

EVA/Rheumatoid Arthritis Study Now Underway.

*by Dr. Marion Allen**

We chose to investigate **Velvet Antler** because of growing public interest in North America in elk velvet antler (EVA) as an alternative therapy, its 2000-year history; and because of the stories we heard about how it has helped people, including symptom relief in rheumatoid arthritis. As well, we knew that it had many active ingredients that could have an effect. Our other motivation was the obvious interest shown by the elk industry people in seeing a human clinical trial conducted using EVA in controlling the symptoms in persons with rheumatoid arthritis.

In 1998, when we conducted a pilot study for the purpose of examining the safety of taking EVA with rheumatoid arthritis medications, we concluded that elk velvet antler could be taken safely in conjunction with a number of rheumatoid arthritis medications and that it may be efficacious in controlling symptoms of rheumatoid arthritis. Our interest spurred by these results, Cindy Ewashkiw and I wrote a booklet intended for the general public, entitled “Velvet Antler- A Gift from Nature”, in which we presented currently known facts about the origins and uses of velvet antler. Following is a description of the completed pilot study as well as the full-scale clinical trial of the effectiveness of elk velvet antler for rheumatoid arthritis, which is currently under way.

An Overview of Rheumatoid Arthritis

Rheumatoid arthritis is a systemic disorder, which causes **chronic inflammation of the joints, tissue around the joints, and other organs** in the body. We are not sure what causes the disease, but environmental factors, genetics, and infectious agents such as viruses, bacteria, and

fungi, have been suggested as possible causative factors. The typical pattern of the disease is one of flare-up and remission, although for some, the symptoms are unremitting. People with RA complain of tender, swollen and painful joints, morning stiffness, and fatigue. These symptoms often cause limitations in ones activities of daily living. It also can affect quality of life.

As there is **no known cure** for arthritis, **treatment has four major objectives**: reducing inflammation and pain, preserving joint function, preventing deformity, and optimizing functional health and well-being. There is an attempt to reduce symptoms through a combination of medications, rest, joint strengthening exercises, and joint protection. Treatment with medications, to reduce swelling and inflammation, usually start with aspirin and ibuprofen. If these don't work well, then slower acting, 'second-line' drugs include gold and immunosuppressives such as methotrexate and cyclophosphamide. Even with aggressive management, symptoms may persist, and progression of the disease can continue. As well, all the drugs that are taken are associated with side effects.

So any **alternative therapy** that would be used would also need to work on one or more of these same objectives: reducing inflammation and pain, preserving joint function, and preventing deformity and optimising functional health and well-being. Elk velvet antler (EVA) is so interesting for this purpose, because of the **active ingredients** it contains, including glycosaminoglycans (GAGs) and omega-3 and 6 fatty acids, which have been shown to contribute to the health of joints, and perhaps decrease the inflammation resulting in less tender and swollen joints. EVA is also said to contain a substance called prostaglandin (a kind of fatty acid) which also has an anti-inflammatory effect.

Pilot Study of EVA

Based on this information we undertook a **pilot study**. Why the pilot? Well, despite widespread use of EVA, its long history, and no reports of adverse interactions with other therapeutic agents in the body, we could not find any systematic study that examined possible drug interactions or other possible toxic effects in human beings, and no clinical trial to assess efficacy in particular disease conditions. As well, because it is a food product, there has been no standardization of dose (so we didn't know how much we should give to people in the larger trial). The purpose then of the pilot was to lay the groundwork for the in-depth trial. The **questions we posed** in the pilot were:

1. What was the tolerance to elk velvet antler at doses of 2, 4, and 6 capsules daily compared to placebo?
2. Was there any evidence of interaction effects of elk velvet antler with commonly used arthritis drugs?
3. What was the relationship between product dose and functional health status?

Procedure: We followed the normal procedures for doing a pilot for assessing safety of a drug. Briefly what we did was to follow for 4 weeks, forty adult patients diagnosed with RA and who were currently taking commonly prescribed or over-the-counter (OTC) medications for their arthritis. We **randomly assigned** them to one of four treatment groups with ten people in each group. Groups received daily either, six placebo capsules; or two, four, or six capsules respectively of elk velvet antler plus identical placebo to bring the total to six. The reason we gave everyone 6 was that there was the possibility that many of the subjects knew each other as many were Dr. Russell's patients and we were concerned that they might talk with each other and figure out which group they were in. The other reason for giving the same number of

capsules to everyone is that this enabled the researchers to remain 'blind', in other words, to work with the subjects and the data collected without being biased by knowing whether the subjects had taken EVA or the placebo. Everyone directly connected to the study was 'blind'. Subjects continued to follow their prescribed treatment regimen, including standard RA medications.

At the beginning and end of the study, we asked them about their health, pain in their joints, and how well they carried out their day-to-day activities. We followed them very closely and questioned them about the presence of any adverse events that were not noted prior to initiation of the trial. **An adverse event** is any reaction, side effect, or other undesirable event that occurs in conjunction with use of a product, whether or not the event is considered product related. Each adverse event was also graded as to severity- mild (discomfort noticed but no disruption of normal activity), moderate (reduced or affected normal daily activity), severe (inability to work or perform normal daily activity); or life threatening (serious health problems which require hospitalization, result in persistent or significant disability/incapacity, are medically significant, require intervention to prevent one of the outcomes listed above, or are fatal).

Findings: Remember that the primary outcome variable in this study was occurrence of adverse events. There were **no significant differences** between the groups in either number of events, relationship to treatment, or level of severity. The three EVA doses and placebo showed the usual array of side effects normally found over a four-week period in patients with these conditions. There was only one adverse effect classified as severe and possibly related to the treatment of EVA. Symptoms resolved themselves and the patient completed the study. Although this event was classified as possibly related to treatment it seems unlikely that there

was a direct association given that the patient had been on the EVA for only two days when symptoms occurred. For all other adverse events, the numbers of participants, type of side-effects, and severity were similar for all groups, including placebo. As all participants were on a variety of other drugs this result was positive relative to the safety of EVA in conjunction with arthritis medications.

We grouped the measures of health that we assessed at the beginning and end of the study into 3 categories: 'Physical' referring to functional ability; 'affect' referring to the impact on social/psychological functioning; and 'symptoms' referring to pain and mobility. Each group **demonstrated an improvement** over the 4 weeks in each category except symptom scores in the 2 EVA group. These changes were not statistically significant. Comparison between groups at baseline and after 4 weeks treatment showed no significant differences for any of the components.

Our next task was to look at the percentage improvement relative to baseline in each group. Here, the largest gains were made by the 6 EVA group for the affect and symptom components, while the 4 EVA group had the largest improvement in the physical component. Overall the greatest improvement was seen in the 6 EVA group and the least in the placebo group. Patient self-reports of overall wellness (global assessment) were not significantly different across groups. However, more participants in the 6 EVA group than in any other category indicated that their general sense of wellness was increased overall.

Although the differences were not statistically significant, these scores **exhibited a trend in favor of EVA** relative to placebo. In particular, the 6EVA group showed an improvement more than triple that of the placebo group for each of physical, affect, and symptom measures. Based on the results in this pilot study, we decided that it was worthwhile to undertake the larger study and that approximately one gram of EVA (total of what was in the 6EVA) was the preferred dose. Although those people who have found relief of RA symptoms by taking EVA might say that they could have already told us this, the pilot was in fact money well spent. As scientists, we need to follow the commonly accepted steps in doing this kind of research. It was the pilot study that was a major contributing factor to our receipt of funding for the large study. Another key contributing factor to our getting funding was the interest and contribution of the industry. We are particularly grateful to the Alberta Elk Association, the Saskatchewan Elk Breeders Association, and Redwater River Ranch for their financial support for the pilot study.

Current Full Scale Clinical Trial Study

The purpose of our current study is to determine the comparative efficacy of EVA and placebo in controlling symptoms in persons with rheumatoid arthritis. Again it is a clinical trial where no one including the people who analyse the data will know what group got what. We will be following 220 people (110 in each group) for 6 months. The people in the study must be diagnosed with Stage 2 and 3 RA (Stage 2 and 3 patients are almost certain to have some symptoms, particularly pain, uncontrolled by treatment), and their prescribed medication dosage stable for at least four weeks prior to study onset. We will eliminate any person whose arthritis began in childhood or who is on steroids.

Outcome Measures: Those criteria, that have been outlined by American College of Rheumatology as important to study in all drug related trials for RA, will be followed in this study:

- < patient assessment of pain
- < tender joint count: assessment of 28 joints -- shoulders, elbows, wrists, metacarpal phalangeal, proximal interphalangeals, and knees
- < swollen joint count on same 28 joints
- < patient global assessment of disease activity
- < physician global assessment of disease activity
- < C-reactive protein as measured by standardized methods (C-reactive protein is a serum protein that increases dramatically in concentration in people suffering from any type of severe inflammatory response.)
- < assessment of functional ability and quality of life

We are hypothesising that there will be a significant difference between EVA and placebo groups after 6 months of treatment in all these areas.

All patients will be seen and screened by a registered nurse, and directed to take one gram in capsules (EVA or matching placebo) every day for the 6 months.

Throughout the study, patients will continue to follow their current RA treatment regimen, and will be requested not to use new medications, including over the counter preparations, to control their RA symptoms.

Patients will be seen at baseline, and at three and six months. They will be contacted by telephone at monthly intervals to assess how they are doing. Patients will be

questioned about adverse events at each visit and telephone call, and will be instructed to contact investigators if troubling symptoms arise between visits.

We have started enrolling people into this study. Due to the length of time that it takes to enrol all the people we require in the study, and the 6 months course of treatment - we won't know the results for around 3 years.

The clinical trial has received full ethical approval from the University of Alberta. Funding for this study has been provided by the Canadian Institute of Health Research (CIHR)(formerly MRC), the Alberta Elk Association, and Redwater River Ranch. I want to formally thank the CIHR, AEA, and Redwater River Ranch for their funding for this study. I also want to thank Cindy Ewashkiw and Rob Pek for their significant efforts to help us get additional funding for the study.

Final results of the full clinical trial will provide information to both the general public, health care providers, and of course the elk industry, allowing for informed decisions and recommendations about the use of EVA for these diseases. This is important because of the current lack of scientific research available about this 2000-year-old remedy. When Canadian Health Minister, Alan Rock, visited Alberta recently, he specifically and proudly referred to this study as a prime example of federal research funding and was quoted in the media to that effect. He also pointed out that it was the first major clinical trial ever federally funded for an alternative therapy in Canada.

Additional Study Proposed: We propose to add an “arm” to the study to test the effectiveness of EVA on osteoporosis, the common problem of thinning of the bones with aging or disease. Frequently rheumatoid arthritis patients also have osteoporosis, so we anticipate that many subjects enrolled in our rheumatoid arthritis study will also be

suffering from osteoporosis. Our proposed added arm to this research would require all of the participants enrolled to have a bone density test at the beginning of their trial, with further testing upon the completion of the course of therapy for those people who had initial evidence of osteoporosis. Being able to research more than one disease with these participants is an opportunity for cost effectiveness, and the additional information can be readily achieved with the addition of this one measure. We would need additional funding to pay for these tests, and thereby enable us to collect information on effectiveness of EVA on both rheumatoid arthritis and osteoporosis.

Number to call: (780) 492-6427 Liz Turnbull RN MN, Project Coordinator. If you know of people who have RA and are not currently taking EVA, ask them to call us to see if they can take part in this study.

* Dr. Marion Allen RN, PhD, is the principal investigator on this study. She has expertise in chronic illness and its effect on the day to day lives of individuals. She has conducted numerous qualitative studies with individuals with chronic illness, examining the effects of chronic illness on quality of life. She has an avid interest in complementary therapies.