

Psoriasis

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Introduction

Briefings such as this one are prepared in response to petitions to add new conditions to the list of qualifying conditions for the Minnesota medical cannabis program. The intention of these briefings is to present to the Commissioner of Health, to members of the Medical Cannabis Review Panel, and to interested members of the public scientific studies of cannabis products as therapy for the petitioned condition. Brief information on the condition and its current treatment is provided to help give context to the studies. The primary focus is on clinical trials and observational studies, but for many conditions there are few of these. A selection of articles on pre-clinical studies (typically laboratory and animal model studies) will be included, especially if there are few clinical trials or observational studies. Though interpretation of surveys is usually difficult because it is unclear whether responders represent the population of interest and because of unknown validity of responses, when published in peer-reviewed journals surveys will be included for completeness. When found, published recommendations or opinions of national organizations medical organizations will be included.

Searches for published clinical trials and observational studies of cannabis therapy are performed using the National Library of Medicine's MEDLINE database using key words appropriate for the petitioned condition. Articles that appeared to be results of clinical trials, observational studies, or review articles of such studies, were accessed for examination. References in the articles were studied to identify additional articles that were not found on the initial search. This continued in an iterative fashion until no additional relevant articles were found. Though the MN medical cannabis program does not allow smoked or vaporized dried cannabis, studies using these forms of cannabis administration were allowed for insight they could provide. Finally, the federal government-maintained web site of clinical trials, clinicaltrials.gov, was searched to learn about trials currently under way or under development and to check whether additional articles on completed trials could be found.

Definition

Psoriasis is a chronic, inflammatory skin condition that is often associated with systemic manifestations, especially arthritis. The cause of psoriasis is not fully understood, but it is known to be mediated through the immune system and there appears to be a genetic component. Approximately 90% of patients have plaque psoriasis, characterized by well-defined round or oval red, scaly plaques of varying size. The plaques can develop anywhere on the body but are most common on the extensor surfaces of the arms, legs, and trunk and on the buttocks and scalp (Weigle 2013). Microscopically, involved areas of the skin are characterized by markedly increased proliferation and incomplete differentiation of the

epidermis and a marked increase in blood flow and white blood cell infiltration (Gudjonsson 2007). In addition to often causing bothersome pruritis (itching) and pain, the lesions often cause significant social morbidity due to reactions - or perceptions of reactions - from others. This can lead to depression, isolation, problems at work and, in general, reduced quality of life. A substantial proportion of patients with psoriasis also develop psoriatic arthritis. Additional comorbidities include metabolic syndrome, heart disease, and inflammatory bowel disease. The nature of these associations is not fully understood; they might not be directly causal. The clinical course of psoriasis is unpredictable (Weigle 2013), typically waxing and waning over time (Gudjonsson 2007).

Prevalence

In Europe and North America psoriasis prevalence is about 2 % in adults (Christopher 2001, Stern 2004), with similar prevalence in males and females (Christopher 2001, Gudjonsson 2007).

Current Therapies

Psoriasis has no known cure but many therapies can reduce severity of symptoms and slow progression of disease (Boehncke 2015). About 70-80% of patients have mild psoriasis that can be controlled using topical therapies alone (Schön 2005), primarily using vitamin D derivatives and glucocorticosteroids (Boehncke 2015).

For patients with moderate to severe disease, light exposure therapies and/or systemic therapy is needed. Phototherapies are very effective but also very time consuming and they are usually only used for short-term control of the disease. Conventional systemic non-biologic therapies in the USA for psoriasis include drugs that suppress the immune system through different mechanisms (methotrexate, cyclosporine, and apremilast [OTEZLA]) and acitretin (a vitamin A derivative thought to slow proliferation of skin cells). Most of the conventional systemic therapies can be used for long-term management of psoriasis, however, careful monitoring is needed due to frequency of drug-drug interactions and cumulative organ toxicities – not infrequently requiring discontinuation (Yeung 2013).

Over the past 15 years several biologic therapies have been developed and approved for the treatment of psoriasis. Most of the biologic therapies are monoclonal antibodies and so far they show little evidence of drug-drug interactions or organ toxicity. The most widely used biological for psoriasis is adalimumab (HUMIRA), a TNF- α inhibitor. Due to their high costs, TNF- α inhibitors are generally used after phototherapy and when conventional systemic therapies have failed, were not tolerated, or were contraindicated (Boehncke 2015). Patients' response to biologic agents can decrease over time as a result of immunogenicity and anti-drug antibodies (Menter 2008). And treatment costs are high. Estimated cost between 2007 and 2012 for biologic therapies for patients with moderate-to-severe psoriasis was over \$30,000 (Feldman 2016).

Despite the variety of therapies, there is a substantial unmet need in the treatment of

patients with mild to moderate disease, particularly those with psoriasis in difficult-to-treat areas such as the scalp, nails, and intertriginous areas (where two skin areas touch or rub together) (Boehncke 2015). According to national surveys, 23% (Stern 2004) to 52% (Armstrong 2013) of patients with psoriasis are unsatisfied with their treatment. Scores of drugs are now in clinical development for psoriasis (National Psoriasis Foundation 2018). US results from a 2012 multi-national survey found that 88% of psoriasis patients and 98% of dermatologists felt there was a strong or moderate need for better therapies (Lebwohl 2016).

Pre-Clinical Research

Separate sections are presented here for studies relevant to potential disease-modifying activity and for those relevant dealing with symptom reduction.

Disease Modification

Research into what causes psoriasis and how it might be treated has been hampered by absence of a good animal model for the disease. However, genetic modifications and immunological manipulations in rodents have resulted in hyperproliferative inflammatory skin disorders believed relevant to the study of psoriasis (Boehncke 2015).

Cannabinoid receptors are present in keratinocytes and a variety of other cell types found in the skin (Kupczyk 2009). Two published papers and an abstract suggest some cannabinoids reduce proliferation and/or differentiation of keratinocytes, the predominant cell type in the skin's outer layer. One studied the effect of cannabidiol (CBD), cannabigerol (CBG), and cannabidivarin (CBVN) on a human keratinocyte cell line often used in research because of its high capacity to replicate and differentiate. CBD and CBG reduced keratinocyte differentiation through regulation of genes that control differentiation. The effect of CBD was through CB1 receptors; the effect of CBG was independent of CB1 and CB2 receptors. CBVN did not inhibit keratinocyte differentiation (Pucci 2013). Another group studied the effect of THC, CBD, CBG, and cannabiol (CBN) on a human papilloma virus – infected keratinocyte cell line (used because of its tendency for rapid cell replication). Each of the four cannabinoids inhibited keratinocyte proliferation in a concentration-dependent manner. The mechanism of action appeared to be something other than activation of CB1 and CB2 receptors (Wilkinson 2007). An abstract with little methodologic detail states inflammation and skin barrier function in a mouse model of psoriasis was improved with topical application of a cannabinoid receptor activator (Kim 2015).

Over the past 20 years there have been important discoveries regarding interaction between the human nervous and immune systems, producing the concept of neural reflexes in inflammation and immunity. An important example is the vagus nerve, which transmits signals from the body's organs and tissues to the brain and messages from the brain to the body's organs. One consequence of increasing signals from the brain to the spleen is reduction in pro-inflammatory cytokines by a type of white blood cell called macrophages (Anderson 2012). A study was recently published showing electrical stimulation of the vagus nerve inhibits cytokine production and attenuates disease severity in patients with rheumatoid arthritis (Koopman 2016). It has been speculated that stimulation of the vagus nerve might also decrease inflammation in psoriasis patients (Derakhshan 2015). However, the impact of cannabinoids on

the vagus nerve is not altogether straightforward and not fully understood. There is some evidence that cannabis at low or moderate doses leads to decreased discharge of vagal nerve fibers from brain to organs (i.e. decreased parasympathetic tone), and at high doses these efferent messages increase (i.e. increased parasympathetic tone) (Fisher 2005). Currently, the role of cannabinoids in modulating inflammation through the vagus nerve is not well defined.

Symptom Reduction

Pruritis – itching – is a common symptom in psoriasis, and it can be very bothersome and difficult to treat. The best-known pruritis-causing substance in the body is histamine. Under certain conditions histamine is released by mast cells and keratinocyte cells in the skin. A review paper on mechanisms of itch and pain in the skin indicates endocannabinoids – cannabinoids produced by the body – reduce itch peripherally and that activation of CB1 receptors suppresses histamine-induced pruritis. The paper does not provide additional explanatory rationale (Chuquilin 2016). Another review paper (Kupczyk 2009) describes preclinical and human studies suggesting cannabinoids can reduce pruritis. Small, observational studies have shown reduced pruritis in large percentages of patients after topical application of a variety of cannabinoids. The studies described in the review paper did not use cannabinoids found in cannabis and did not involve patients with psoriasis.

Clinical Trials

No randomized, controlled clinical trials have been published for cannabis or cannabinoids as therapy for psoriasis. In March, 2017 One World Cannabis Ltd (Israel) announced in a press release “positive preliminary clinical efficacy tests results” of its proprietary topical cannabis cream to treat psoriasis and its plan to extend the size and scope of the efficacy study. It reported “up to 70% improvement in a variety of inflammation markers directly associated with psoriasis.” Publication of additional details and results of the expanded study have not been found, and the only study found on [clinicaltrials.gov](https://www.clinicaltrials.gov) is a small safety study funded by One World Cannabis Ltd (n=26; primary outcome = adverse event incidence rate; study start date = February 2017 and estimated completion date = July 2017).

<https://www.clinicaltrials.gov/ct2/show/NCT02976779?cond=psoriasis+marijuana&rank=1>).

Observational Studies

No published observational studies of cannabis or cannabinoids for the treatment of psoriasis were found.

National Medical Organization Recommendations

No guidance documents or recommendations from national medical organizations for the therapeutic use of cannabis or cannabinoids in the management of psoriasis were found.

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Minnesota Department of Health
Office of Medical Cannabis
PO Box 64882
St. Paul, MN 55164-0882
651-201-5598
health.cannabis@state.mn.us
www.health.state.mn.us

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