

## ALTERNATIVE MEDICINE

AN EVIDENCE-BASED APPROACH

## Prolotherapy for Chronic Back Pain

## History and Rationale for Use

Prolotherapy, or proliferative injection therapy, involves the injection of irritant substances into regions of ligaments and tendons with the intention of strengthening the ligaments through local proliferation of granulocytes, fibroblasts, macrophages, and growth factors.

Similar techniques were used in the late 19th century for hernia repair and in the

1930s for subluxation of the temporomandibular joint. Prolotherapy gained popularity after Dr. George S. Hackett gave a presentation on it at the American Medical Association's annual meeting in 1955.

A variety of substances from three classes of proliferants have been used with this technique, with osmotic proliferants being the most common. This class includes solutions of glucose, glycerin, and zinc sulfate that act by provoking cellular osmotic shock, causing the release of pro-inflammatory cytokines. A second category, referred to as irritants, includes phenol, tannic acid, and guaiaco, and can damage cell surfaces, rendering them antigenic. The third type, chemotactics, also cause a local influx of inflammatory cells. Sodium morrhuate belongs to this class.

## Clinical Studies

A recent Cochrane review identified five high-quality studies that included 366 patients aged 18 years and older with chronic low back pain. The protocols were notably heterogeneous, which the authors acknowledged made intertrial comparisons difficult and meta-analysis and levels of evidence summaries impossible (Cochrane Database Syst. Rev. 2007;doi:10.1002/14651858CD004059.pub3).

One study compared injections of a solution containing glucose, glycerin, phenol, and lidocaine with injections of a control solution of normal saline, and two studies compared a glucose, glycerin, phenol, and lidocaine solution with a lidocaine control solution. A fourth compared a glucose plus lidocaine solution with saline solution, and the fifth compared a solution of phenol, dextrose, glycerin, and procaine with a procaine control solution.

In two of the studies, only three injection treatments were given, using only 10 mL of solution. In the other studies, at least six treatments were given, using at least 20 mL of solution. Other protocol differences were related to prior administration of triamcinolone and lidocaine into muscle tender points and lumbosacral ligaments.

The authors of the review reported that three studies that compared prolotherapy alone with control injections alone found no evidence for efficacy, whereas benefits were seen in the two studies that compared prolotherapy plus other modalities such as spinal manipulation and exercise.

Of the two positive studies, one that included 79 patients found a greater proportion of patients in the active prolotherapy group had achieved a decrease of 50% or more in pain or disability 6 months after a series of six weekly injections, compared with patients in the control group, who received injections of xylocaine/saline solution (J. Spinal Disord. 1993; 6:23-33).

Another study that included 81 patients found a regimen of spinal manipulation plus proliferant injections of a dextrose, glycerin, and phenol solution was more effective in reducing pain than was a program of sham manipulation plus saline injections. Significant differences favoring the prolotherapy treatment also were seen between the groups in the proportion of patients who had an improvement in disability scores of more than 50% at 6 months. This proportion was 88% in the group receiving prolotherapy, manipulation, and exercise, compared with 55% in the control group (Lancet 1987;2:143-6).

This last study "has some of the most impressive results for low back pain I've ever seen," the lead author of the Cochrane re-

view, Simon Dagenais, D.C., Ph.D., said in an interview. He and his colleagues have sought permission from the Food and Drug Administration to conduct further studies, but the agency has been reluctant to accept any of the older data. He has completed two animal toxicity studies, and once the data analysis is complete, he plans to file an investigational new drug application for a phase I study of the mixture of dextrose, glycerin, phenol, and lidocaine.

## Safety Concerns

With the burgeoning of prolotherapy in the 1950s came clinical experimentation with a variety of irritant solutions, sometimes by inexperienced practitioners, and several serious adverse events occurred. A 50-year-old woman who received injections of a solution of zinc sulfate and phenol solution de-

veloped adhesive arachnoiditis and hematoma and died. A 53-year-old woman was injected with vegetable oil and anesthetic and developed spastic paraplegia that was unrelieved by laminectomy. A 56-year-old man was injected in the lower back with an unknown substance and developed pain and

nausea, urinary urgency, and incontinence and later died (Spine 2005;5:310-28).

Adverse events other than spinal puncture headache have not been reported with injection of solutions containing dextrose, glycerin, and phenol. The safety of prolotherapy is likely comparable to that of other commonly used injections for chronic low back pain, such as epidural steroid injections, said Dr. Dagenais, of the division of orthopedic surgery, University of Ottawa, and CAM Research Institute, a nonprofit organization based in Irvine, Calif., that is sponsoring this research.

—Nancy Walsh

## LEXAPRO® (escitalopram oxalate) TABLETS/ORAL SOLUTION

(3% and <1%); Anorgasmia<sup>2</sup> (2% and <1%). \*Events reported by at least 2% of patients treated with Lexapro are reported, except for the following events which had an incidence on Lexapro: headache, upper respiratory tract infection, back pain, pharyngitis, inflamed injury, anxiety. †Primarily ejaculatory delay. ‡Denominator used was for males only (N=225 Lexapro; N=188 placebo). §Denominator used was for females only (N=490 Lexapro; N=404 placebo). **Generalized Anxiety Disorder Table 3** enumerates the incidence, rounded to the nearest percent of treatment-emergent adverse events that occurred among 429 GAD patients who received Lexapro 10 to 20 mg/day in placebo-controlled trials. Events included are those occurring in 2% or more of patients treated with Lexapro and for which the incidence in patients treated with Lexapro was greater than the incidence in placebo-treated patients. The most commonly observed adverse events in Lexapro patients (incidence of approximately 5% or greater and approximately twice the incidence in placebo patients) were nausea, ejaculation disorder (primarily ejaculatory delay), insomnia, fatigue, decreased libido, and anorgasmia (see TABLE 3). **TABLE 3. Treatment-Emergent Adverse Events: Incidence in Placebo-Controlled Clinical Trials for Generalized Anxiety Disorder\* (Lexapro (N=429) and Placebo (N=427)).** **Autonomic Nervous System Disorders:** Dry Mouth (5% and 5%); Sweating (increased) (4% and 1%); **Central & Peripheral Nervous System Disorders:** Headache (24% and 17%); Paresthesia (2% and 1%); **Gastrointestinal Disorders:** Nausea (18% and 8%); Diarrhea (8% and 6%); Constipation (5% and 4%); Indigestion (3% and 2%); Vomiting (3% and 1%); Abdominal Pain (2% and 1%); Flatulence (2% and 1%); Toothache (2% and 0%). **General:** Fatigue (8% and 2%); Influenza-like symptoms (5% and 4%); **Musculoskeletal:** Neck/Shoulder Pain (3% and 1%); **Psychiatric Disorders:** Somnolence (13% and 7%); Insomnia (12% and 6%); Libido Decreased (7% and 2%); Dreaming Abnormal (3% and 2%); Appetite Decreased (3% and 1%); Lethargy (3% and 1%); Yawning (2% and 1%). **Urogenital: Ejaculation Disorder<sup>1,2</sup>** (14% and 2%); Anorgasmia<sup>2</sup> (6% and <1%); Menstrual Disorder (2% and 1%). \*Events reported by at least 2% of patients treated with Lexapro are reported, except for the following events which had an incidence on placebo: Lexapro: inflamed injury, dizziness, back pain, upper respiratory tract infection, rhinitis, pharyngitis. †Primarily ejaculatory delay. ‡Denominator used was for males only (N=182 Lexapro; N=195 placebo). §Denominator used was for females only (N=247 Lexapro; N=232 placebo). **Dose Dependency of Adverse Events** The potential dose dependency of common adverse events (defined as an incidence rate of ≥5% in either the 10 mg or 20 mg Lexapro groups) was examined on the basis of the combined incidence of adverse events in two fixed-dose trials. The overall incidence rates of adverse events in 10 mg Lexapro-treated patients (66%) was similar to that of the placebo-treated patients (61%), while the incidence rate in 20 mg/day Lexapro-treated patients was greater (86%). **Table 4** shows common adverse events that occurred in the 20 mg/day Lexapro group with an incidence that was approximately twice that of the 10 mg/day Lexapro group and approximately twice that of the placebo group. **TABLE 4. Incidence of Common Adverse Events in Patients with Major Depressive Disorder Receiving Placebo (N=311), 10 mg/day Lexapro (N=310), 20 mg/day Lexapro (N=125):** Insomnia (4%, 7%, 14%); Diarrhea (5%, 6%, 14%); Dry Mouth (3%, 4%, 9%); Somnolence (1%, 4%, 9%); Dizziness (2%, 4%, 7%); Sweating Increased (<1%, 3%, 8%); Constipation (1%, 3%, 6%); Fatigue (2%, 2%, 6%); Indigestion (1%, 2%, 6%). †Adverse events with an incidence rate of at least 5% in either the Lexapro groups and with an incidence rate in the 20 mg/day Lexapro group that was approximately twice that of the 10 mg/day Lexapro group and the placebo group. **Male and Female Sexual Dysfunction with SSRIs** Although changes in sexual desire, sexual performance, and sexual satisfaction often occur as manifestations of a psychiatric disorder, they may also be a consequence of pharmacologic treatment. In particular, some evidence suggests that SSRIs can cause such untoward sexual experiences. Reliable estimates of the incidence and severity of untoward experiences involving sexual desire, performance, and satisfaction are difficult to obtain, however, in part because patients and physicians may be reluctant to discuss them. Accordingly, estimates of the incidence of untoward sexual experience and performance cited in product labeling are likely to underestimate their actual incidence. **Table 5** shows the incidence rates of sexual side effects in patients with major depressive disorder and GAD in placebo-controlled trials. **TABLE 5. Incidence of Sexual Side Effects in Placebo-Controlled Clinical Trials (In Males Only: Lexapro (N=407) and Placebo (N=383):** Ejaculation Disorder (primarily ejaculatory delay) (12% and 1%); Libido Decreased (6% and 2%); Impotence (2% and <1%). (In Females Only: Lexapro (N=737) and Placebo (N=636): Libido Decreased (3% and 1%); Anorgasmia (3% and <1%) There are no adequately designed studies examining sexual dysfunction with escitalopram treatment. Prapris has been reported with all SSRIs. While it is difficult to know the precise risk of sexual dysfunction associated with the use of SSRIs, physicians should routinely inquire about such possible side effects. **Vital Sign Changes** Lexapro and placebo groups were compared with respect to (1) mean change from baseline in vital signs (pulse, systolic blood pressure, and diastolic blood pressure) and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. These analyses did not reveal any clinically important changes in vital signs associated with Lexapro treatment. In addition, a comparison of supine and standing vital sign measures in subjects receiving Lexapro indicated that Lexapro treatment is not associated with orthostatic changes. **Weight Changes** Patients treated with Lexapro in controlled trials did not differ from placebo-treated patients with regard to clinically important change in body weight. **Laboratory Changes** Lexapro and placebo groups were compared with respect to (1) mean change from baseline in various serum chemistry, hematology, and urinalysis variables, and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. These analyses revealed no clinically important changes in laboratory test parameters associated with Lexapro treatment. **ECG Changes** Electrocardiograms from Lexapro (N=625), racemic citalopram (N=351), and placebo (N=527) groups were compared with respect to (1) mean change from baseline in various ECG parameters and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. These analyses revealed (1) a decrease in heart rate of 2.2 bpm for Lexapro and 2.7 bpm for racemic citalopram, compared to an increase of 0.3 bpm for placebo and (2) an increase in QTc interval of 3.9 msec for Lexapro and 3.7 msec for racemic citalopram, compared to 0.5 msec for placebo. Neither Lexapro nor racemic citalopram were associated with the development of clinically significant ECG abnormalities. **Other Events Observed During the Premarketing Evaluation of Lexapro** Following is a list of WHO terms that reflect treatment-emergent adverse events, as defined in the introduction to the **ADVERSE REACTIONS** section, reported by the 1428 patients treated with Lexapro for periods of up to one year in double-blind or open-label clinical trials during its premarketing evaluation. All reported events are included except those already listed in **Tables 2 & 3**, those occurring in only one patient, event terms that are so general as to be uninformative, and those that are unlikely to be drug related. It is important to emphasize that, although the events reported occurred during treatment with Lexapro, they were not necessarily caused by it. Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring on one or more occasions in at least 1/100 patients; infrequent adverse events are those occurring in less than 1/100 patients but at least 1/1000 patients. **Cardiovascular - Frequent:** palpitation, hypertension, **Infrequent:** bradycardia, tachycardia, ECG abnormal, flushing, varicose vein, Central and Peripheral Nervous System Disorders - **Frequent:** light-headed feeling, migraine. **Infrequent:** tremor, vertigo, restless legs, shaking, twitching, dysequilibrium, tics, carpal tunnel syndrome, muscle contractions involuntary, sluggishness, coordination abnormal, faintness, hyperreflexia, muscular tone increased. **Gastrointestinal Disorders - Frequent:** heartburn, abdominal cramp, gastroenteritis. **Infrequent:** gastroesophageal reflux, bloating, abdominal discomfort, dyspepsia, increased stool frequency, belching, gastritis, hemorrhoids, gagging, polyposis gastric, swallowing difficult. **General - Frequent:** allergy, pain in limb, fever, hot flushes, chest pain. **Infrequent:** edema of extremities, chills, tightness of chest, leg pain, asthenia, syncope, malaise, anaphylaxis, fall. **Hemic and Lymphatic Disorders - Infrequent:** bruise, anemia, nosebleed, hematoma, lymphadenopathy cervical. **Metabolic and Nutritional Disorders - Frequent:** increased weight. **Infrequent:** decreased weight, hyperglycemia, thirst, bilirubin increased, hepatic enzymes increased, gout, hypercholesterolemia. **Musculoskeletal System Disorders - Frequent:** arthralgia, myalgia. **Infrequent:** jaw stiffness, muscle cramp, muscle stiffness, arthritis, muscle weakness, back discomfort, arthropathy, jaw pain, joint stiffness. **Psychiatric Disorders - Frequent:** appetite increased, lethargy, irritability, concentration impaired. **Infrequent:** jitteriness, panic reaction, agitation, apathy, forgetfulness, depression aggravated, nervousness, restlessness aggravated, suicide attempt, amnesia, anxiety attack, bruxism, carbohydrate craving, confusion, depersonalization, disorientation, emotional lability, feeling unreal, tremulousness nervous, crying abnormal, depression, excitability, auditory hallucination, suicidal tendency. **Reproductive Disorders/Female - Frequent:** menstrual cramps, menstrual disorder. **Infrequent:** menorrhagia, breast neoplasm, pelvic inflammation, premenstrual syndrome, spotting between menses. \*Based on female subjects only. **H-305 Respiratory System Disorders - Frequent:** bronchitis, sinus congestion, coughing, nasal congestion, sinus headache. **Infrequent:** asthma, breath shortness, laryngitis, pneumonia, tracheitis. **Skin and Appendages Disorders - Frequent:** rash. **Infrequent:** pruritus, acne, alopecia, eczema, dermatitis, dry skin, folliculitis, lipoma, furunculosis, dry lips, skin nodule. **Special Senses - Frequent:** vision blurred, linitus. **Infrequent:** taste alteration, sarcoma, conjunctivitis, vision abnormal, dry eyes, eye irritation, visual disturbance, eye infection, pupils dilated, metallic taste. **Urinary System Disorders - Frequent:** urinary frequency, urinary tract infection. **Infrequent:** urinary urgency, kidney stone, dysuria, blood in urine. **Events Reported Subsequent to the Marketing of Escitalopram** - Although no causal relationship to escitalopram treatment has been found, the following adverse events have been reported to have occurred in patients and to be temporally associated with escitalopram treatment during post marketing experience and were not observed during the premarketing evaluation of escitalopram: abnormal gait, acute renal failure, aggression, akathisia, allergic reaction, anger, angioedema, atrial fibrillation, choreoathetosis, delirium, delusion, diplopia, dysarthria, dyskinesia, dystonia, ecchymosis, erythema multiforme, extrapyramidal disorders, fulminant hepatitis, hepatic failure, hypoaesthesia, hypoglycemia, hypokalemia, INR increased, gastrointestinal hemorrhage, glaucoma, grand mal seizures (or convulsions), hemolytic anemia, hepatic necrosis, hepatitis, hypotension, leucopenia, myocardial infarction, myoclonus, neuroleptic malignant syndrome, nightmares, nystagmus, orthostatic hypotension, pancreatitis, paranoia, photosensitivity reaction, priapism, prolactinemia, prothrombin decreased, pulmonary embolism, QT prolongation, rhabdomyolysis, seizures, serotonin syndrome, SIADH, spontaneous abortion, Stevens Johnson Syndrome, tardive dyskinesia, thrombocytopenia, thrombosis, torsade de pointes, toxic epidermal necrolysis, ventricular arrhythmia, ventricular tachycardia and visual hallucinations. Rev. 07/07 © 2007 Forest Laboratories, Inc.

## Crystal Shape, Size Distinguish Types of Gout

BY DIANA MAHONEY  
New England Bureau

BOSTON — To differentiate definitively between acute gout and pseudogout, look at the crystals.

On UV light microscopy, fluid aspirated from the inflamed joint of a patient with pseudogout will be teeming with rhomboid-shaped calcium pyrophosphate dihydrate (CPPD) crystals, which are morphologically different from the needle-shaped monosodium urate (MSU) crystals implicated in the pain and swelling of acute gout, Dr. Dwight R. Robinson said at a meeting on rheumatology sponsored by Harvard Medical School. "[CPPD] crystals are less well formed and show more variation in size and shape than [MSU] crystals."

Like MSU crystals in gout patients, the deposition of CPPD crystals in pseudogout causes acute pain and swelling the joints. The acute attacks can last from 1 day to 4 weeks and may be accompanied by fever, leukocytosis, and elevated acute-phase reactants, said Dr. Robinson, a rheumatologist and professor of medicine at Harvard Medical School, Boston. The latter signs

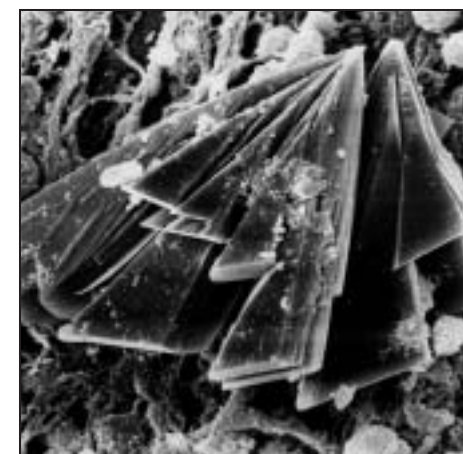
also may be indicative of septic arthritis, so sepsis first must be excluded by Gram stain and culture of synovial fluid.

CPPD crystals have a predilection for depositing in articular and fibrocartilage, said Dr. Robinson. In pseudogout, this process commonly involves the knee or wrist joint but also may involve the first metatarsophalangeal joint, as occurs in gout, or almost any other joint. Radiographically, the diagnosis of pseudogout often can be confirmed by evidence of chondrocalcinosis in the affected joint.

In addition to mimicking the clinical patterns of gout, CPPD joint disease symptoms may overlap with other inflammatory conditions. It may be asymptomatic in many patients.

CPPD disease develops in patients older than age 50. In younger patients, "it's more likely to be a complication of osteoarthritis, a late consequence of joint trauma or knee meniscectomy, or related to an underlying metabolic disease." There also may be a familial component.

The exact mechanism for the development of CPPD deposition disease is uncertain, but an overactivity of enzymes



Rhomboid-shaped calcium phosphate crystals are typical of pseudogout.

that break down nucleoside triphosphates has been implicated, as have genetic defects.

Acute attacks can be treated effectively with nonsteroidal anti-inflammatory drugs, said Dr. Robinson. Given the risks of gastrointestinal and renal toxicities associated with NSAIDs, particularly in elderly patients, intra-articular corticosteroid injection into the affected joint is a reasonable treatment option, he said. ■