A Non- Randomized, Open-Label Trial Evaluating the Efficacy of LEVARE®, a Blend of 12 Specific Medicinal Herbs, for the General Relief of Pain in Healthy Volunteers.

Lomax L, Ferguson P, Pohlman K

Abstract

For Centuries herbal remedies have been used to treat various ailments and conditions[1-16]. Furthermore, the effectiveness and safety profiles of many of these remedies have been proven by modern science[17-22]. There are many pain relief products currently on the market, some available over the counter (OTC) and others by prescription. Although they are different, they are similar in terms of the risks that are generally associated with their usage[23-31]. Thus consumers are now more than ever actively looking for safer alternatives. Our goal was to develop a natural alternative that would be just as effective, if not better than, and safer than pharmaceutical pain relief products that are currently available. We conducted a non-randomized, open-label trial evaluating the efficacy of a blend of 12 specific medicinal herbs, for the general relief of pain in healthy volunteers. A total of 62 patients participated. Various parameters were specifically evaluated. We found that LEVARE (patent pending) was effective, well tolerated and that most of the participants would not only recommend it to others but would utilize it as their primary pain reliever in the future. We ultimately concluded that LEVARE is a very safe and effective pain reliever and will become a very popular alternative to typical OTC and prescription pain relief products.

Background

People of all ages, genders and races suffer at some point from various types of pain. This ranges from general muscle aches and headaches, to significant pain from arthritis, acute injuries; surgery related pain as well as pain from chronic conditions. Chronic pain in fact is the leading cause of adult disability in the United States and is one of the most common reasons for patient visits to primary care clinicians[23]. Conventional treatment with prescribed and over the counter (OTC) non-steroidal anti-inflammatory drugs (NSAID's), COX-2 inhibitors (e.g. Celebrex) and narcotics have remained the mainstay of current treatments. Among the NSAIDs numerous classes exist, representing a wide variety of pharmacokinetic and pharmacodynamic properties. Primary classes include salicylates, nonacetylated salicylates, propionic acids, fenamates (anthranilic acids), acetic acids, naphthylalkanones, oxicams, and COX-2 inhibitors. Although most of the agents ultimately affect similar inflammatory and nocioceptive pathways, the chemistry, pharmacokinetic, and pharmacodynamic differences among classes allow clinicians flexibility when selecting patient-centered initial therapy.

While these agents are generally effective in providing relief of pain, they are also typically associated with significant adverse side effects (gastrointestinal, cardiovascular and addiction). In particular, because of the widespread use of NSAIDs and COX-2 inhibitors, the risks associated with their use are of increasing concern. In the recently concluded 2009 American Geriatrics Society (AGS) annual meeting; as a result of their troubling side effect profiles, the revised AGS guidelines on the management of persistent pain to be published in the August issue of the Journal of the American Geriatrics Society adopted the position and will advise physicians to have their elderly patients avoid the use of NSAIDs and COX-2 inhibitors and consider the use of low-dose opioid therapy instead. A position that reflects the general safety concerns with the use of these agents.

Adverse Events Associated with Nonsteroidal Anti-inflammatory Drug Therapy: Gastrointestinal

The NSAIDs are among the most frequently used class of drugs worldwide, with yearly over-the-counter sales amounting to $30 billion. Gastrointestinal safety continues to be a high priority for patients and clinicians when choosing an NSAID treatment for pain. In fact, the gastrointestinal harm induced by NSAIDs may be the most prevalent adverse event associated with any drug class[24]. Clinical manifestations of adverse gastrointestinal events include gastric and duodenal mucosal erosions, ulcers and ulcer complications, dyspepsia, abdominal pain and nausea. Dyspeptic symptoms include epigastric pain, bloating, nausea, and heartburn, which account for the most common reason for discontinuation of NSAID therapy. Gastric or duodenal ulceration occurs in about 20% of NSAID users, and 40% of these individuals develop a serious complication[25]. Other problems in the lower gut linked to the use of NSAIDs are gut inflammation, increase in gut permeability, stricture, protein malabsorption, bleeding, and perforation[26].

Therefore as a result of the widespread use of these agents, the potential for a significant number of adverse events, particularly gastrointestinal related, is high. Gastrointestinal adverse events associated with NSAID use are reported to account for more than 100,000 hospitalizations and more than 15,000 deaths annually[27]. Noteworthy are the numbers of hospitalizations for patients taking long-term, low-dose aspirin who are admitted with upper gastrointestinal bleeding. This accounts for about 10-15% of the hospital admissions for upper gastrointestinal bleeding. The resulting economic costs incurred in managing NSAID related gastrointestinal adverse events are significant; where it is estimated that $0.66-1.25 of every dollar spent on the cost of the NSAID is associated with treating adverse events[28].

Cardiovascular Events

Selective (COX-2) inhibitors have demonstrated improved gastrointestinal tract safety over traditional NSAIDs drugs. There is important evidence from clinical trials showing that compared with traditional NSAIDs, COX-2 inhibitors are associated with a reduced rate of serious GI events such as bleeding, perforation and obstruction, and other symptoms such as dyspepsia, as well as a reduced requirement for concomitant gastroprotective therapies such as proton pump inhibitors. This relative benefit may be related to a lack of COX-1–mediated inhibition of gastric mucous production and a lack of effect on platelet thromboxane production. However, the differential effects of COX-2 inhibitors compared with traditional NSAIDs on platelet aggregation, prostacyclin/thromboxane balance, and inflammatory mediators involved in the development of atherosclerosis have also led to concerns that there is a physiological basis for COX-2 inhibitors to increase the risk for thrombotic events[29].

These negative cardiotoxic effects (myocardial infarctions) of the COX-2 inhibitors were first documented in the Vioxx Gastrointestinal Outcomes Research (VIGOR) trial and the Celecoxib Long-term Arthritis Safety Study (CLASS) [25, 30]. Although the cardiotoxic effects were thought to be limited to myocardial infarctions, a subsequent meta analysis showed an increase in the occurrence of arrhythmias in COX-2 treated patients as well[31].The ensuing body of evidence relating to adverse cardiovascular outcomes prompted the FDA to remove rofecoxib (Vioxx) from the market and led to modified warnings and use of (Celecoxib) Celebrex. Additionally, resulting changes to pain treatment recommendations have led to a significant decline in the use of the COX-2 inhibitors.

Nonetheless, as the population ages, more patients will experience osteoarthritis, rheumatoid arthritis, chronic back pain, chronic musculoskeletal injuries, and migraine. Other ailments such as pain from overexertion, perimensual pain, etc, will also necessitate treatment. It is therefore very likely that gastrointestinal problems will continue to increase as the use of the traditional nonselective NSAIDs in the United States increases because of the concern for cardiovascular complications associated with the COX-2 inhibitors. The elderly are especially at risk for gastrointestinal events, including serious complications. There therefore remain a clear need among patients and practitioners alike for more effective and safer alternatives for the treatment of pain[32, 33].

Many anecdotal as well as recent studies support the use of natural remedies (herbal) for relief of pain[34-43]. Historically herbal remedies have not only been reported as effective, but they have been used to treat various ailments and conditions and generally have had very low risk profiles[19-22]. The objectives of this phase II study were to determine if LEVARE is effective at providing general relief of various types of pain and compare the subjective results participants obtained with LEVARE to other OTC or prescription pain relief products they commonly use, as well as describe any adverse events they experienced.

Methods

Extensive research was preliminarily done on medicinal herbs that had been historically utilized to treat various conditions such as arthritis, menstrual cramps, headaches etc., as well as on herbs that had been known for their anti-oxidant qualities and for those known to inhibit certain cytokines/mediators of pain and inflammation e.g. PGE2, COX-2, TNF, IL-1 etc[2,4-10,12-18] 12 specific medicinal herbs (shown below) were chosen and then processed utilizing specific manufacturing techniques to obtain a tablet of specific dosage.

Core Ingredients	**Synergistic Ingredients**
Boswellia Serrata	Chiococca Alba
Harpagophytum Procumbens	Dihydroxybergamottin
Turmeric	Lactuca Virosa
White Willow	Mimosa Pudica
Phellodendron Amurense	Naringen
	Paullinia Tomentosa
	Yerba Mate

Study population

Patients selected for inclusion in the trial were:

Generally otherwise healthy and experiencing pain; acute or chronic

*At least 16 years of age and able to complete a questionnaire capturing self reported use of OTC/prescription analgesics for pain relief.

Able to comprehend and comply with requirements of the study

(*Participants who were currently utilizing pain medication were advised to discontinue it during the study, unless medically contraindicated. Potential risks associated with concomitant use of multiple pain products were also explained in detail to participants prior to their inclusion).

Patients were excluded from the trial if:

They had participated in a study involving OTC/prescription pain relief products within the past 12 months.

They had a known allergy to any of the ingredients in LEVARE.

If they were pregnant, trying to become pregnant or breastfeeding.

They had previous treatment with herbal pain relief remedies with similar ingredients.

They had a medical condition, in the judgment of the examiner and/or study investigators, that may preclude their safe participation in the protocol or prevent completion of the study, such as: uncontrolled angina and/or congestive heart failure, severe chronic obstructive pulmonary disease, active treatment for cancer, major psychiatric disease, other systemic disease, or significant abnormalities of hematological, cardiac, pulmonary, metabolic, renal, hepatic, gastrointestinal or other systems.

They were currently using anti-coagulants (Coumadin, heparin, aspirin > 325mg day)

They had a history of drug and/or alcohol abuse sufficient to hinder compliance with treatment or follow up procedures.

The study began in November 2008 and ended in July 2009. A total of 62 healthy volunteers, age range 16-77 participated. There were 38 females, and 24 males. One group of 32 was required to take LEVARE for at least 4 weeks for various pain related conditions e.g. degenerative arthritis, post-surgical etc. The remaining 30 were asked to take LEVARE on an as needed basis for acute pain relief e.g. headaches, menstrual cramps, toothaches etc. Questionnaires were designed to assess how effective LEVARE was at relieving their pain, compare it with other pain relievers they've taken in the past and also assess any adverse events. The following parameters were also assessed: pain severity(mild, moderate, severe), relief after using LEVARE (poor, okay, good, amazing, revolutionary), onset of action (e.g. 20 min, 1hr etc.), duration of relief, # of pills needed to achieve desired effect, adverse events/side effects, and if they would continue to utilize LEVARE and possibly recommend it to others.

Results

Table 1: Baseline Characteristics of Subjects

Characteristic	Treatment Group
Age — yr	
Range	**16-77**
Sex — number (%)	
Female	**38 (61.3)**
Male	**24 (38.7)**
Pain Severity — number	
Mild	**5**
Moderate	**38**
Severe	**19**
Past Pain Reliever Use	
Advil	**10**
Aleve	**8**
Aspirin	**7**
Diclofenac	**1**
Ibuprofen	**28**
Imitrex	**1**
Methadone	**1**
Mobic	**1**
Nubaine	**1**
Naproxen	**2**
Oxycodone	**1**
Tylenol	**12**
Tylenol, Extra Strength	**4**
Ultram	**1**
Vicodin	**2**
Cause of Painful Condition	
Osteoarthritis of the spine, hip, knee, hands and shoulder	
Rheumatoid arthritis	
Chronic rotator cuff tears	
Tendonitis	
Menstrual cramps	
Headaches (tension, migraine)	
Muscle strains (cervical, lumbar)	

General aches
Motor vehicle accident
High level sports related muscle soreness
Post Surgical

62 healthy volunteers completed the study. Patients in this trial had an age range of 16-77 years with a significant proportion of the study population being females (61%). A significant proportion of patients rated their pain as either moderate or severe, 61% and 31% respectively. Prior to entry in the trial, patients consumed a wide variety of medications for their pain. Ibuprofen, Tylenol including the extra strength variety and Advil were the most widely used analgesics. On entering the trial, patients listed an assortment of reasons as the causative nature of their pain; these are listed in table 1 above.

Relief Experienced w/ LEVARE by pain scale
Mild Group
Okay (2)
Good (2)
Amazing/Revolutionary (1)

Moderate Group
Okay (3)
Good (10)
Amazing (20)
Amazing/Revolutionary (1)
Revolutionary (4)

Moderate/Severe Group
Amazing (3)
Revolutionary (1)

Severe Group
Poor (1)
Good (5)
Good/Amazing (1)
Amazing (5)
Revolutionary (3)

Figure 1: Responder Response to Symptoms Across Pain Scales

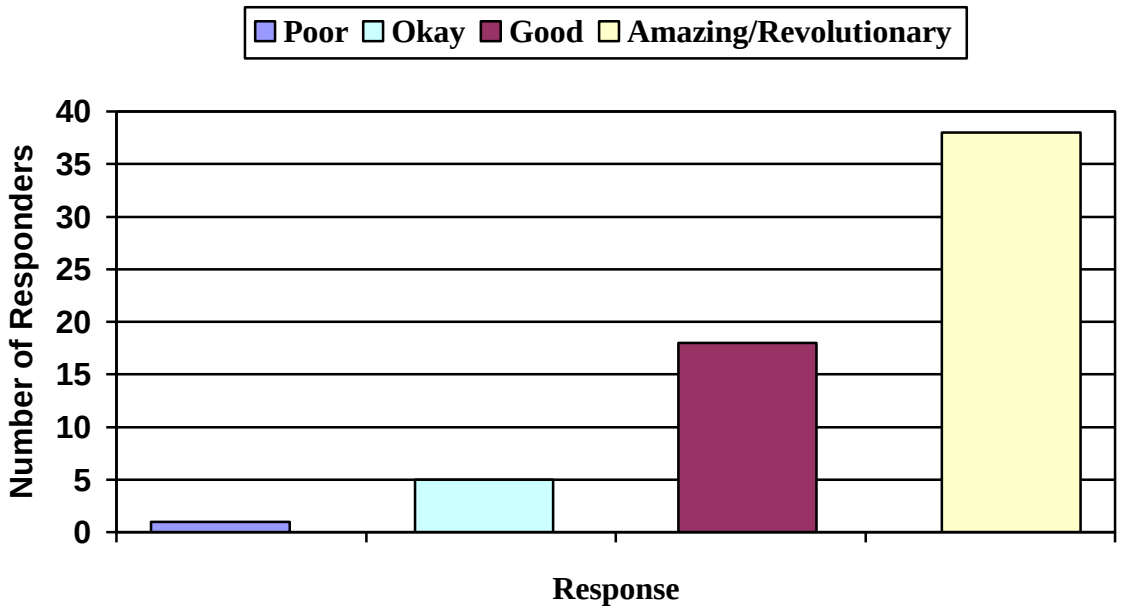

Figure 1 shows patient response to treatment with LEVARE**.** Responders were asked to rate their level of pain relief after using LEVARE as either poor, okay, good, amazing or revolutionary. 56 (90.4%) of patients rated their response as good, amazing or revolutionary. Significantly, 38 patients rated their response as either amazing or revolutionary. Overall response to treatment was similar when patients were assessed based on their initial assessment of pain rated as mild, moderate, or severe. Of all the patients followed, only 1 patient (in the severe pain group) rated their response as poor. However, even in this group of patients with severe pain, 8 of 15 patients rated their pain relief as amazing or revolutionary while the remaining 6 patients rated their relief as good or amazing.

Onset of Action ranged from 10 minutes to 1 hour with 76% experiencing relief within 30 minutes and the remaining 24% within the first hour.

Figure 2: Onset of Analgesic Effect

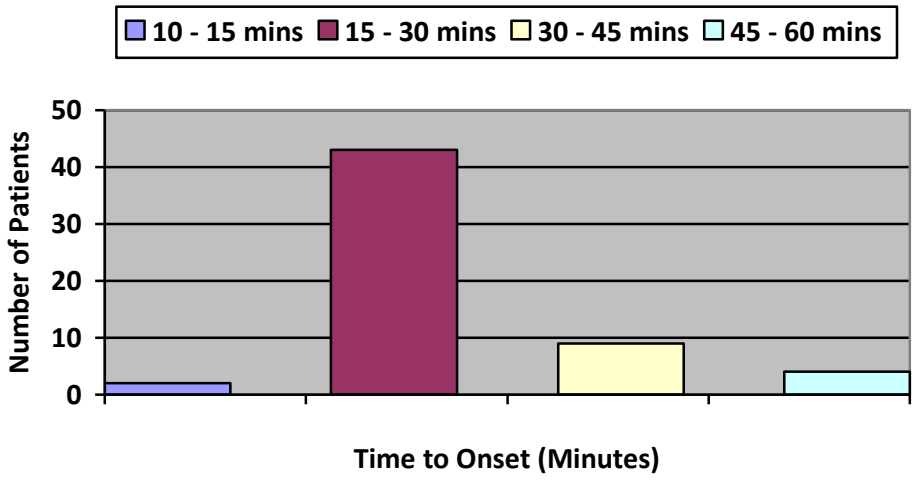

Figure 2 shows the onset of action of LEVARE**.** Onset of action was predictable, with most patients, Seventy six (76 %) percent achieving pain relief within 30 minutes after dosing. Ninety four (94%) percent of patients achieved relief within 45 minutes and after 1 hour all patients reported having relief of pain.

Figure 3: Duration of Pain Relief

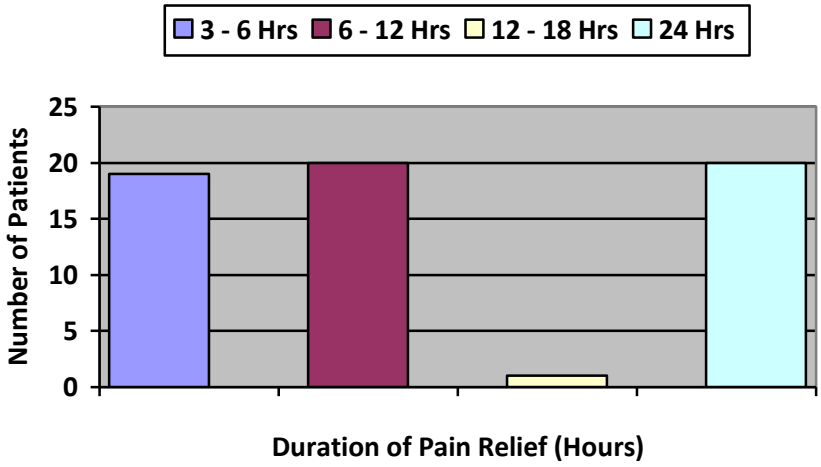

Figure 3 summarizes the duration of pain relief achieved with use of LEVARE**.** Duration of relief ranged from 3hrs to all day; one patient even reported relief of osteoarthritis pain for 4 days. Thirty four (34%) percent experienced at least 6-16 hours of relief and thirty three (33%) percent reported all day relief of symptoms.

Number of pills utilized to achieve desired effects ranged from 1 to 4 per dose.

Patients	# of pills per dose
3	1
23	2
14	3
22	4

Reported adverse events/Side effects*

Constipation (1)
Heartburn (1)**
Sedation (1)
Abdominal cramping (1) ***

LEVARE was generally well tolerated with the only adverse events reported being single reports of constipation, heartburn, sedation and abdominal cramping respectively. *In the patients reporting adverse events all except the patient who experienced abdominal cramping still reported achieving amazing, okay, and okay relief of their pain complaints respectively. Furthermore, 2 of the 3 would also consider taking LEVARE in the future and would recommend it to others.

**This patient had a history of gastritis and was concomitantly taking ibuprofen despite our specifically advising her to discontinue it.

***This patient had a history of significant gastroesophageal reflux disease.

Would make LEVARE their primary pain relief choice and recommend to others.

Yes (58)
No (2)
Will use in combination with other meds (1)
Maybe (1)

Conclusion

The prevalence of pain in today's society is significant, which obviates the need for effective treatment modalities. Typically, OTC and prescription NSAID's, COX-2 inhibitors and narcotics are utilized by consumers. Unfortunately their usage is not without risks and many studies have confirmed this[23-31]. The authors of this study agree with the recent position adopted in the revised AGS guidelines on the management of persistent pain advising physicians to have their elderly patients avoid the use of NSAIDs and COX-2 inhibitors. Further, they feel that the risks associated with the use of these products are unacceptable and therefore, decided to develop a safer alternative.

After developing LEVARE a blend of twelve specific natural ingredients, we performed a non-randomized, open-label study evaluating its efficacy in healthy volunteers. The results which are documented above demonstrate that LEVARE was at a minimum as effective if not more effective as the reported OTC and prescription NSAID's typically utilized by the consumers, who voluntarily participated in this study. Furthermore, the very low incidence of reported adverse events supports the historically excellent safety profiles of the ingredients used in the blend. Overall LEVARE was shown to be both effective and safe.

The authors do acknowledge that this was not a randomized blinded study; and therefore, does have some weaknesses and that results will vary from individual to individual. However, as the information provided was given subjectively from volunteer participants who received no compensation, except free product during the study, potential bias is mitigated. We feel confident that based on its efficacy and safety, LEVARE will become a very attractive OTC natural pain relief alternative for consumers.

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