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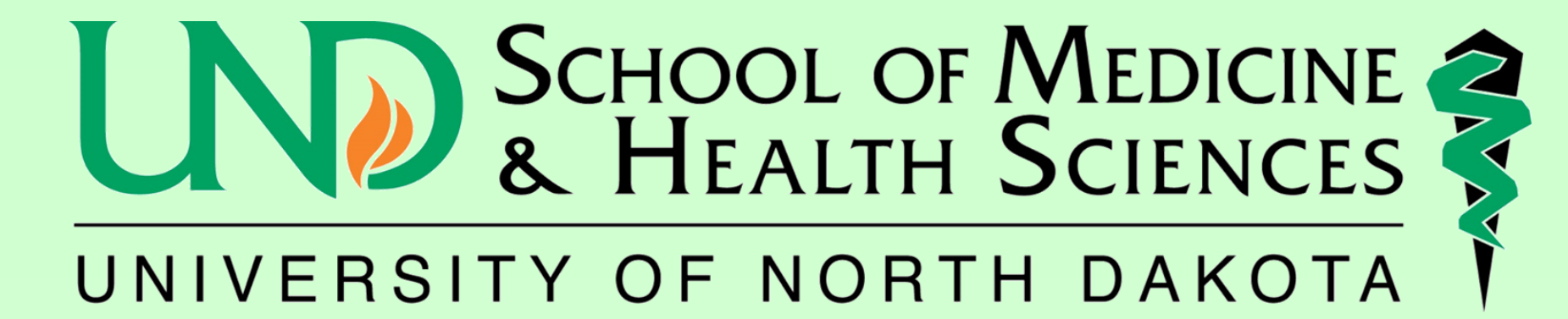
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Migraine Prophylaxis with Petasites Hybridus.

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Abstract

- ❖ Petasites hybridus (butterbur) as an effective prophylaxis for migraine disorders.
- ❖ Computerized literature searches were carried out in DynaMed, COCHRANE, EBSCO, CINAHL and MEDLINE.
- ❖ The examination of literature will comprise of trials that evaluate Petasites hybridus extract Petadolex® in various dosages and placebo.
- ❖ Petasites hybridus extract Petadolex® demonstrates a decreased frequency of migraine attacks and a greater improvement (>50%) after 3-4 month than placebo.
- ❖ Further studies are indicated to investigate extract recommendation for dosing and duration of treatment in pediatric population.
- ❖ Additional studies are required to confirm effectiveness and safety in long-time use before treatment with Petasites hybridus extract can be suggested as an alternative option for the prophylaxis of migraine.
- ❖ Trials reviewed for this paper suggests that the patented Petasites hybridus extract Petadolex® is a safe and excellently tolerated treatment for migraine prevention.

Introduction

- ❖ A migraine is a common headache disorder that affects adults and children.
- ❖ It is characterized by attacks that consist of various neurologic, gastrointestinal, and autonomic symptoms.
- ❖ Pharmacotherapy used may be acute to abort the migraine attack or prophylactic to prevent the migraine attack from occurring. Patients who experience frequent, severe migraines often require both approaches.
- ❖ The purpose of this literature review is to examine the usefulness of Petasites hybridus (butterbur) as an effective prophylaxis for migraine disorders

Statement of the Problem

- ❖ Preventative treatment of migraine with Petasites hybridus extract is increasingly used to deter the progression of the neurological disease of migraine and decrease its frequency.
- ❖ Petasites hybridus has been used medically in conditions like migraine, asthma, back pain, and urinary tract spasm mainly for its spasmolytic and analgesic effects.

Research Question

- ❖ In patients with frequent migraines, does prophylactic treatment with Petasites hybridus extract, compared to placebo, decrease the frequency and intensity of migraines?
- ❖ In patients with migraines, does the treatment with Petasites hybridus extract (compared to not having a treatment) increase risk of adverse events?
- ❖ For patients that treated with Petasites hybridus extract, what are the safety concerns?

Literature Review

Pathophysiology of Migraine Headache

- ❖ The disorder is accompanied by both genetic and environmental factors, along with a variance in symptoms. Attacks are characterized by a mixture of headache with a multiplicity of neurogenic, gastrointestinal, and autonomic symptoms (Silberstein, 2005).
- ❖ Migraine headaches can afflict any age group, and is the most common headache condition occurring in children
- ❖ Currently, there are three theories that attempt to explain the cause of migraines.
 1. Vascular theory suggests that vasodilatation or vasoconstriction may be a factor in a pain associated with migraines (Charles, 2013).
 2. Neurological theory suggests that migraines are ascribed to hyper-excitability of neurons in the brain that are mediated by alterations in neurotransmission system.
 3. Series of metabolic and neurophysiological events are associated with development of migraine headaches. Vasodilatation and increased serotogenic activity leads to an inflammatory response by a number of substances that are released from the trigeminal nerve system; resulting in excitement of pain mediating C fibers, which then transmit amplified stimuli back to the trigeminal system.
- ❖ Genetic risk factors, such as autosomal dominant inheritance pattern in familial hemiplegic migraine (FHM) appear to play a role in development of migraine.
- ❖ Elements that appear to trigger the onset of a migraine include stress, climate changes, alteration in sleeping patterns, and sensory stimuli.
- ❖ Numerous food products are documented as being the trigger factor to migraine:
 - 1) byproduct of food aging
 - 2) food with chemicals comparable to the neurotransmitters in the brain
- ❖ Hormonal changes during puberty may explain the elevated prevalence of emergent migraines in adolescent girls (Merikangas, 2013).

Alternative Herbal Remedies

- ❖ Petasites hybridus extract, Petadolex®, demonstrated persuasive evidence as a herbal medicinal product in deterrence of migraine headaches.
- ❖ Petasites hybridus extract is marketed in the United States (US) as a food supplement and considered a food product. Therefore, it's not subject to FDA approval or standardization in formulation.
- ❖ Active components of Petasites hybridus are petasin and isopetasine, clinically demonstrated a potent calcium channel blocking effect, may counteract vasoconstriction and “play a role in preventing hyper-excitation of the neurons via blockage of calcium specific ion gates in the cerebral arteries” (Utterback et al., 2014, p. 62).
- ❖ Powerful vasodilatory components of petasin and isopetasine were found to have anti-inflammatory and vasodilatory effects on the cerebral arteries by inhibition lipoxigenase and leukotriene that are thought to be involved in the inflammatory cascade associated with migraine.

Petadolex® Therapy

- ❖ Grossman et al. (2001) found that Petadolex® diminished the incidence of attacks from 3.3 ± 1.5 baseline to 1.7 ± 0.9 after 12 weeks compared to a decrease from 2.9 ± 1.2 to 2.2 ± 0.7 with placebo. The incidence of migraine attacks decreased with Petadolex® was a maximum of 60 percent when compared to the baseline. There were no significant reduction of the severity of headaches after 12 weeks of the trial.

Figure 1. Frequency of migraine attacks

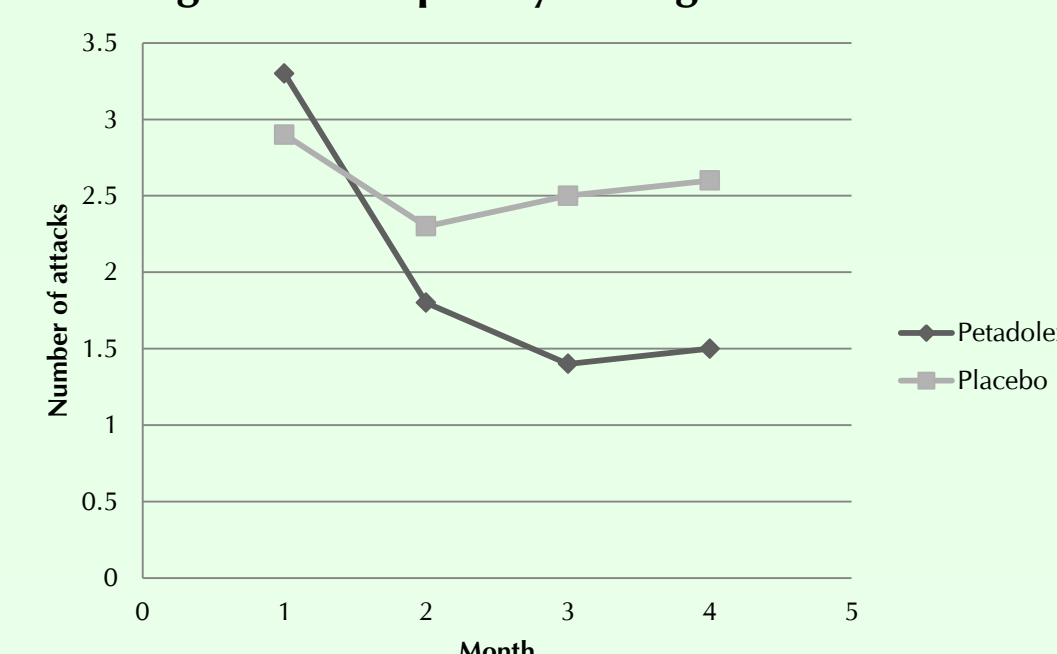
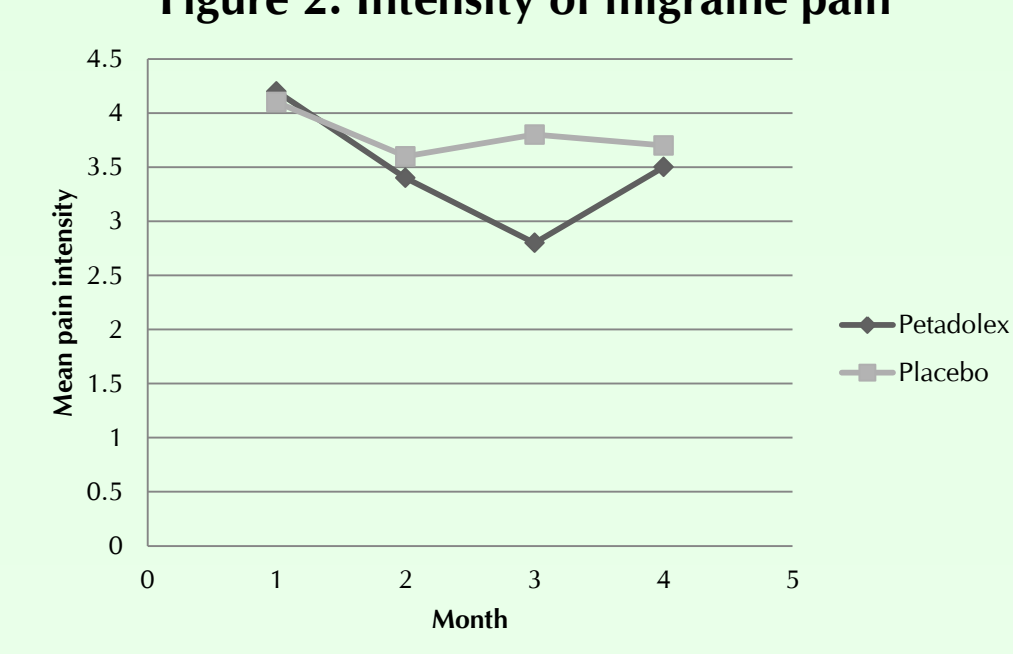


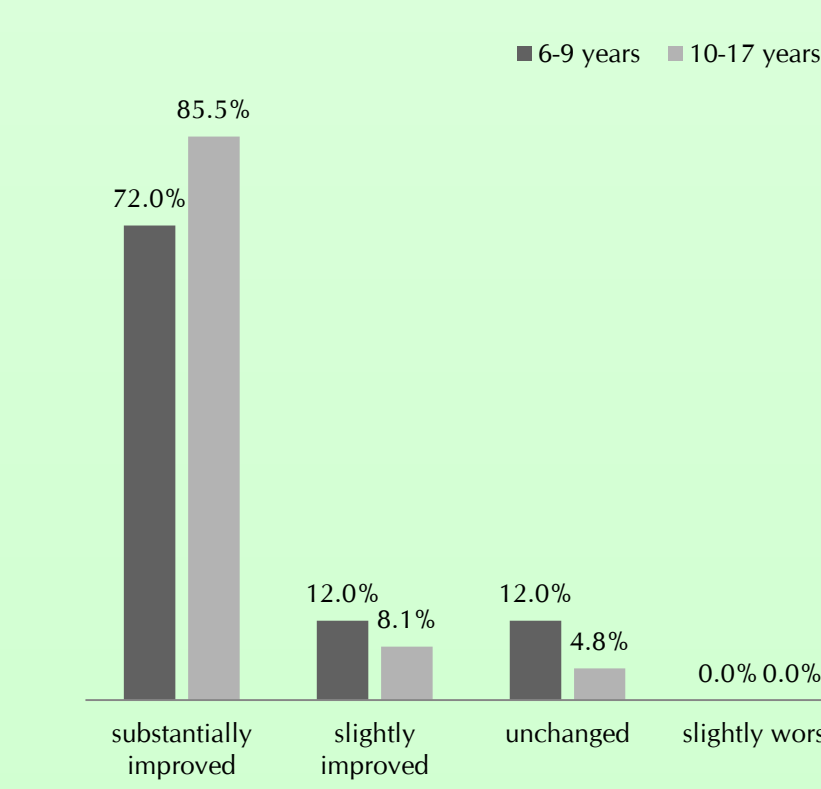
Figure 2. Intensity of migraine pain



- ❖ In the large study by Lipton et al. (2004) evaluated Petadolex® 75 mg twice daily and 50 mg twice daily versus placebo. Incidence of migraine attacks were significantly reduced with 75 mg Petadolex versus placebo at month 1, 3, and 4. Safety and adverse events were recorded over the four month trial.

Adverse event	Petasites 75 mg	Petasites 50 mg	Placebo
Cardiac disorders	1 (1.3%)	0	0
Disorders of ears and labyrinth	0	1 (1.3%)	1 (1.3%)
Gastrointestinal disorders	17 (22.4%)	20 (25.6%)	5 (6.7%)
General disorders	1 (1.3%)	0	0
Infections and Infestations	0	2	0
Neurologic disorders	1 (1.3%)	4 (5.1%)	1 (1.3%)
Renal and urinary disorders	0	0	1 (1.3%)
Respiratory disorders	1 (1.3%)	0	0
Eye disorders	0	0	1 (1.3%)
Skin and subcutaneous tissue disorders	2 (2.6%)	0	1 (1.3%)

- ❖ Diener et al. (2004) found a reduction in the incidence of migraine attacks of at least 50% in the drug group using Petadolex® versus 15% in the placebo group. The extent of migraine attacks and the intensity favored the group treated with Petadolex® 50 mg., 25% reduction in duration and 20% reduction in severity of migraine attacks.
- ❖ Pothman et al. (2005) carried out an open-label prospective trial consisting of 108 children between ages of 6 and 17. Prophylactic treatment with Petadolex® successfully reduced the duration of migraine attacks from 10 hours on average to 7 hours in 66.7% of younger patients and 61.1% in adolescence. Eighty sixth percent of children and 74.1% of adolescence experienced reduction in their monthly migraines for at least of 50%. Approximately 91.8% of the patients felt an improvement of their condition than before the clinical trial.



- ❖ A 28 week trial was carried out by Oelkers-Ax et al. (2007). This study included 58 children between ages 8 and 12. The frequency of migraine attacks in all groups was considerably reduced compared to baseline. In follow-up period Petadolex® was superior to placebo (p=0.044). Migraine attack incidences were also considerably reduced by Petadolex® at about 40% from baseline.

Discussion

- ❖ Migraine-preventive drugs are more commonly being used to reduce migraine attack frequency, attenuate the disease progression and to increase effectiveness of acute medications (Silberstein, 2005).
- ❖ Synthetic anti-migraine medications have been linked to the risk of adverse events and may significantly affect patient compliance. Therefore, complementary and alternative treatments have been studied for the prophylaxis of migraines.
- Does Petadolex® decreases the frequency and intensity of migraines?**
- ❖ Grossman et al. (2001) utilized 50 mg bid Petadolex® to reduce the frequency of migraine attacks by maximum of 60% as compared to baseline. The study also suggests the prevention of migraines with Petasites hybridus extract may be more effective in patients with a higher frequency of attacks.
- ❖ The Lipton et al. (2004) study supports the efficacy of 75 mg bid Petadolex® in reducing migraines frequency in patients, and reports that the 50 mg bid dose did not reach statistical significance in this study. At the end of third month the number of attacks were reduced by 58% with 75 mg Petadolex®, followed by Petadolex® 50 mg (42%) and placebo (26%).
- ❖ Diener et al. (2004) argues that 50 mg of Petasites hybridus extract is clinically effective in preventing migraine attacks. The number of migraines per month was considerably reduced by 48% at the end of the therapy.
- ❖ Rothman et al. (2004) studied the efficacy Petasites hybridus extract in the reduction of migraine frequency in children and adolescents. On an average the 6-9 age group was treated with 50 mg Petadolex® daily and 10-17 age group dosing recommendations were 150 mg Petadolex® daily. The attack reduction in the total patient population was 63%.
- ❖ Regarding the reduction in intensity Grossman et al. (2001) reports a statistically significant difference only at the end of the second month, but not at the end of the treatment.
- ❖ Diener et al. (2004) agrees that migraine intensity was mostly reduced at the end of first and second month, and reports insignificant reduction at the end of twelve weeks.
- ❖ Rothman et al. (2004) reports in his study of 108 participants that 67% of the children and 49% of the adolescents felt that attack severity had been reduced by Petasites hybridus extract.

Does the treatment with Petadolex® increase risk of adverse events?

- ❖ In the study conducted by Grossman et al. (2001) patients demonstrated an excellent acceptance of Petasites hybridus extract Petadolex® and high compliance to the study protocol.
- ❖ Similar results were found in the Diener et al. (2004) study.
- ❖ In the large randomized trial study by Lipton et al. (2004) the most significant adverse effect recorded in all groups: 50 mg Petadolex®, 75 mg Petadolex®, and placebo was burping.
- ❖ A study carried out by Rothman et al. (2004) reports that Petasites hybridus extract was very well tolerated by a group of children and adolescents between ages 6 and 17 .
- Safety considerations in treatment of migraines with Petasites hybridus.**
- ❖ A major challenge in the pharmaceutical industry is to maintain consistent quality of herbal and non-herbal medicinal products.
- ❖ Petasites hybridus plant contains pyrrolizidine alkaloids (PAs), commercially prepared extracts is virtually PA free and appropriate for treatment of patients with migraines.
- ❖ PAs have been associated with the development of benign and malignant epithelial hepatic tumors, liver damage, and have pro-thrombic activity as reported by National Toxicology Program (2009).
- ❖ Petadolex® is extract-standardized to provide PA free product, and has been manufactured since 1988 according to a patented process.
- ❖ Safety of a long-term use has not been established, currently it's advised to limit Petadolex® use to a 16 week treatment time period.
- ❖ Additional quality research studies should be completed before Petadolex® is used during pregnancy, lactation or in children less than 6 years old.
- ❖ Safety has not been established for pediatric dosing higher than 150 mg, providers may need to adjust pediatric dosing for a specific age group.

Applicability to Clinical Practice

- ❖ Doctors and mid-level providers must understand the importance of prescribing a “highly standardized” product versus “herbal drug”.
- ❖ Clinical evidence indicates that Petadolex® may reduce frequency of migraine attacks in patients that start with a 75 mg dose of the product. Full benefit can be achieved after 3-4 month of treatment with doses up to 150 mg daily.
- ❖ Longer period of times (more than 16 weeks) has been called into question and currently is not recommended.
- ❖ Petadolex® 50-150 mg daily is an effective alternative to established drugs for prophylactic migraine treatment in children older than 6 years and adolescents.
- ❖ Petasites hybridus extract is very well tolerated in all clinical trials and their participants.
- ❖ Mild eructation is the only significant side effect reported in reviewed clinical trials.
- ❖ Clinicians and patients need to be aware of potential liver damage or liver cancer by unpurified butterbur extract contaminated by pyrrolizidine alkaloids.
- ❖ Concomitant use of butterbur extract with agents containing PAs or those that induce cytochrome P450 should be avoided since there is potential for toxicity.

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