text word] OR "clobetasol 17-Propionate"[text word] OR "clobetasol 17 Propionate"[text word] OR clobex[text word] OR Cormax[text word] OR OLUX[text word] OR Dermovate[text word] OR Embeline[text word] OR Embeline E[text word] OR Temovate[text word]))

ADA-EBD

"Oral lichen planus"

Studies are categorized on this data base by the topic. All the relevant search results were retrieved for reviewing and evaluation.

Biosis

Oral lichen planus" AND "steroid"

Web of Science

"Oral lichen planus" AND "steroid"

Cochrane Library

#1 MeSH descriptor: [Oral lichen planus] explode all trees

#2 "OLP" (Word variations have been searched)

#3 #1 or #2

#4 "clobetasol" or "clobetasol propionate" or "temovate" (Word variations have been searched)

#5 MeSH descriptor: [steroid] explode all trees

#6 steroid (word variations have been searched)

#7 #4 or #5 or #6

#8 #3 and #7

Hand Searching

1. WWW.clinical trials.gov
2. Journal of Oral Pathology and Medicine
3. Academy of Oral Medicine
4. American Academy of Dermatology

2.3 Determination of the Relevance of the Found Literature to the Correlatory Hypothesis

The search process started by entering the search strategy into the respective six different search engines. This resulted in obtaining an initial sum of 261 papers.

After that, systematic steps were followed to further funnel the found sum of papers in accordance with their relevance to the specific aim of this review.

Often, many of these papers get published on more than just one search engine at the same time, so a step of removing potential duplicates followed. This resulted in narrowing down the total number of found papers to 53, on which the inclusion/exclusion criteria were applied and this in turn brought the number of relevant studies down to 7. Six of these seven studies weren't adhering to the PICOTS question of this review and thus were eliminated.

The final result of all the above filtering steps was the attainment of one paper which constituted the bibliome of this part of the systematic review.

The research process for the correlatory hypothesis is summarized in diagram (3).

2.3.A Relevance for Inclusion

- Age > 20 years
- English-language papers only
- Both genders and all ethnicities
- All OLP clinical presentations

2.3.B Relevance for Exclusion

- Studies with a mixed population of vesiculo-bullous lesions
- Studies about OLP and other topical steroids or systemic steroids
- Patients age 20 years and less
- Patients with systemic diseases
- Any drug use
- Patients with photosensitivity
- Patients who had lesion/s with dysplasia
- Oral Lichenoid Lesions (OLL)
- Case-control studies, narrative reviews, expert opinions and laboratory studies
- Patients who received treatment for OLP at least 1 month previous to the beginning of the study

3. Measurements for the Hypotheses

3.1 Level of the Evidence

Part of the appraisal of this review's bibliome was the evaluation of the level of evidence based on the US Preventive Services Task Force. Figure (2) explains the level of the evidence.

3.2 Quality of the Evidence

Two independent readers were recruited to evaluate the quality of the bibliome using a reliable, validated instrument (Ex-GRADE) as will be discussed further. A prerequisite for the use of the tool is the standardization (the establishment of inter-rater reliability, coefficient of agreement) between the different independent readers. Standardization of the two readers was first conducted by grading studies not part of the bibliome using the instrument before moving on to evaluate the bibliome. One-on-one meetings were held when needed to discuss any major discrepancies in grading the papers in an attempt to resolve these discrepancies and unify the view on the appraisal criteria of the domains of the instrument.

The average of the sum of the two readers' scores for each single question for each one of the four studies evaluated was used for the acceptable sampling analysis which will be discussed later, along with the use of the total of this sum.

The above quantification assessment of the quality of evidence and relative risk of bias in the collected evidence, provided by the use of such an instrument like the Ex-GRADE that was used here, authorizes further quantitative analysis.

The average of the sum of the readers' scores and the total of this sum were used for the acceptance sampling, which will be discussed, further.

3.3 Validating the Quality of the Evidence and Strength of Recommendation

To allow the assessment of the quality of the evidence and the strength of recommendations, the GRADE Working Group developed an instrument in 2004. The Grading of Recommendations' Assessment, Development, and Evaluation (GRADE) evaluates studies by looking at four components: the study design, study quality, consistency and directness. This instrument forms a link between clinical practices and evidence-based health practices (EBHP).

It produced a qualitative statement using a scale to evaluate each section as high, moderate, low and very low.

The instrument was later developed and expanded to quantify the main two arms of it, the quality of the evidence and strength of recommendations. The revised quantitative instrument was called Ex-GRADE (Phi et al., 2012).

The quality of the evidence was defined by the GRADE Working Group as "the extent to which one can be confident that an estimate of effect is correct", and defined the strength of recommendation as "the extent to which one can be confident that adherence to the recommendation will do more good than harm" (Atkins et al., 2004).

For the evaluation of the quality of evidence of this part of this systematic review, the revised risk of bias instrument was used (Barkhordarian et al., 2013). The revised risk of bias has four domains pertaining to the design, consistency, directness and precision with which a particular study under evaluation was conducted. The ROB instrument is shown in diagram (4).

And for evaluating the strength of recommendations, a set of questions and their respective grading criteria were used. Both arms of the Ex-GRADE are displayed in diagram (5).

3.4 Acceptable Sample Analysis

It is a statistical analysis to determine whether the gathered evidence in the case of this review should be accepted or rejected (Barkhordarian et al., 2013).

Based on the acceptance sampling results, papers of low quality will be eliminated and the highest scoring ones will be retained. This sampling is also a preliminary step to establish the ability to perform an overarching statistical analysis (meta-analysis) after proving the existence of non-heterogeneity between studies.

There are three different ways in which this statistical analysis could be performed:
1) Convention: accepting the top 10 percentile of papers based on the score of the quality of the evidence (e.g., low Risk of Bias).
2) Confidence interval (CI95): accepting the papers of which the scores fall at or beyond the upper confidence limit at 95%, obtained with mean and variance of the scores of the entire bibliome.

3) Statistical analysis: accepting the papers that sustain sequential repeated Friedman analysis. "Friedman test is a non-parametric equivalent of the analysis of variance (ANOVA) for factorial designs".

The first method was used for the purpose of this review. Papers of the bibliome, which scored below the cut-off point, were eliminated. Their low scores reflected an inherent low quality, from which no inferential consensus should be made. These papers disqualified from inclusion into the final bibliome and from any potential further statistical analysis of any kind.
Other papers that scored above the 10% cut-off point were interpreted as having high quality and subsequently were accepted in the final bibliome.

Chapter 3

Results

1A. Search Results for Main Hypothesis

The initial search for relevant systematic reviews, clinical trials and observational studies was conducted using six different search engines, which resulted in producing an initial sum of 121 publications. After removing the duplicates, the number went down to 69 papers. These papers were then examined against the inclusion/exclusion criteria and they number dropped down to 8 papers. Four papers out of these eight had to be eliminated because they didn't adhere to the specific PICOTS question of this review. That resulted in the composition of a bibliome of 4 studies.

These studies were 3 randomized clinical trials and 1 non-randomized clinical trial.

The breakdown of this final bibliome was the following:

1. Efficacy of Laser Phototherapy in Comparison to Topical Clobetasol for the Treatment of Oral Lichen Planus: A Randomized Controlled Trial (Dillenburg *et al*, 2014).
2. A Comparative Study of Toluidine Blue-Mediated Photodynamic Therapy versus Topical Corticosteroids in the Treatment of Erosive-Atrophic Oral Lichen Planus: A Randomized Clinical Controlled Trial (Jajarm *et al*., 2015).
3. A Comparative Pilot Study of Low Intensity Laser versus Topical Corticosteroids in the Treatment of Erosive-Atrophic Oral Lichen Planus (Jajarm *et al*, 2011).
4. A Comparative Evaluation of Low-Level Laser and Topical Steroid Therapies for the Treatment of Erosive-Atrophic Lichen Planus (ElShenawy and Eldin, 2015).

1B. Assessment of Clinical Trials for Main Hypothesis

Clinical trials were evaluated using the Ex-GRADE instrument.

The total of the average sum of the two readers' scores for each one of the four studies evaluated was used for the acceptable sampling analysis.

The set 10% cut-off point corresponded to a score of (37.8).

Three papers of the final bibliome scored less than that, hence they were disqualified.

Thus the final bibliome consisted of one randomized clinical trial:

1. Efficacy of Laser Phototherapy in Comparison to Topical Clobetasol for the Treatment of Oral Lichen Planus: A Randomized Controlled Trial (Dillenburg *et al*, 2014).

Table (7) shows the acceptable sampling data.

1C. Data Extraction for Main Hypothesis

The final bibliome was thoroughly examined to retrieve data out of it. The PICOTS question and key questions were used along to help guide this process. Concise summary statements were obtained from the study and formed the platform for the qualitative consensus.

2A. Search Results for Correlatory Hypothesis

The initial search for relevant systematic reviews, clinical trials and observational studies was conducted using 2ive different search engines, and by hand searching four different sources.

That resulted in producing an initial sum of 261 publications. After removing the duplicates, the number went down to 50 papers.

These papers were then examined against the inclusion/exclusion criteria and they number dropped down to 7 papers. Six papers out of these seven had to be eliminated because they didn't adhere to the specific PICOTS question of this review. That resulted in the composition of a bibliome of one study.

This bibliome consisted of one randomized clinical trial:

1. Topical Clobetasol in the Treatment of Atrophic-Erosive Oral Lichen Planus: A Randomized Controlled Trial to Compare Two Preparations with Different Concentrations (Carbone *et al*, 2009).

2B. Assessment of Clinical Trial of Correlatory Hypothesis

Since the bibliome consisted of a clinical trial, it was evaluated using the Ex-GRADE instrument.

The set 10% cut-off point for acceptable sampling corresponded to a score of (37.8).

The bibliome, Carbone *et al* 2009, scored higher than the cut-off point, thus it qualified to form the final bibliome.

2C. Data Extraction of Correlatory Hypothesis

The final bibliome was thoroughly examined to retrieve data out of it. The PICOTS question and key questions were used along to help guide this process. Concise summary statements were obtained from the study and formed the platform for the qualitative consensus.

C h a p t e r 4

Discussion

1. Interpretation of the Results of the Main and Correlatory Hypotheses

For the main hypothesis, the acceptable sampling process yielded one study after eliminating the rest of the bibliome that scored low by the two independent readers who evaluated the quality of the evidence in each study of the original bibliome of four studies.

For the correlatory hypothesis, the acceptable sampling process yielded the qualification of one study, being above the cut-off point that was independently graded by two independent readers who evaluated its quality of the evidence.

The initial aim this study took off with was to perform a meta-analysis by identifying and analyzing the best available evidence. Meta-analysis integrates results from independent studies, at least two or more, and produces a quantifiable statistical summary of their data. An essential pre-requisite for a meta-analysis is the collection of non-heterogeneous data.

Given the fact that one study only survived through all the stages of scrutiny and qualified to form the final bibliome, a meta-analysis or any other quantitative data analysis could not be performed. This fact routed the initial direction of the review to a qualitative (descriptive) data analysis as follows.

1.1 Qualitative Analysis of the Results of Main Hypothesis

Dillenburg *et al* 2014

While topical 0.05% Clobetasol and LPT (laser phototherapy) were both effective in OLP management, the results indicate that the LPT (with a wavelength of 660 nm, output density of 1000 mW/cm^2 and energy density of 6 J/cm^2) is more effective than 0.05% Clobetasol for treating OLP lesions and preventing their recurrence.

Reductions in symptoms, clinical, functional and BAI scores were observed throughout the treatment period. No side effects were observed in the LPT subjects.

Clobetasol 0.05% was tolerated by patients and caused no change was observed in endogenous cortisol levels. The recurrence of OLP lesions observed also during follow-up visits after Clobetasol treatment was described as a rebound effect that can occur when the steroids are discontinued abruptly.

While 0.05% Clobetasol was observed to deliver inferior performance compared to LPT, especially at follow-up visits, the maintenance of the improvement in clinical signs and symptoms up to two months after the end of treatment with LPT demonstrated longer control of OLP in compared to that achieved with Clobetasol.

While cost-effectiveness of LPT was surpassed by that of the Clobetasol, serious steps are being made toward overcoming that issue. And given the history of light source development mentioned in this review, potentials are high that issue would be resolved in the near future.

The data of this study strongly indicated that LPT is a promising therapeutic modality for OLP.

Tables 8-12 summarize the characteristics of the study included, its severity tools, reported side effects, a summary of the study and a list of the excluded studies that didn't adhere to the criteria of this review.

1.2 Qualitative Analysis of the Results of Correlatory Hypothesis

Carbone *et al* 2009

This study states that Clobetasol propionate in 4% hydroxyethyl cellulose gel would appear to be a treatment of choice for patients with atrophic-erosive OLP, independent of the concentration used. Both concentrations were safe, well-tolerated and provided comparable clinical efficacy.

A larger concentration of the active molecules cannot result in further improvement of the therapeutic findings nor it can optimize the obtained results in a significant manner.

During follow-up, Clobetasol 0.025% patients were observed less stable than Clobetasol 0.05% patients, even though no statistical differences were found. No side effects of topical corticoid treatment were present and no change in the cortisol levels in plasma occurred.

Tables 13-17 summarize the characteristics of the study included, its severity tools, reported side effects, a summary of the study and a list of the excluded studies that didn't adhere to the criteria of this review.

1.2.1 Notes Related to the Investigation of the Correlatory Hypothesis

While researching this correlatory hypothesis, two subsets of clinically relevant questions were briefly investigated on the side as they emerged early in the research process. The first one was pertaining to the effectiveness of the most used topical steroid, Clobetasol, in comparison to the second most used one, fluocinonide acetonide. The second question was pertaining to the effectiveness of topical steroids as immunosuppressants in comparison to immunomodulators such as cyclosporine, tacrolimus and pimecrolimus. These questions can help direct the thinking process for future research projects.

3. Limitations

3.1 Limitations of Previous Studies

Throughout the whole course of conducting this review, there were very limited accessible publications on the topic of oral lichen planus and photodynamic therapy.

The number of accessible published literature comparing the two modalities of steroids and photodynamic therapy for oral lichen planus treatment was so low, among which the number of RCT's was extremely low and there were no systematic reviews relevant to the scope of this review (Yang *et al.*, 2016). In the only three systematic reviews pertaining to OLP that were found (Cheng *et al.*, 2012; Chan *et al.*, 2000; Thongprasom *et al.*, 2011), PDT was mentioned in the first as only one "on-going" study by that time and thus there was no report about it, and was mentioned in the second in the form of photochemotherapy. Inconclusive results were frequently observed in the OLP literature.

Opposite to the methodological utilization of histological assessment for diagnosis that was mostly consistent and followed a clearly set criteria (Kramer, WHO, 1978) in most of the studies, different methods were shown in evaluating the clinical outcome.

Among all the studies included in the bibliome, there appears to be a lack of consensus on the methods used to measure the outcomes of treatment for OLP. While many studies shared the use of VAS, reduction in lesion size and Thongprasom scale to measure these outcomes, some studies only used one or two of these measures (e.g., Cafaro *et al.,* 2014; ElShenawy and Eldin, 2015). Other studies used other scales, or their own criteria for evaluation (Dillenburg *et al.,* 2014; Jajarm *et al*., 2014). All these limitations, added to the wide range of different steroids and variations in photodynamic therapies that were used in the included studies of this review, resulted in heterogeneous data due to discrepancies between the studies. As a result, that hampered the execution of an overarching quantitative statistical analysis.

3.2 Limitations of the Current Study

The extremely limited number of final bibliome, manifested in only one study, constitutes a large limitation encountered through the process of this review.

Performing the important step of setting inclusion/exclusion criteria for the sake of focusing the process of bibliomic sampling search, and though these criteria sat were lenient and largely inclusive, added a restriction in regards to the total number of accepted studies. Among these accepted, an even smaller number of studies were accepted following the evaluation of the quality of evidence in them.

The step of setting up a focused research question, "i.e., PICOTS question" added a stringency criteria that limited the bibliome and made it very specific to that question. If the decision was made to relax the details of the PICO question, more results could have been yielded out of the search for relevant literature.

The decision to use the Ex-GRADE and the risk of bias instruments in this review among other validated and reliable tools to assess the quality of the evidence could pose a limitation of the current study, since not all these instruments available share the same criteria for evaluating the quality of the evidence and they focus on different domains that fundamentally pertain to that quality of the evidence.

Choosing one over the other with no sound reasoning could result in data misinterpretation of the study being appraised, having it scoring in a pattern inconsistent with its real content.

Since the R-Wong instrument examines the quality of research design, methodology and data

analysis, and since the revision of the assessment of multiple systematic reviews instrument (R-AMSTAR) examines the quality of the methodology of systematic reviews, the Ex-GRADE was the most suitable instrument for the aims of this review. The Ex-GRADE evaluates the following: study design, study quality, consistency and directness, all of which are needed for the scope of this review (Chiappelli, 2014; Phi *et al.*, 2012).

The restatement of the conclusions of the bibliome and not performing a qualitative analysis is another limitation of this review. By using qualitative analysis, the main themes of the bibliome can be extracted and quantified, thus allowing researchers to begin to go toward statistical analysis.

Another limitation of this review is the decision to investigate topical clobetasol propionate only among the other available alternatives of topical and systemic steroids used for OLP treatment. The correlatory hypothesis was focused only on comparing two concentrations of the most frequently used topical steroid in the field, covering only a small area of clinical interest and leaving a great area for future research endeavors on all the other types of steroids out there.

For the correlatory hypothesis and in addition to the previously mentioned limitations, the hand searching performed was restricted to publications of only five most important journals in the field of oral medicine and oral pathology, posing a potential limitation of missing publications from other journals that were not hand-searched.

4. Conclusion and Recommendations

4.1 Conclusion

Currently, topical corticosteroids are widely accepted as the first-line therapy for patients with OLP, even with what seems like there is no enough evidence of their efficacy for the treatment of OLP (Scully *et al.*, 1998; Lozada-Nur *et al.*, 1997; Eisen *et al.*, 2005), and even with the long-clinical record of adverse effects associated with steroid intake.

Given the existence of some OLP presentations that are resistant to corticosteroids, and given the existence of cases where corticosteroids cannot be administered, the continual search for alternative therapies is justified. Under the current rate of scientific breakthroughs and major advancements shaping up faster than ever in a collaborative effort between sometimes distantly related fields of science, there is an urgent importance to revisit old hypotheses and to keep up with the current state of knowledge without compromising the scientific rigor.

The qualitative consensus of this research synthesis, based on the best available evidence that was reached utilizing rigorous steps and quality assessment, favors the use of laser phototherapy for treatment of atrophic-erosive oral lichen planus over the use of topical steroids (Dillenburg *et al.,* 2014), and when a clinical decision is made to treat OLP with a Clobetasol topical steroid, its concentration of either 0.025% or 0.05% doesn't have an effect on improving therapeutic findings or on optimizing the obtained results in a significant manner (Carbone *et al.,* 2009).

These reported results seem to be coinciding with what Yeager et al concluded in 2004 by saying "the clinical view that glucocorticoids act solely as anti-inflammatory agents needs to be re-assessed because it is now clear that varying doses of glucocorticoids do not lead simply to varying degrees of inflammation suppression. Glucocorticoids can, and do, exert a full range of clinical effects from permissive to stimulatory to suppressive" (Yeager *et al.*, 2004). This validates the conclusion of this review's both main and correlatory hypotheses.

These observations warrant initiatives to investigate what the field of photodynamic therapy could offer as it also warrants revisions of the standard clinical protocols.

The stringency of this review might have posed a limitation hampering the attainment of a bigger bibliome, and that stringency could have been overcome by relaxing the criteria of the PICOTS questions or simply by eliminating this step of setting up a PICO question altogether. As doing so would have resulted in a bibliome twice the size, as in the case of the main hypothesis for example, but it would have also produced a much less specific bibliome and thus the ultimate answer would have been much less specific too.

The findings of this review, representing an evidence-based health care model, affirm the still standing challenge in the field of immunology to solve some of its mysteries. These findings also emphasize the gap between the research world and routine clinical practices; a gap that is ought to be filled by translational research efforts.

4.2 Clinical Recommendations

Healthcare providers, caregivers, patients and everyone who has a stake in the matter of OLP are encouraged to familiarize themselves with the scientific research synthesis. Healthcare providers bear huge responsibility in that regard given their authority.

This systematic review concludes that laser phototherapy is a more effective approach for treating OLP than 0.05% topical Clobetasol, with the only disadvantage of LPT being the upfront cost of the equipment and the specialized training requirement.

This is a cost-effective approach that benefits the patient and should be addressed in the decision-making process.

A proposed algorithm based on the findings of this review is presented in diagram (6).

4.3 Research Recommendations

There is a great need for more primary and secondary research in the field of oral lichen planus in general. The primary research should aim to produce homogenous results by using standardized measures and research protocols.

Standardization of the assessment methods used to measure outcomes of these studies and the way data is reported are essential to build strong foundations for the knowledge base about the condition and for future advancement of the field.

The effectiveness of topical and systemic steroids used for OLP treatment, other than clobetasol propionate reviewed here, should be researched in the future. Also, as this review compared the effectiveness of a class of immunosuppressants against PDT, the other OLP treatment modalities known and mentioned in this review “PUVA, drug withdrawal, surgery” can be researched using the same approach followed in conducting this current study.

While the Ex-GRADE and risk of bias instruments were utilized in this review, other quality assessment instruments for the critical appraisal of publications can be used for future projects, since all these instruments examine the quality of the evidence but each individual instrument looks at that from an aspect slightly different from the other.

Also, a qualitative assessment of the statement of data of the found bibliome in this review can be performed in the future and a possible statistical analysis can be conducted.

It is also important to produce critical summaries of the results from these studies and disseminate them to all stakeholders.

4.4 Practical Implications

The recommendations of this systematic review, as with any other evidence-based research, should be made accessible and available to all strata of stakeholders; primary stakeholders (e.g., patients, immediate family members), key stakeholders (e.g., friends and relatives), secondary stakeholders (e.g., OLP patient communities' websites and public health advocates) and allied stakeholders (e.g., healthcare staff, hospital employees, insurance agents, legal staff) in a timely, uncomplicated and clearly stated manner (Barkhordarian *et al.*, 2015).

Table (18) shows definitions of different groups of stakeholders.

TABLES AND DIAGRAMS

Tables (1) - (4) summarize important epidemiology of OLP.

The use of these tables here was authorized by the main author, courtesy of C.H. Carvalho.

"Carvalho, C. H., Santos, B. R., Vieira Cde, C., Lima, E., Santos, P. P., & Freitas Rde, A. (2011). An epidemiological study of immune-mediated skin diseases affecting the oral cavity. *An Bras Dermatol, 86*(5), 905-909."

TABLE 1: Distribution of the immune-mediated skin diseases affecting the oral cavity

Histological type	Frequency	
	n	%
Lichen planus	54	65.8
Pemphigus vulgaris	22	26.8
Pemphigoid	6	7.3
Total	82	100

TABLE 2: Distribution of the immune-mediated skin diseases affecting the oral cavity in accordance with patient gender

Histological type	Gender				
	Female		Male		Total
	n	%	n	%	%
Lichen planus	33	61.1	21	38.9	100
Pemphigus vulgaris	17	77.3	5	22.7	100
Pemphigoid	4	66.6	2	33.3	100

TABLE 3: Distribution of the immune-mediated skin diseases affecting the oral cavity in accordance with the anatomical site affected

Histological type	Anatomical site															
	Cheek mucosa		Gingiva		Soft palate		Hard palate		Lip		Retromolar region		Tongue		Alveolar border	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Lichen planus	28	44.2	3	5	5	8.2	2	3.30	8	9.8	1	1.6	2	16.4	7	11.5
Pemphigus vulgaris	9	53.8	3	7.6	1	7.6	1	7.6	2	15.3	1	7.6	0	0	0	0
Pemphigoid	4	60	2	40	0	0	0	0	0	0	0	0	0	0	0	0
Total	37	46.8	6	7.6	6	7.6	3	3.80	8	10.1	2	2.5	1	12.7	7	8.9

TABLE 4: Distribution of the immune-mediated skin diseases affecting the oral cavity in accordance with the age-group affected

Age-group	Histological type					
	Lichen planus		Pemphigus vulgaris		Pemphigoid	
	n	%	n	%	n	%
11 - 20 years	4	8.16	2	0	0	0
21 - 30 years	4	8.16	6	31.5	3	50
31 - 40 years	9	16.6	3	10.5	0	0
41 - 50 years	13	24.1	5	21	0	0
51 - 60 years	13	24.1	3	15.8	2	33.3
61 - 70 years	5	10.2	1	5.3	1	16.6
Data missing	6	12.2	3	15.9	0	0
TOTAL	54	100	23	100	6	100

Table (5) Primary Effects of Glucocorticoids

Anti-inflammatory	Inhibit inflammation by blocking the action of inflammatory mediators (transrepression), or by inducing anti-inflammatory mediators (transactivation)
Immunosuppressive	Suppress delayed hypersensitivity reactions by directly affecting T-lymphocytes
Anti-proliferative	Inhibit DNA synthesis and epidermal cell turnover
Vasoconstrictive	Inhibit the action of histamine and other vasoconstrictive mediators

Table (6) Characteristics of an Ideal Photosensitizer

- Highly selective tumor accumulation.
- Low toxicity and fast elimination from the skin and epithelium.
- Absorption peaks in the low-loss transmission window of biological tissues.
- Optimum ratio of the fluorescence quantum yield to the interconversion quantum yield (The first parameter determines the photosensitizer diagnostic capabilities, and plays a key role in monitoring the photosensitizer accumulation in tissues and its elimination from them; the second parameter determines the photosensitizer ability to generate singlet oxygen).
- High quantum yield of singlet oxygen production in vivo.
- Cost-effectiveness and commercial availability.
- High solubility in water, injection solutions, and blood substitutes.
- Storage and application light stability.

Diagram (1). Types of Study Designs

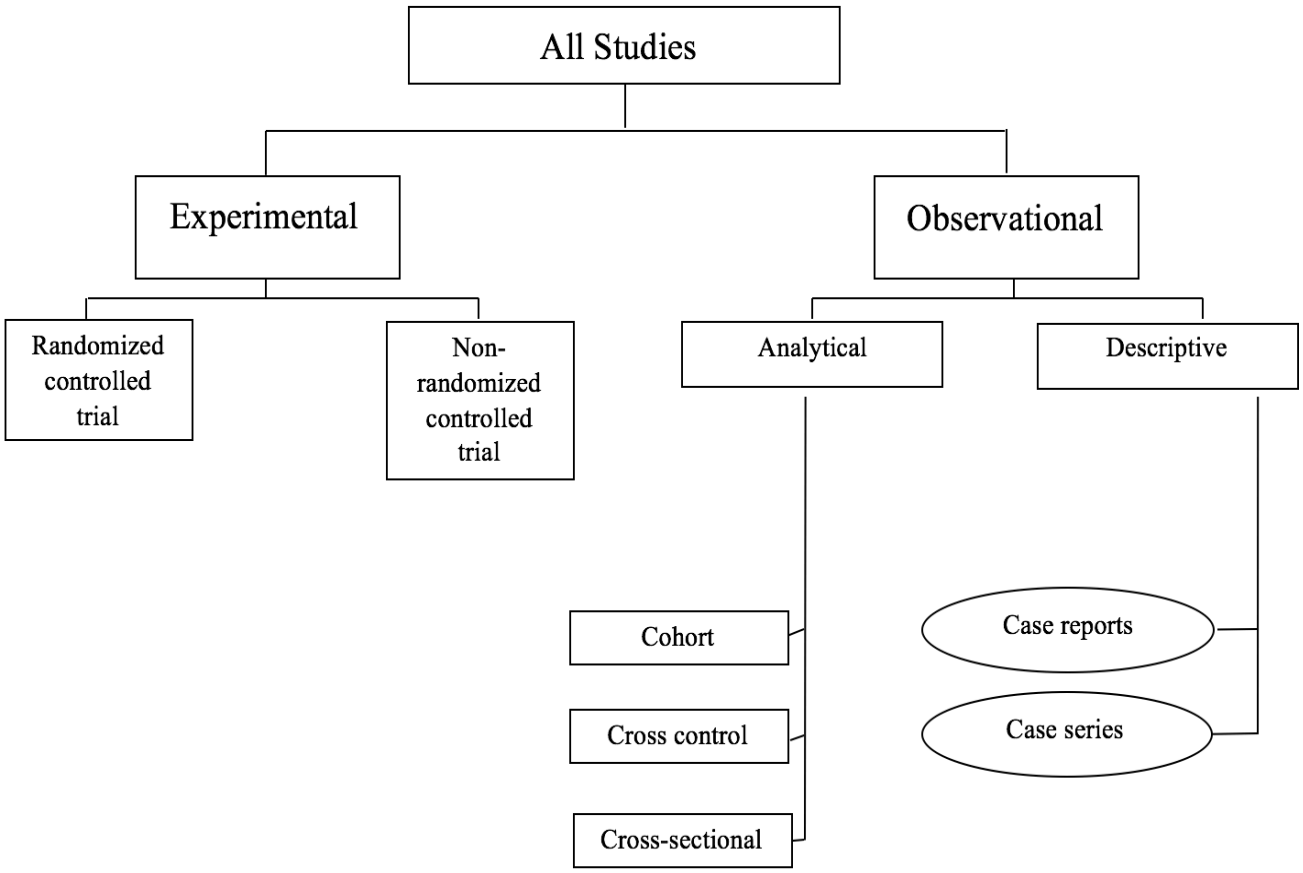

Diagram (2) Search Strategy for the Main Hypothesis

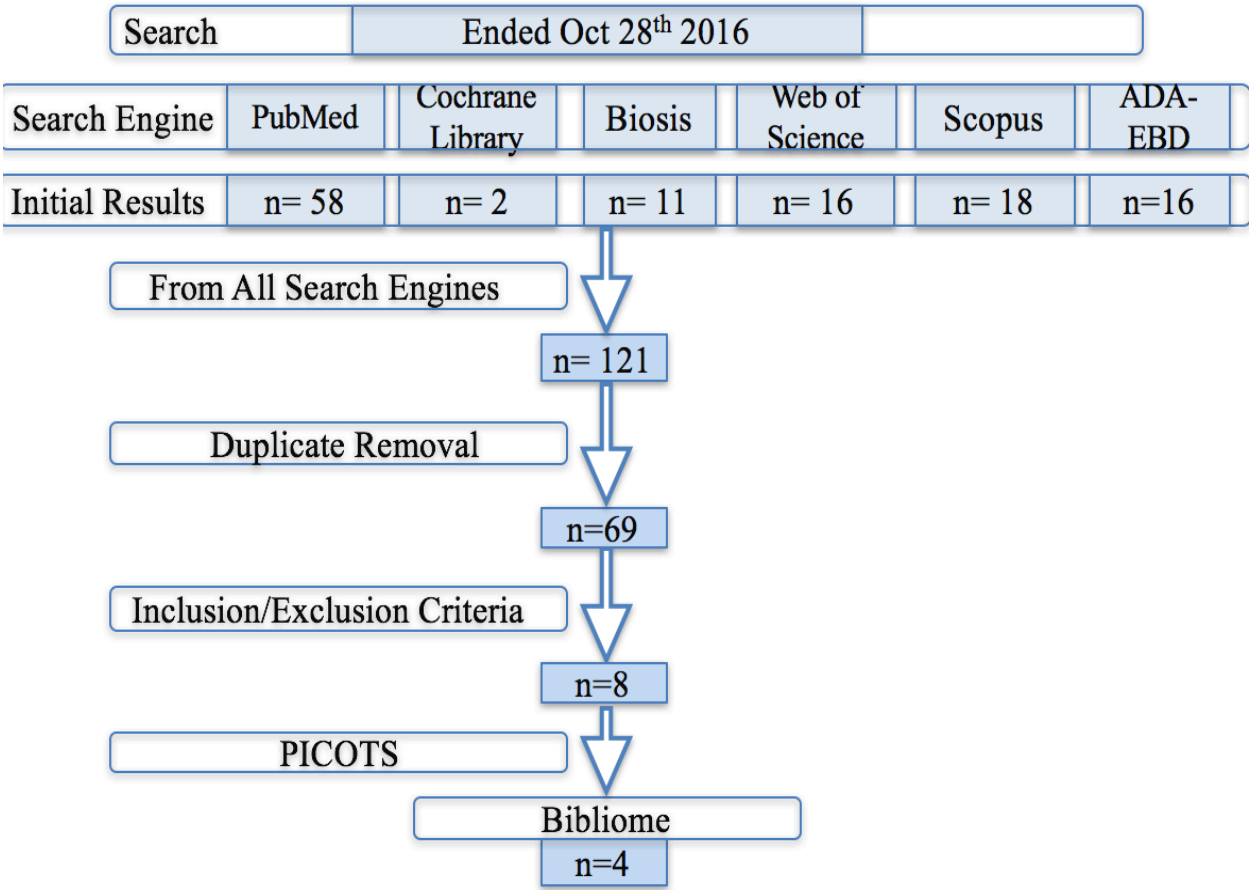

Diagram (3) Search Strategy for the Correlatory Hypothesis

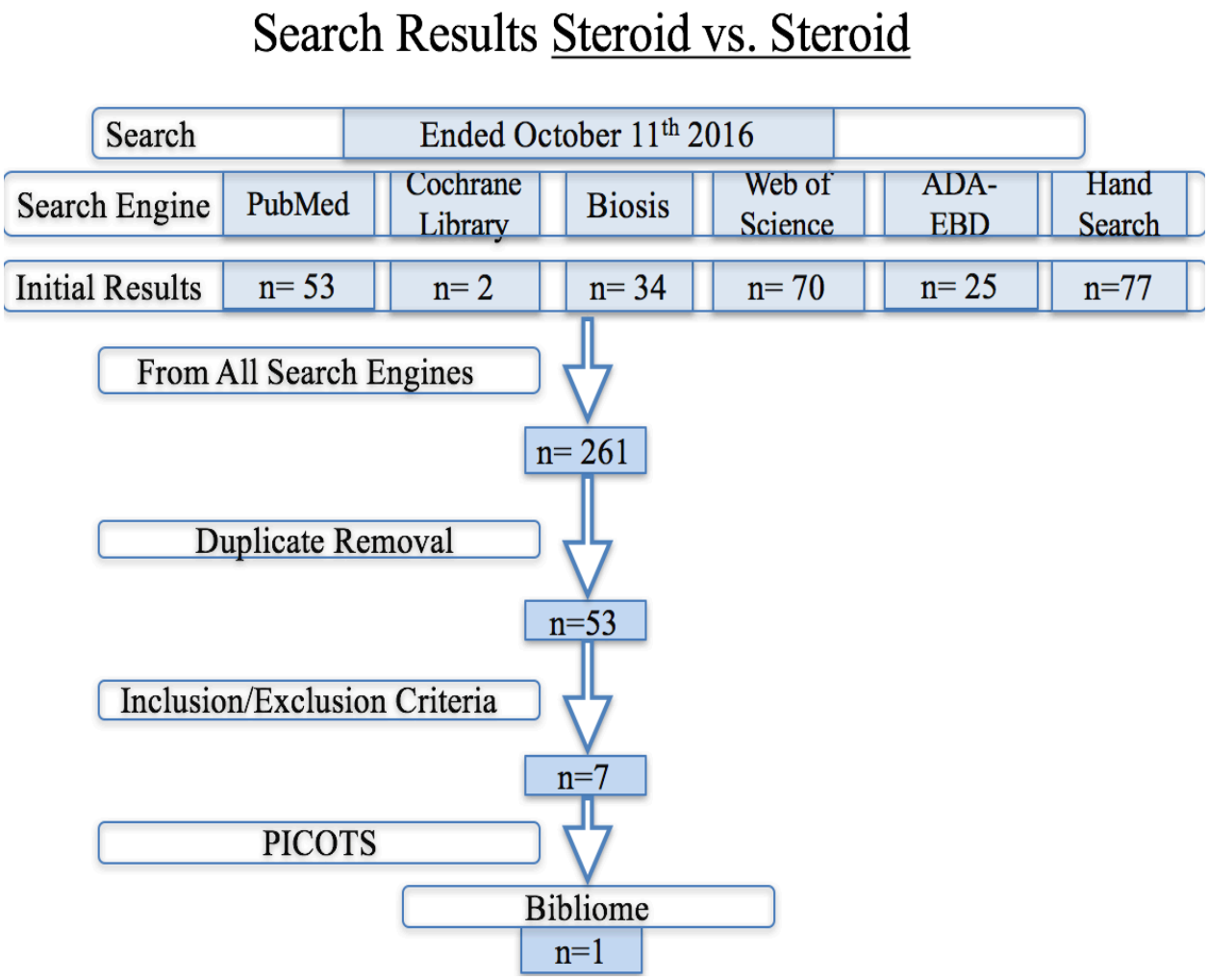

Diagram (4) The Revised Risk of Bias Instrument

Evidence of Reporting Assessment

Number of Studies (Subjects)	**Domains Pertaining to Strength of Evidence**				**Magnitude of Effect and Strength of Evidence (SOE)**
	Risk of Bias: Design/Quality	*Consistency*	*Directness*	*Precision*	*Absolute Risk Difference per 100 patients*

Risk of Bias- Study design and study conduct for individual studies.

Principle criteria
A. Bias in study design.
B. Bias in methodology.
C. Bias in study conduct.

Possible ratings are (*Low/moderate/high/excessive*)

4 points	(Low)	No bias evident in study design, methodology or conduct.
3 points	(Moderate)	Some bias determined in at least one of the criteria (design, methodology, conduct).
2 points	(High)	Bias determined in two of the three criteria (design, methodology, conduct).
1 point	(Very high)	Bias determined in all three criteria.

Consistency- Degree of similarity in the effect sizes of different studies within an evidence base

A. Inconsistent evidence bases have significant unexplained clinical statistical heterogeneity

B. Meta-analysis should use appropriate test, Cochran's Q test or 12 statistics.

Possible ratings are (*Consistent/Questionable/Inconsistent*)

3 points	(Consistent)	Both criteria (A & B) are satisfied.
2 points	(Questionable)	1 of the 2 criteria (A or B) satisfied only.
1 point	(Inconsistent)	Neither criteria satisfied or unknown.

Directness- Either a single direct link between the interventions of interest and the ultimate health outcome under consideration or multiple links in a casual chain. With multiple links, strength of evidence is only as strong as the weakest link.

A. A single direct link between the interventions of interest and the ultimate health outcome under consideration.
B. Reliance on multiple links, evidence of a casual chain (with multiple links, strength of evidence is only as strong as the weakest link).

Possible ratings are (*Direct/Unclear/Indirect*)

3 points	(Direct)	Either criteria (A or B) clearly established.
2 points	(Unclear)	Criteria not fully satisfied in either case.
1 point	(Indirect)	Neither criteria clearly established.

Precision- The degree of certainty for estimate of effect with respect to a specific outcome.

A. Includes statistical significance for effect estimates.
B. Includes confidence intervals for those effect estimates
C. Include any summary estimate of effect size

Possible ratings are (*Precise/Moderate/Questionable/Imprecise*)

4 points	(Precise)	Three criteria satisfied.
3 points	(Moderate)	Two of the three criteria satisfied.
2 points	(Questionable)	One of the three criteria satisfied.

1 point	(Imprecise)	None of the criteria satisfied.

Risk of Bias score:

Σ =

Possible sum ranges from 4 (highest risk of bias) to 14 (lowest risk of bias).

Additional domains serve as tools to qualify the scores of individual papers in addition to the criteria (satisfied or not) for each of the four items of the principal components of Strength of Evidence (Risk of bias, Consistency, Directness, Precision).

Additional Domains (if Applicable)			
Dose-response association	*Plausible cofounders*	*Strength of association*	*Publication bias*

Dose response association- Pattern of a larger effect with greater exposure (dose, duration, adherence)

- Rate if studies give level of exposure.

  Present/Not Present/ Not Applicable or Not Tested

Plausible Confounders- Consider whether or not plausible confounding exists that would decrease the observed effect.

Present/Absent

Strength of Association- The likelihood that the observed effect is large enough that it cannot have occurred solely as a result of bias from potential confounding factors.

- Consider when effect size is particularly large.

  Strong/Weak

Publication bias- Studies may have been published selectively.

- Estimated effects of an intervention that are based on published studies do not reflect true effect.

- Should take into account the ratings of consistency and the calculation of a summary confidence interval for an effect.
- Add comments on publication bias when relevant empirical findings, particularly negative or no-difference findings, have not been published or are not otherwise available.

Strength of Evidence Grades- Reflect a global assessment of presented evidence.

- Takes into account the required 4 domains.
- Incorporates judgments about the additional domains as needed.

For each comparison of interest, rate strength of evidence for

- Each major benefit
- Each major harm
- Both benefits and harms
    - Focus on the outcomes most relevant to patients, clinicians, and policymakers

High/Moderate/Low/Insufficient

- The use of High/Moderate/Low implies that a body of evidence actually exists.

Level of evidence- See chart for grading procedure

Diagram (5) The Ex-GRADE for the Quality of the Evidence and Strength of Clinical Recommendations' Assessment

APPENDIX 1

The "Strength of Recommendation" section of the Ex-GRADE (Expansion of the Grading of Recommendation Assessment, Development, and Evaluation) is graded on a point-based system, with 1 being the lowest score possible per question and 4 being the highest score possible per question. With a total of 8 questions, the minimum total score possible a primary source or systematic review will receive is 8 & the maximum total score possible is 32.

1. **Are the findings and quality of evidence of the study applicable to the specific recommendation?** (Score from "quality of evidence" section. *E.g. A clinical trial that receives a score of 23 using the R-Wong scale would fulfill 2 criteria: 1 criterion for scoring at least 19 & 1 criterion for scoring at least 22 → hence will receive a score of 3 using the Ex-GRADE according to the grading scale below.*)
   - Fulfills 3 of the criteria → 4
   - Fulfills 2 of the criteria → 3
   - Fulfills 1 of the criteria → 2
   - Fulfills 0 of the criteria → 1

   CRITERIA:
   For Primary Sources

R-Wong score of at least 25 for clinical trials OR at least 22 for all other primary sources
R-Wong score of at least 22 for clinical trials OR at least 20 for all other primary sources
R-Wong score of at least 19 for clinical trials OR at least 17 for all other primary sources

   For Systematic Reviews:

Systematic Reviews – R-AMSTAR score of at least 40 for systematic reviews
Systematic Reviews – R-AMSTAR score of at least 36 for systematic reviews
Systematic Reviews – R-AMSTAR score of at least 31 for systematic reviews

2. **Are risk and affordability considered when given the recommendation for the intervention?**
   - Fulfills 3 of the criteria → 4
   - Fulfills 2 of the criteria → 3
   - Fulfills 1 of the criteria → 2
   - Fulfills 0 of the criteria → 1

   CRITERIA:

Recognition of risk for the intervention is directly stated, or acknowledgement of risk can be inferred
Recognition of possible adverse effects post-intervention is directly stated, or acknowledgement of possible adverse effects post-intervention can be inferred
Recognition of cost for the intervention is directly stated, or approximate and/or relative cost for the intervention can be inferred
Recognition of affordability is directly stated or can be inferred

3. **Are alternative recommendations given, if appropriate?**
   - Fulfills 3 of the criteria → 4
   - Fulfills 2 of the criteria → 3
   - Fulfills 1 of the criteria → 2
   - Fulfills 0 of the criteria → 1

   CRITERIA:

Alternative suggestions or recommendations were given with regards to risk during the intervention

Alternative suggestions or recommendations were given with regards to possible adverse effects following the intervention
Alternative suggestions or recommendations were given with regards to cost & affordability
Explicitly states that no alternative recommendations are appropriate with regards to risk during the intervention
Explicitly states that no alternative recommendations are appropriate with regards to possible adverse effects following the intervention
Explicitly states that no alternative recommendations are appropriate with regards to cost & affordability

4. **Is availability of resources for the population of interest taken into account prior to formulating the recommendation?** *[Is the recommendation practical for the population of interest?]*

- Fulfills 3 of the criteria → 4
- Fulfills 2 of the criteria → 3
- Fulfills 1 of the criteria → 2
- Fulfills 0 of the criteria → 1

CRITERIA:

Insurance coverage is available for the recommended intervention at hand *[Some research on various insurance plans may need to be done]*
Other alternative funding aside from insurance is available for the recommended intervention at hand *[Some research for alternative funding may need to be done]*
Resources in terms of equipment & supplies for the recommendation are easily accessible in clinical practice *[This may require some prior knowledge of the equipments & supplies provided in the standard setting of the population of interest]*

5. **Is a measureable guideline provided to monitor the intended outcome(s) of the recommendation?** [Was there a method provided that can measure the effectiveness of the recommendations? How did they/will they measure the outcomes or results?]

- Fulfills 3 of the criteria → 4
- Fulfills 2 of the criteria → 3
- Fulfills 1 of the criteria → 2
- Fulfills 0 of the criteria → 1

CRITERIA:

Method of monitoring the intended outcome of the recommendation is given
Method of monitoring the intended outcome can produce tangible data for the researcher
Method of analyzing the data produced from monitoring the intended outcome is provided

6. **Are the results of the intervention *statistically* significant?**

- Fulfills 3 of the criteria → 4
- Fulfills 2 of the criteria → 3
- Fulfills 1 of the criteria → 2
- Fulfills 0 of the criteria → 1

CRITERIA:

Chosen methodology of the research is appropriate for the intended recommendation at hand
Methodology of the research (e.g. methodology of the clinical trial, methodology of the systematic review, etc.) is executed properly & accurately
Statistical analysis of the data shows statistical significance with $p < 0.05$

7. **Are the results *clinically* significant?**

- Fulfills 3 of the criteria → 4
- Fulfills 2 of the criteria → 3
- Fulfills 1 of the criteria → 2
- Fulfills 0 of the criteria → 1

CRITERIA:

For curative medicine/care, palliative medicine/care, or aesthetic/cosmetic care:

The intervention alters the pathophysiology of the disease/issue in question
The intervention can be realistically carried out & successfully executed in the clinical setting
The time it takes for noticeable results to be seen post-intervention is reasonable taking into consideration the total cost of the intervention (Cost = monetary expenses & risk, both during the intervention & post-intervention)

For preventive medicine/care:

The intervention does not alter the pathophysiology of the disease/issue in question
The intervention does not induce another pathology aside from the disease/issue in question
The intervention can be realistically carried out & successfully executed in the clinical setting

8. **Is the patient likely to comply with the suggested recommendation?**

- Fulfills 3 of the criteria → 4
- Fulfills 2 of the criteria → 3
- Fulfills 1 of the criteria → 2
- Fulfills 0 of the criteria → 1

CRITERIA:

Minimal level of invasiveness to the patient
Minimal level of side effects after the given intervention
Benefits of the recommendation outweigh its total cost (Cost = monetary expenses & risk, both during the intervention & post-intervention)

Table (7) Acceptable Sampling Analysis for the Main Hypothesis

	A	B	C	D	E	F	G	H	I	J	K	L	M
1	ExGRADE	ROB	Consistency	Directness	Precision	Q2	Q3	Q4	Q5	Q6	Q7	Q8	TOTAL
2	Dillenburg	4	3	3	3	4	4	2	4	4	4	4	38
3	Jajarm 14	4	3	3	3	2	1	1	4	4	4	4	32
4	Jajarm 11	4	3	3	3	2	1	1	4	4	4	4	32
5	AlShenawy	3	3	3	3	2	1	1	4	3	3	4	29
6	SD	0.5	0	0	0	1	1.5	0.5	0	0.5	0.5	0	
7	Mm	3.75	3	3	3	2.5	1.75	1.25	4	3.75	3.75	4	

Table (8) Characteristics of the Included Study for Main Hypothesis

Dillenburg 2014	
Methods	Randomized controlled trial to compare laser phototherapy and topical clobetasol
Participants	Total n = 42 patients (LPT group had 21 patients, clobetasol group had 21 patients)
Interventions	• A: Topical 0.05% clobetasol propionate • B: LPT using continuous diode laser (InGaAlP, MM Optics, Brazil) of 660 nm wavelength and 6 J/Cm^2 energy density • 3 sessions of LPT for 4 consecutive weeks, 4 weeks of clobetasol administration
Outcomes	1. Clinical score 0 to 5 (Thongprasom 1992) 2. VAS 3. Functional score (Lilleby 2006) 4. Clinical Resolution(CR) and Recurrence Rate(RR) 5. Beck anxiety inventory(BAI) • Treatment outcomes were defined as changes in sign, symptom and size of the lesions between baseline and the last session. Positive and negative values were considered as improvement and worsening, respectively
Assessment Points	• Day: 0, 7, 14, 21, 30 • FU: Day 60 and 90
Side-Effects Reported	• No side effects in the LPT group • 3 patients in the clobetasol group reported transient local burning sensation immediately after the first 2 days of drug application and 2 patients reported gastrointestinal distress
Reported Results	• LPT is more effective than clobetasol for treating OLP lesions and preventing their recurrence • LPT is a promising therapeutic strategy for OLP
Level of Evidence	High
Risk of Bias	Low
Consistency	Consistent
Directness	Direct
Precision	Moderate

Table (9) Summary of the Included Study for the Main Hypothesis

Dillenburg *et al* 2014

Intervention A	Intervention B	Frequency	Treatment Duration	Assessment Points	Assessment Methods	Methods of Diagnosis	Reported Results
LPT	Topical 0.05% clobetasol propionate gel	A: 3 sessions for 4 weeks B: 4 weeks	1 month	Day 0, 7, 14, 21, 30	1. Clinical score 0 to 5 (Thongprasom 1992), 2. VAS, 3. Functional score (Lilleby 2006), 4. Clinical Resolution (CR) and Recurrence Rate (RR), 5. Beck anxiety inventory (BAI)	Histology and clinical	1. LPT is more effective than clobetasol for treating OLP lesions and preventing their recurrence 2. LPT is a promising therapeutic strategy for OLP

Table (10) Severity Tools Used for the Primary Outcomes of Dillenburg 2014 *et al*

Study	Clinical Severity	Symptoms
Dillenburg 2014	Clinical scores 0 to 5 (Thongprasom 1992)	• VAS • BAI • Functional score

Table (11) Side Effects Reported in Dillenburg 2014 *et al*

Study	Intervention A	Intervention B	Side- effects
Dillenburg 2014	Topical 0.05% clobetasol propionate	LPT using continuous diode laser (InGaAlP, MM Optics, Brazil) of 660 nm wavelength and 6 J/Cm^2 energy density	• LPT group: No side effects • Clobetasol group: 3 patients reported transient local burning sensation immediately after the first 2 days of drug application and 2 patients reported gastrointestinal distress

Table (12) Characteristics of Excluded Studies for Main Hypothesis

Study	Reason for Exclusion
Agha-Hosseini 2006	Case report
Agha-Hosseini 2013	Editorial letter
AlHashimi 2007	Review paper, doesn't fit inclusion/exclusion criteria
AlNasser 2014	Review paper, doesn't fit inclusion/exclusion criteria
Bagan 2012	Review paper
Béhcherel 1998	Doesn't adhere to PICO
Bombeccari 2013	Doesn't adhere to PICO
Carrozzo 1999	Review paper, doesn't fit inclusion/exclusion
Chamani 2015	Doesn't fit inclusion/exclusion
Chan 2008	Doesn't fit inclusion/exclusion criteria
Chen 1989	Photochemotherapy
Cheng 2015	Doesn't fit inclusion/exclusion criteria
Davari 2014	Doesn't fit inclusion/exclusion criteria
Dillenburg 2015	Epigenetic Modifications in OLP
Di Stasio 2014	Review paper on OLP and RCM
Fazel 2014	Review paper, doesn't adhere to inclusion/exclusion
Feily 2009	Aloe Vera review
Gonzalez 1984	Photochemotherapy
Gursoy 2012	Review paper, doesn't adhere to PICO
Guyot 2007	Extracorporeal photochemotherapy
Halender 1987	Photochemotherapy
Ismail 2007	Review paper, doesn't fit PICO
Issa 2013	Mucosal lesions and malignancy, doesn't adhere to PICO
Jansén 1987	Photochemotherapy
Kalmar 2007	Review paper, doesn't adhere to PICO
Kang 2009	Case report, doesn't adhere to PICO
Kapoor 2008	Editorial letter
Kassem 2012	Photochemotherapy
Katta 2000	Doesn't adhere to PICO
Konopka 2007	PDT for head and neck, doesn't adhere to PICO
Köllner 2003	Case report
Kolm 2013	Lichenoid reaction
Kurgansky 1994	LP, doesn't adhere to PICO

Kuusilehto 1990	Photochemotherapy
Kuusilehto 1997	Photochemotherapy, lichenoid lesions
Kvaal 2007	Review paper, doesn't adhere to PICO
Kvaal 2013	Doesn't fit inclusion/exclusion criteria
Kvaal 2013	Editorial reply
Lodi 2012	Doesn't fit inclusion/exclusion criteria
Lang 1981	Case report, doesn't adhere to PICO
Lehtinen 1989	Photochemotherapy
Lundquist 1995	Photochemotherapy
Maloth 2016	Doesn't fit inclusion/exclusion criteria
McCreary 1999	Review paper
Mostafa 2015	Review paper
Nanda 2001	Case report, childhood LP
Nanda 2003	Case report
Orfanos 1987	Retinoids, doesn't adhere to PICO
Ortonne 1978	Photochemotherapy, LP
Ortonne 1979	Photochemotherapy, LP
Panwar 2014	Review paper, premalignant lesions
Pavlic 2014	Review paper
Sadaksharm 2012	Doesn't fit inclusion/exclusion criteria
Setterfield 2000	Doesn't adhere to PICO
Sharma 2012	Review paper, doesn't adhere to PICO
Shirasuna 2013	Review paper, OLP and malignancy
Sigurgeirsson 1992	Skin disease and malignancy, doesn't adhere to PICO
Simon 2000	Doesn't adhere to PICO, French language
Sobaniec 2013	Doesn't fit inclusion/exclusion criteria
Stein 2007	Psoriasis
Thongprasom 2011	Doesn't fit inclusion/exclusion criteria
Trehan 2004	Doesn't fit inclusion/exclusion
Volc-Platzer 1990	Photochemotherapy
Wackernagel 2007	Photochemotherapy
Wennberg 2015	Genital, not oral LP
Yang 2016	Review paper
Yoke 1998	Photochemotherapy
Zakrzewska 2005	Systematic review, doesn't fit inclusion/exclusion
Zingoni 2010	Photochemotherapy

Table (13) Characteristics of Included Study for the Correlatory Hypothesis

Carbone 2009	
Methods	Randomized controlled trial to compare two preparations of topical clobetasol with different concentrations
Setting	Oral Medicine Section, University of Turin
Participants	Total n = 30 (Clobetasol 0.025% n= 15, Clobetasol 0.05% n = 15)
Interventions	A: Topical clobetasol propionate 0.025% B: Topical clobetasol propionate 0.05% Applied BDS for two months with antimyotic prophylaxis for both groups
Outcomes	1. Symptoms (VAS 0-10): Symptom response at end of treatment (week 8) compared to baseline defined as follows: Complete response: absence of any discomfort or symptom Partial response: decrease in VAS Persistence: no change in VAS Worsening: increase in VAS 1. Clinical response (Thongprasom 0-5): Complete response: disappearance of all lesions Partial response: decrease in score Persistence: no change in score Worsening: increase in score
Assessment Points	Week 0, 2, 4, 6, 8, 16
Side-Effects Reported	None reported
Level of Evidence	High
Reported Results	No difference between the two groups at two months period, measured by clinical score/response and VAS
Risk of Bias	Low
Consistency	Moderate
Directness	High
Precision	High

Table (14) Summary of the Included Study for the Correlatory Hypothesis

Carbone *et al* 2009

Intervention A	Intervention B	Frequency	Treatment Duration	Assessment Points	Assessment Methods	Methods of Diagnosis	Reported Results
Topical clobetasol propionate 0.025%	Topical 0.05% clobetasol propionate	Twice per day for both	2 months	Week 0, 2, 4, 6, 8, 16	1. VAS 2. Clinical score 0 to 5 (Thongprasom 1992)	Histology and clinical	No statistically significant difference between the two groups

Table (15) Severity Tools used for Primary Outcomes of Carbone 2009 *et al*

Study	Clinical Severity	Symptoms
Carbone 2009	Clinical scores 0 to 5 (Thongprasom 1992)	VAS 0 to 100

Table (16) Side Effects Reported in Carbone 2009 *et al*

Study	Intervention A	Intervention B	Side- effects
Carbone 2009	Topical clobetasol propionate 0.025%	Topical clobetasol propionate 0.05%	No side effects

Table 17. Characteristics of Excluded Studies for Correlatory Hypothesis

Study	Reason for Exclusion
Sivaraman et al 2016	Doesn't adhere to PICO question
Hettiarachchi et al 2016	Doesn't adhere to PICO question
Lauritano et al 2016	Doesn't adhere to PICO question
Vigarios et al 2015	Oral hairy leukoplakia
Chamani et al 2015	Doesn't adhere to PICO question
Dillenburg et al 2015	Epigenetic modifications of DNA in OLP
Rosa et al 2015	In situ carcinoma
Decani et al 2014	Cushing's syndrome
Pereira et al 2014	Candida and OLP
Rivarola et al 2014	Doesn't adhere to PICO question
Davari et al 2014	Doesn't adhere to PICO question
Hilger, Megahed 2014	Doesn't adhere to inclusion/exclusion
Czerninski et al 2013	OLP and dental implants
Kolois et al 2013	Doesn't adhere to PICO question
Law Ping Man et al 2013	Doesn't adhere to PICO question
Sonthalia, Singal 2012	Doesn't adhere to PICO question
Kaplan et al 2012	Doesn't adhere to PICO question
Varoni et al 2012	Doesn't adhere to PICO question
Cheng et al 2012	Doesn't adhere to PICO question
Samycia, Lin 2012	Doesn't adhere to PICO question
Scatarella et al 2011	OLP and dental hygiene
Machado et al 2010	Doesn't adhere to PICO question
Cilurzo et al 2010	Doesn't adhere to PICO question
Gonzalez-Moles, Scully 2010	Doesn't adhere to PICO question
Mattson et al 2010	Squamous cell carcinoma and OLP
Motta et al 2009	Doesn't adhere to PICO question
Pramick, Whitmore 2009	Doesn't adhere to PICO question
Corrocher et al 2008	Doesn't adhere to PICO question
Radfar et al 2008	Doesn't adhere to PICO question
Bäckman, Jontell 2007	Oral lichenoid reactions
Lodi et al 2007	Doesn't adhere to PICO question
Solomon et al 2007	OLP pemphigoides
Petruzzi et al 2007	Isolated LP of the lip
Levell 2006	Editorial letter

Conrotto et al 2006	Doesn't adhere to PICO question
Petruzzi et al 2005	Peno-gingival LP
Campisi et al 2004	Doesn't adhere to PICO question
Gunning, Turiansky 2003	Doesn't adhere to PICO question
Stoopler et al 2003	Desquamative gingivitis
Carbone et al 2003	Doesn't adhere to PICO question
Gonzalez-Moles et al 2003	Doesn't adhere to inclusion/exclusion criteria
Gonzalez-Moles et al 2002	Editorial letter
Gonzalez-Moles et al 2002	Doesn't adhere to PICO question
Lo Muzio et al 2001	Doesn't adhere to PICO question
Chainani-Wu et al 2001	Doesn't adhere to PICO question
Katta 2000	Doesn't adhere to PICO question
Carbone et al 1999	Doesn't adhere to PICO question
Sardella et al 1998	Doesn't adhere to PICO question
Brown et al 1997	Case report of lichen sclerosus et atrophicus
Carbone et al 1997	Doesn't adhere to PICO question
Lozada-Nur et al 1994	Doesn't adhere to PICO question
Roed-Petersen, Roed-Petersen 1992	Doesn't adhere to PICO question, Danish language

Diagram (6). Proposed Algorithm for OLP Treatment Based on the Best Available Evidence of this Study

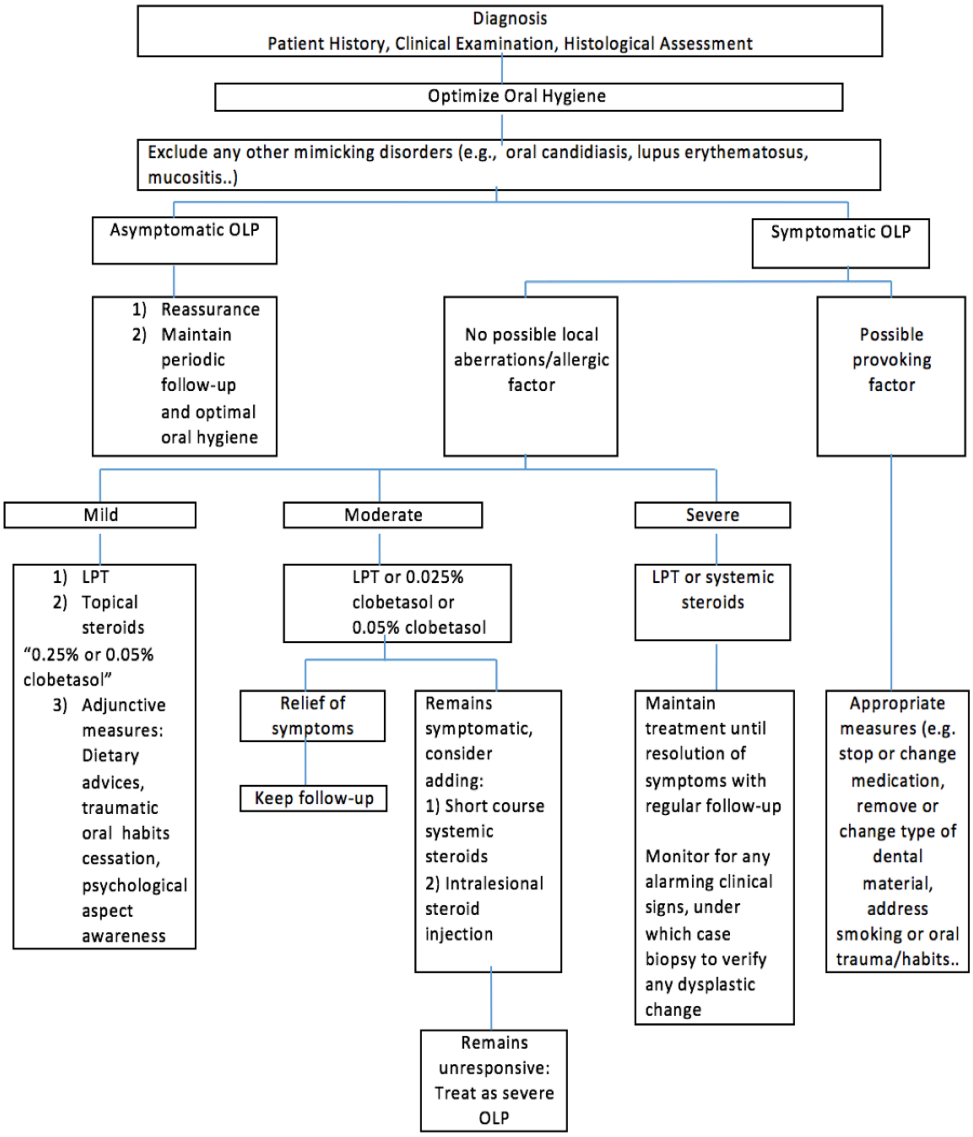

Table (18) Types of Stakeholders in Translational Science

Primary Stakeholders	Individuals who are ultimately and directly affected, either positively or negatively, by the healthcare outcomes (e.g., patients, the immediate family members, caregivers of patients who cannot represent themselves)
Key Stakeholders	Individuals who may or may not be primary stakeholders, but have a significant influence on the decision-making process (e.g., relatives, friends or caregivers empowered by a legal document or directive to make healthcare decisions on behalf of the patient)
Secondary Stakeholders	Individuals indirectly affected by the outcomes, or indirectly involved in the patient' s care process
Allied Stakeholders	Individuals who are involved in the patient' s care, but are indirectly affected by the healthcare outcome (e.g., medical, dental, nursing and pharmacy staff, other hospital employees, insurance agents, legal staff and lawyers

Miscellaneous Table (19) The Thongprasom Score, 1992

Score 0	No lesion, normal mucosa
Score 1	Mild white striae, no erythematous area
Score 2	White striae with atrophic area less than 1 cm^2
Score 3	White striae with atrophic area more than 1 cm^2
Score 4	White striae with erosive area less than 1 cm^2
Score 5	White striae with erosive area more than 1 cm^2

Glossary

Acceptable Sampling Analysis: A process to disqualify studies of low quality level of the evidence from inclusion into the subsequent step of statistical analysis.

Assessment of Level of Evidence: An analytical parameter based on the type of design used in the reported studies of the gathered literature

Bibliome: The literature of a specified or contextually implied field.

Best Available Evidence (Fundamentals of Evidence-Based Health Care and Translational Science, 2014): It is the objective that derives evidence-based health care and used in producing evidence-based revisions of clinical practice guidelines and evidence-based clinical recommendations. Generated from high quality systematic reviews and high quality clinically relevant complex systematic reviews, it is the result from the consensus statement of said research synthesis and systematic reports.

Clinical Practice Guideline (ADA Definition): These are the strongest resources to aid professionals in clinical decision making and help incorporate evidence gained through scientific investigation into patient care. They provide recommendations for patient treatment based on a scientific assessment of therapeutic options. ADA Clinical Practice Guidelines are developed by a panel of experts under the guidance of the ADA Council on Scientific Affairs. The expert panel critically appraises, summarizes, and interprets the clinical relevance of the body of evidence to develop practical recommendations. They are intended to optimize patient care by including recommendation statements that are informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options.

Critical Summary (ADA Definition): Helps to quickly learn the principal findings of a

systematic review. The critical summary offers a peer-reviewed opinion concerning the quality of the review and the validity of the interpretations, and it offers additional insights into the implications for clinicians. A critical summary includes: 1) a brief summary of the systematic review; 2) a critique of the systematic review methods as well as the identified evidence; and 3) implications for clinicians.

Ex-GRADE: Expansion of the grading of clinical recommendations' assessment, development and evaluation.

Final Bibliome: The whole body of accessible and available evidence which pertains to the PICO question.

Fixed Effect Model Meta-Analysis: A special case of the random effects model where the outcomes (dependent variables) are considered "fixed" by non-random criteria that arise from the independent explanatory and predictor variables. It assumes a common treatment effect where only within-study variation considered, and it provides a weighted average of the study estimates. The size of the study and number of events are the main determinants; thus large studies bias this model since these studies get larger weights than the smaller ones resulting in skewing the meta-analysis' fixed-point toward them.

Grey Bibliome: Scientific reports that have not been subjected to peer review.

Level of Evidence: Two main systems, American and British, are used for assessment of a study's design to help construct a quick idea about the validity of it. The following narration of the systems is from Chiappelli's Fundamentals of Evidence-Based Health Care and Translational Science, 2014.

A) US Preventive Services Task Force:

Level I: Evidence obtained from at least one properly designed randomized controlled trial.

Level II-1: Evidence obtained from well-designed controlled trials without randomization.

Level II-2: Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one center or research group.

Level II-3: Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled trials might also be regarded as this type of evidence.

Level III: Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.

B) UK National Health Services:

Level A: Consistent randomized controlled clinical trials, cohort study, with clinical decision rule validated in different populations.

Level B: Consistent retrospective cohort, exploratory cohort, ecological study, outcomes research, case-control study, or extrapolations from level A studies.

Level C: Case-series study or extrapolations from level B studies.

Level D: Expert opinion without explicit critical appraisal or based on physiology, bench research, or first principles.

Meta-analysis: Performed to derive a summary estimate of effect**.** Done by means of fixed or random models on studies that report comparable, non-heterogeneous quantitative data and have a low degree of variation in their findings.

OLP: A common chronic inflammatory disease associated with cell-mediated immunological dysfunction.

Overarching Statistical Significance: Overarching statistics combine data across many studies or data sets and results in summary estimates of effects in a meta-analysis. It serves to increase the sample size, which thereby increases the power of the test statistics.

Patient-Centered Outcomes Research (PCOR Definition): It:

1) Assesses the benefits and harms of preventive, diagnostic, therapeutic, palliative, or health delivery system interventions to inform decision making, highlighting comparisons and outcomes that matter to people;
2) Is inclusive of an individual's preferences, autonomy, and needs, focusing on outcomes that people notice and care about such as survival, function, symptoms, and health-related quality of life;
3) Incorporates a wide variety of settings and diversity of participants to address individual differences and barriers to implementation and dissemination; and
4) Investigates (or may investigate) optimizing outcomes while addressing burden to individuals, availability of services, technology, and personnel, and other stakeholder perspectives.

Patient-Oriented Outcomes: Outcomes that matter to patients and not necessarily so to researchers or other individuals. These outcomes deal with the health span of patients, including quality of life, reduced mortality, or lower expenses.

PDT: A procedure based on the activation of molecules of various chemical agents (photosensitizers) by light emitting radiation using a selected wavelength. After activation, cytotoxic free radicals are released and subsequently result in the destruction of targeted cells.

PICOTS: A PICO question, with T for "time interval of intended intervention" and S for "setting of where the population can be found".

Plain Language Summaries (ADA Definition): short, easy-to-read summaries of systematic reviews. They are written so that an informed patient can understand the key points of scientific evidence without getting into the clinical details behind the analysis. With this knowledge, the dentist and patient can work together on the best treatment options.

Quality of Evidence: Obtained by means of fully validated and reliable tools, designed to quantify the quality of the reported research, based on common standard criteria of research design, methodology and statistical analysis.

R-AMSTAR: Revised scale for the assessment of multiple systematic reviews.

Random Effect Model Meta-Analysis: A more common model than the fixed effect model and involves an assumption that the effects being estimated in the different studies follow some distribution but are not identical. It is used in situations where some degree of heterogeneity is recognized.

Stakeholders: People with a stake in the matter, including primary intended users, policy makers, researchers, and others.

Strength of Recommendation: Indicates the extent to which one can be confident that adherence to the recommendation will do more good than harm.

Systematic Review: A report of a systematic process of research synthesis. It is a critical assessment of existing evidence that addresses a focused clinical question, includes a comprehensive literature search, appraises the quality of studies, and reports results in a systematic manner, performing all that in relevance to that original clinical question only.

Systematic Review (ADA Definition): In the hierarchy of evidence, systematic reviews are preferable to narrative reviews for answering focused clinical questions. They are conducted according to transparent and repeatable processes considering all of the published evidence, not just that of which the reviewer may have prior knowledge or favor. The process also includes assessing the quality of each study, the overall quality of the body of evidence, and a summary of the clinical results. A systematic review typically involves:

- An exhaustive search for studies (the evidence).
- Procedures to maximize objectivity and minimize bias.
- Selection of best available evidence having the strongest study design.
- Critical appraisal of the quality of each study.
- A summary of the results of the included studies.
- Interpretation of the evidence for clinicians and researchers.

References

1. Agha-Hosseini, F., Moslemi, E., & Mirzaii-Dizgah, I. (2012). Comparative evaluation of low-level laser and CO(2) laser in treatment of patients with oral lichen planus. *Int J Oral Maxillofac Surg, 41*(10), 1265-1269. doi:10.1016/j.ijom.2012.06.001

2. Al-Hashimi, I., Schifter, M., Lockhart, P. B., Wray, D., Brennan, M., Migliorati, C. A., . . . van der Waal, I. (2007). Oral lichen planus and oral lichenoid lesions: diagnostic and therapeutic considerations. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod, 103 Suppl*, S25 e21-12. doi:10.1016/j.tripleo.2006.11.001

3. Aljabre, S. H. (1994). Grinspan's syndrome. *J Am Acad Dermatol, 30*(4), 671.

4. Atkins, D., Best, D., Briss, P. A., Eccles, M., Falck-Ytter, Y., Flottorp, S., . . . Group, G. W. (2004). Grading quality of evidence and strength of recommendations. *BMJ, 328*(7454), 1490. doi:10.1136/bmj.328.7454.1490

5. Barkhordarian, A., Demerjian, G., Jan, A., Sama, N., Nguyen, M., Du, A., & Chiappelli, F. (2015). Stakeholder engagement analysis - a bioethics dilemma in patient-targeted intervention: patients with temporomandibular joint disorders. *J Transl Med, 13*, 15. doi:10.1186/s12967-014-0366-z

6. Barkhordarian, A., Pellionisz, P., Dousti, M., Lam, V., Gleason, L., Dousti, M., . . . Chiappelli, F. (2013). Assessment of risk of bias in translational science. *J Transl Med, 11*, 184. doi:10.1186/1479-5876-11-184.

7. Barnes, P. J. (2006). How corticosteroids control inflammation: Quintiles Prize Lecture 2005. *Br J Pharmacol, 148*(3), 245-254. doi:10.1038/sj.bjp.0706736.

8. Bauer, J., Spackman, S., Chiappelli, F., Prolo, P., & Stevenson, R. (2006). Evidence-based dentistry: a clinician's perspective. *J Calif Dent Assoc, 34*(7), 511-517.

9. Bulat, V., Situm, M., Dediol, I., Ljubicic, I., & Bradic, L. (2011). The mechanisms of action of phototherapy in the treatment of the most common dermatoses. *Coll Antropol, 35 Suppl 2*, 147-151.

10. Burns, P. B., Rohrich, R. J., & Chung, K. C. (2011). The levels of evidence and their role in evidence-based medicine. *Plast Reconstr Surg, 128*(1), 305-310. doi:10.1097/PRS.0b013e318219c171.

11. Carbone, M., Arduino, P. G., Carrozzo, M., Caiazzo, G., Broccoletti, R., Conrotto, D., . . . Gandolfo, S. (2009). Topical clobetasol in the treatment of atrophic-erosive oral lichen planus: a randomized controlled trial to compare two preparations with different concentrations. *J Oral Pathol Med, 38*(2), 227-233. doi:10.1111/j.1600-0714.2008.00688.x

12. Carrozzo, M., & Gandolfo, S. (1999). The management of oral lichen planus. *Oral Dis, 5*(3), 196-205.

13. Chamani, G., Rad, M., Zarei, M. R., Lotfi, S., Sadeghi, M., & Ahmadi, Z. (2015). Efficacy of tacrolimus and clobetasol in the treatment of oral lichen planus: a systematic review and meta-analysis. *Int J Dermatol, 54*(9), 996-1004. doi:10.1111/ijd.12925.

14. Chan, E. S., Thornhill, M., & Zakrzewska, J. (2000). Interventions for treating oral lichen planus. *Cochrane Database Syst Rev*(2), CD001168. doi:10.1002/14651858.CD001168.

15. Cheng, S., Kirtschig, G., Cooper, S., Thornhill, M., Leonardi-Bee, J., & Murphy, R. (2012). Interventions for erosive lichen planus affecting mucosal sites. *Cochrane Database Syst Rev*(2), CD008092. doi:10.1002/14651858.CD008092.pub2.

16. Chiappelli, F., *Fundamentals of Evidence-Based Health Care and Translational Science*, Springer Heidelberg New York Dordrect London; 2014.

17. Chou, A. F., Vaughn, T. E., McCoy, K. D., & Doebbeling, B. N. (2011). Implementation of evidence-based practices: Applying a goal commitment framework. *Health Care Manage Rev, 36*(1), 4-17. doi:10.1097/HMR.0b013e3181dc8233.

18. Coutinho, A. E., & Chapman, K. E. (2011). The anti-inflammatory and immunosuppressive effects of glucocorticoids, recent developments and mechanistic insights. *Mol Cell Endocrinol, 335*(1), 2-13. doi:10.1016/j.mce.2010.04.005.

19. Davari, P., Hsiao, H. H., & Fazel, N. (2014). Mucosal lichen planus: an evidence-based treatment update. *Am J Clin Dermatol, 15*(3), 181-195. doi:10.1007/s40257-014-0068-6.

20. Dillenburg, C. S., Martins, M. A., Munerato, M. C., Marques, M. M., Carrard, V. C., Sant'Ana Filho, M., . . . Martins, M. D. (2014). Efficacy of laser phototherapy in comparison to topical clobetasol for the treatment of oral lichen planus: a randomized controlled trial. *J Biomed Opt, 19*(6), 068002. doi:10.1117/1.JBO.19.6.068002.

21. Di Stasio, D., Guida, A., Salerno, C., Contaldo, M., Esposito, V., Laino, L., . . . Lucchese, A. (2014). Oral lichen planus: a narrative review. *Front Biosci (Elite Ed), 6*, 370-376.

22. Eisen, D. (1999). The evaluation of cutaneous, genital, scalp, nail, esophageal, and ocular involvement in patients with oral lichen planus. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod, 88*(4), 431-436.

23. Eisen, D., Carrozzo, M., Bagan Sebastian, J. V., & Thongprasom, K. (2005). Number V Oral lichen planus: clinical features and management. *Oral Dis, 11*(6), 338-349. doi:10.1111/j.1601-0825.2005.01142.x

24. Elshenawy, H. M., Eldin, A. M., & Abdelmonem, M. A. (2015). Clinical Assessment of the Efficiency of Low Level Laser Therapy in the Treatment of Oral Lichen Planus. *Open Access Maced J Med Sci, 3*(4), 717-721. doi:10.3889/oamjms.2015.112.

25. Eversole, Lewis R. (2002). Clinical Outline for Oral Pathology, diagnosis and treatment. 3rd Edition, London. BC Decker Inc.

26. Fitzpatrick, S. G., Hirsch, S. A., & Gordon, S. C. (2014). The malignant transformation of oral lichen planus and oral lichenoid lesions: a systematic review. *J Am Dent Assoc, 145*(1), 45-56. doi:10.14219/jada.2013.10

27. Goldstein, G. R. (2002). What is evidence based dentistry? *Dent Clin North Am, 46*(1), 1-9, v.

28. Gorouhi, F., Davari, P., & Fazel, N. (2014). Cutaneous and mucosal lichen planus: a comprehensive review of clinical subtypes, risk factors, diagnosis, and prognosis. *ScientificWorldJournal, 2014*, 742826. doi:10.1155/2014/742826.

29. Gursoy, H., Ozcakir-Tomruk, C., Tanalp, J., & Yilmaz, S. (2013). Photodynamic therapy in dentistry: a literature review. *Clin Oral Investig, 17*(4), 1113-1125. doi:10.1007/s00784-012-0845-7.

30. Higgins, J. P., Altman, D. G., Gotzsche, P. C., Juni, P., Moher, D., Oxman, A. D., . . . Cochrane Statistical Methods, G. (2011). The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ, 343*, d5928. doi:10.1136/bmj.d5928.

31. Ismail, S. B., Kumar, S. K., & Zain, R. B. (2007). Oral lichen planus and lichenoid reactions: etiopathogenesis, diagnosis, management and malignant transformation. *J Oral Sci, 49*(2), 89-106.

32. Jajarm, H. H., Falaki, F., & Mahdavi, O. (2011). A comparative pilot study of low intensity laser versus topical corticosteroids in the treatment of erosive-atrophic oral lichen planus. *Photomed Laser Surg, 29*(6), 421-425. doi:10.1089/pho.2010.2876

33. Jajarm, H. H., Falaki, F., Sanatkhani, M., Ahmadzadeh, M., Ahrari, F., & Shafaee, H. (2015). A comparative study of toluidine blue-mediated photodynamic therapy versus topical corticosteroids in the treatment of erosive-atrophic oral lichen planus: a randomized clinical controlled trial. *Lasers Med Sci, 30*(5), 1475-1480. doi:10.1007/s10103-014-1694-1

34. Jori, G., Fabris, C., Soncin, M., Ferro, S., Coppellotti, O., Dei, D., . . . Roncucci, G. (2006). Photodynamic therapy in the treatment of microbial infections: basic principles and perspective applications. *Lasers Surg Med, 38*(5), 468-481. doi:10.1002/lsm.20361

35. Kalmar, J. R. (2007). Diagnosis and management of oral lichen planus. *J Calif Dent Assoc, 35*(6), 405-411.

36. Kassem, R., Yarom, N., Scope, A., Babaev, M., Trau, H., & Pavlotzky, F. (2012). Treatment of erosive oral lichen planus with local ultraviolet B phototherapy. *J Am Acad Dermatol, 66*(5), 761-766. doi:10.1016/j.jaad.2011.04.017.

37. Konopka, K., & Goslinski, T. (2007). Photodynamic therapy in dentistry. *J Dent Res, 86*(8), 694-707.

38. Kragballe, K. (1989). Topical corticosteroids: mechanisms of action. *Acta Derm Venereol Suppl (Stockh), 151*, 7-10; discussion 47-52.

39. Kubler, A., Niziol, C., Sidhu, M., Dunne, A., & Werner, J. A. (2005). [Analysis of cost effectiveness of photodynamic therapy with Foscan (Foscan-PDT) in comparison with palliative chemotherapy in patients with advanced head-neck tumors in Germany]. *Laryngorhinootologie, 84*(10), 725-732. doi:10.1055/s-2005-861048

40. Kurago, Z. B. (2016). Etiology and pathogenesis of oral lichen planus: an overview. *Oral Surg Oral Med Oral Pathol Oral Radiol, 122*(1), 72-80. doi:10.1016/j.oooo.2016.03.011

41. Kuusilehto, A., Lehtinen, R., Happonen, R. P., Heikinheimo, K., Lehtimaki, K., & Jansen, C. T. (1997). An open clinical trial of a new mouth-PUVA variant in the treatment of oral lichenoid lesions. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod, 84*(5), 502-505.

42. Kvaal, S. I., Angell-Petersen, E., & Warloe, T. (2013). Photodynamic treatment of oral lichen planus. *Oral Surg Oral Med Oral Pathol Oral Radiol, 115*(1), 62-70. doi:10.1016/j.oooo.2012.08.448

43. Lavanya, N., Jayanthi, P., Rao, U. K., & Ranganathan, K. (2011). Oral lichen planus: An update on pathogenesis and treatment. *J Oral Maxillofac Pathol, 15*(2), 127-132. doi:10.4103/0973-029X.84474.

44. Liu, D., Ahmet, A., Ward, L., Krishnamoorthy, P., Mandelcorn, E. D., Leigh, R., . . . Kim, H. (2013). A practical guide to the monitoring and management of the complications of systemic corticosteroid therapy. *Allergy Asthma Clin Immunol, 9*(1), 30. doi:10.1186/1710-1492-9-30.

45. Lodi, G., Carrozzo, M., Furness, S., & Thongprasom, K. (2012). Interventions for treating oral lichen planus: a systematic review. *Br J Dermatol, 166*(5), 938-947. doi:10.1111/j.1365-2133.2012.10821.x

46. Lodi, G., Scully, C., Carrozzo, M., Griffiths, M., Sugerman, P. B., & Thongprasom, K. (2005). Current controversies in oral lichen planus: report of an international consensus meeting. Part 2. Clinical management and malignant transformation. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod, 100*(2), 164-178. doi:10.1016/j.tripleo.2004.06.076.

47. Lozada-Nur, F., & Miranda, C. (1997). Oral lichen planus: topical and systemic therapy. *Semin Cutan Med Surg, 16*(4), 295-300.

48. Machin, S. E., McConnell, D. T., & Adams, J. D. (2010). Vaginal lichen planus: preservation of sexual function in severe disease. *BMJ Case Rep, 2010*. doi:10.1136/bcr.08.2009.2208.

49. Mohanty, N., Jalaluddin, M., Kotina, S., Routray, S., & Ingale, Y. (2013). Photodynamic therapy: the imminent milieu for treating oral lesions. *J Clin Diagn Res, 7*(6), 1254-1257. doi:10.7860/JCDR/2013/5767.3088.

50. Morris, Z. S., Wooding, S., & Grant, J. (2011). The answer is 17 years, what is the question: understanding time lags in translational research. *J R Soc Med, 104*(12), 510-520. doi:10.1258/jrsm.2011.110180.

51. Mostafa, D., & Tarakji, B. (2015). Photodynamic therapy in treatment of oral lichen planus. *J Clin Med Res, 7*(6), 393-399. doi:10.14740/jocmr2147w.

52. Munde, A. D., Karle, R. R., Wankhede, P. K., Shaikh, S. S., & Kulkurni, M. (2013). Demographic and clinical profile of oral lichen planus: A retrospective study. *Contemp Clin Dent, 4*(2), 181-185. doi:10.4103/0976-237X.114873.

53. Ozog, D., Rkein, A., Fabi, S., Gold, M., Goldman, M., Loew, N., Martin, G., Munavalli, G. (2016). Photodynamic threapy: a clinical consensus guide. *Dermatol surg,* 42(7), 804-27. doi: 10.1097/DSS.0000000000000800.

54. Phi, L., Ajaj, R., Ramchandani, M. H., Brant, X. M., Oluwadara, O., Polinovsky, O., . . . Chiappelli, F. (2012). Expanding the Grading of Recommendations Assessment, Development, and Evaluation (Ex-GRADE) for Evidence-Based Clinical Recommendations: Validation Study. *Open Dent J, 6*, 31-40. doi:10.2174/1874210601206010031.

55. Radwan-Oczko, M. (2013). Topical application of drugs used in treatment of oral lichen planus lesions. *Adv Clin Exp Med, 22*(6), 893-898.

56. Salva, K. A. (2002). Photodynamic therapy: unapproved uses, dosages, or indications. *Clin Dermatol, 20*(5), 571-581.

57. Scully, C., Beyli, M., Ferreiro, M. C., Ficarra, G., Gill, Y., Griffiths, M., . . . Wray, D. (1998). Update on oral lichen planus: etiopathogenesis and management. *Crit Rev Oral Biol Med, 9*(1), 86-122.

58. Scully, C., Eisen, D., & Carrozzo, M. (2000). Management of oral lichen planus. *Am J Clin Dermatol, 1*(5), 287-306.

59. Sharma, A., Bialynicki-Birula, R., Schwartz, R. A., & Janniger, C. K. (2012). Lichen planus: an update and review. *Cutis, 90*(1), 17-23.

60. Shenoi, S. D., Prabhu, S., Indian Association of Dermatologists, V., & Leprologists. (2014). Photochemotherapy (PUVA) in psoriasis and vitiligo. *Indian J Dermatol Venereol Leprol, 80*(6), 497-504. doi:10.4103/0378-6323.144143.

61. Silverman, S., Jr., Gorsky, M., Lozada-Nur, F., & Giannotti, K. (1991). A prospective study of findings and management in 214 patients with oral lichen planus. *Oral Surg Oral Med Oral Pathol, 72*(6), 665-670.

62. Singh, V., Pal, M., Gupta, S., Tiwari, S. K., Malkunje, L., & Das, S. (2013). Turmeric - A new treatment option for lichen planus: A pilot study. *Natl J Maxillofac Surg, 4*(2), 198-201. doi:10.4103/0975-5950.127651.

63. Sobaniec, S., Bernaczyk, P., Pietruski, J., Cholewa, M., Skurska, A., Dolinska, E., . . . Pietruska, M. (2013). Clinical assessment of the efficacy of photodynamic therapy in the treatment of oral lichen planus. *Lasers Med Sci, 28*(1), 311-316. doi:10.1007/s10103-012-1153-9.

64. Stanbury, R. M., & Graham, E. M. (1998). Systemic corticosteroid therapy--side effects and their management. *Br J Ophthalmol, 82*(6), 704-708.

65. Thongprasom, K., & Dhanuthai, K. (2008). Steriods in the treatment of lichen planus: a review. *J Oral Sci, 50*(4), 377-385.

66. Thongprasom, K., Carrozzo, M., Furness, S., & Lodi, G. (2011). Interventions for treating oral lichen planus. *Cochrane Database Syst Rev*(7), CD001168. doi:10.1002/14651858.CD001168.pub2.

67. Thongprasom, K., Prapinjumrune, C., & Carrozzo, M. (2013). Novel therapies for oral lichen planus. *J Oral Pathol Med, 42*(10), 721-727. doi:10.1111/jop.12083.

68. Uman, L. S., Chambers, C. T., McGrath, P. J., & Kisely, S. (2008). A systematic review of randomized controlled trials examining psychological interventions for needle-related procedural pain and distress in children and adolescents: an abbreviated cochrane review. *J Pediatr Psychol, 33*(8), 842-854. doi:10.1093/jpepsy/jsn031.

69. Uman, L. S. (2011). Systematic reviews and meta-analyses. *J Can Acad Child Adolesc Psychiatry, 20*(1), 57-59.

70. Uva, L., Miguel, D., Pinheiro, C., Antunes, J., Cruz, D., Ferreira, J., & Filipe, P. (2012). Mechanisms of action of topical corticosteroids in psoriasis. *Int J Endocrinol, 2012*, 561018. doi:10.1155/2012/561018

71. van der Meij, E. H., Schepman, K. P., Smeele, L. E., van der Wal, J. E., Bezemer, P. D., & van der Waal, I. (1999). A review of the recent literature regarding malignant transformation of oral lichen planus. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod, 88*(3), 307-310.

72. Van Weelden, H., Baart de la Faille, H., Young, E., & van der Leun, J. C. (1990). Comparison of narrow-band UV-B phototherapy and PUVA photochemotherapy in the treatment of psoriasis. *Acta Derm Venereol, 70*(3), 212-215.

73. West, S., King, V., Carey, T. S., Lohr, K. N., McKoy, N., Sutton, S. F., & Lux, L. (2002). Systems to rate the strength of scientific evidence. *Evid Rep Technol Assess (Summ)*(47), 1-11.

74. Wilson E (1869). On lichen planus. *J Cutan Med Dis Skin* vol.3: 117-132.

75. Yang, H., Wu, Y., Ma, H., Jiang, L., Zeng, X., Dan, H., . . . Chen, Q. (2016). Possible alternative therapies for oral lichen planus cases refractory to steroid therapies. *Oral Surg Oral Med Oral Pathol Oral Radiol, 121*(5), 496-509. doi:10.1016/j.oooo.2016.02.002

76. Yeager, M. P., Guyre, P. M., & Munck, A. U. (2004). Glucocorticoid regulation of the inflammatory response to injury. *Acta Anaesthesiol Scand, 48*(7), 799-813. doi:10.1111/j.1399-6576.2004.00434.x

77. Zakrzewska, J. M., Chan, E. S., & Thornhill, M. H. (2005). A systematic review of placebo-controlled randomized clinical trials of treatments used in oral lichen planus. *Br J Dermatol, 153*(2), 336-341. doi:10.1111/j.1365-2133.2005.06493.x