

# Fibromyalgia: Tailored Tx Proved Successful

BY BRUCE JANCIN

FROM THE ANNUAL EUROPEAN CONGRESS OF RHEUMATOLOGY

ROME — A tailored combination of cognitive-behavioral therapy and physical exercise training has achieved the largest treatment benefit ever reported for fibromyalgia in a randomized, placebo-

controlled clinical trial.

The durability of the results was particularly impressive. The large improvements in psychological and physical functioning that were documented at the end of the 8-week treatment program were maintained at the 6-month follow-up, Saskia van Koulil said.

The success of this customized treatment approach hinged upon a two-stage screening process. First, patients who have had their fibromyalgia for fewer than 5 years and were at high risk of long-term dysfunction were selected because prior studies indicated that such individuals tend to have better treatment outcomes in general.

Within this group of high-risk patients, specific cognitive-behavioral patterns seemed to drive their fibromyalgia pain and disability. It is possible to screen for these patterns of thought and behavior. One school of thought among clinical psychologists, including Ms. van Koulil, holds that there are two main patterns: pain avoidance and pain persistence. The treatment programs for the two are quite different, explained Ms. van Koulil of St. Radboud University Medical Center in Nijmegen, the Netherlands.

The high treatment success rate in this randomized trial validated this concept of the pain-avoidance and pain-persistence fibromyalgia subtypes, she said.

In her experience, close to two-thirds of patients with fibromyalgia of fewer than 5 years' duration have a high-risk profile. This is characterized by high levels of anxiety and/or negative mood on standard measures of distress, along with worse physical functioning, greater impact of fibromyalgia on daily life, and obvious maladaptive cognitive-behavioral patterns such as high levels of helplessness and worrying. This high-level psychological distress is an indicator of treatment motivation, Ms. van Koulil noted.

In the randomized trial, 158 high-risk fibromyalgia patients (95% of whom were women) were evaluated with a brief screening instrument for pain-avoidance behavior. Those with a high score were assigned to the pain-avoidance treatment group or a wait-list control arm, whereas patients with a low score were randomized to the pain-persistence group or the control arm.

The pain-avoidance subtype of fibromyalgia is characterized by fear of pain, hypervigilance, catastrophizing, and zealous avoidance of pain. In contrast, the pain-persistence subtype is characterized by an overactive lifestyle and low levels of pain avoidance.

Both subtypes end up via different routes at the same place, which is marked by functional disability, psychological distress, fatigue, and chronic pain.

Of the study participants, 53% were categorized as pain avoidant, whereas

*Continued on following page*

Each 4-hour treatment session included cognitive behavioral therapy and exercise training.



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**Information for Patients:** LEVEMIR® must only be used if the solution appears clear and colorless with no visible particles. Patients should be informed about potential risks and advantages of LEVEMIR® therapy, including the possible side effects. Patients should be offered continued education and advice on insulin therapies, injection technique, life-style management, regular glucose monitoring, periodic glycosylated hemoglobin testing, recognition and management of hypo- and hyperglycemia, adherence to meal planning, complications of insulin therapy, timing of dosage, instruction for use of injection devices and proper storage of insulin. Patients should be informed that frequent, patient-performed blood glucose measurements are needed to achieve effective glycemic control to avoid both hyperglycemia and hypoglycemia. Patients must be instructed on handling of special situations such as intercurrent conditions (illness, stress, or emotional disturbances), an inadequate or skipped insulin dose, inadvertent administration of an increased insulin dose, inadequate food intake, or skipped meals. Refer patients to the LEVEMIR® "Patient Information" circular for additional information. As with all patients who have diabetes, the ability to concentrate and/or react may be impaired as a result of hypoglycemia or hyperglycemia. Patients with diabetes should be advised to inform their health care professional if they are pregnant or are contemplating pregnancy (see PRECAUTIONS, Pregnancy). **Laboratory Tests:** As with all insulin therapy, the therapeutic response to LEVEMIR® should be monitored by periodic blood glucose tests. Periodic measurement of HbA<sub>1c</sub> is recommended for the monitoring of long-term glycemic control. **Drug Interactions:** A number of substances affect glucose metabolism and may require insulin dose adjustment and particularly close monitoring. The following are examples of substances that may reduce the blood-glucose-lowering effect of insulin: corticosteroids, danazol, diuretics, sympathomimetic agents (e.g., epinephrine, albuterol, terbutaline), isoniazid, phenothiazine derivatives, somatropin, thyroid hormones, estrogens, progestogens (e.g., in oral contraceptives). The following are examples of substances that may increase the blood-glucose-lowering effect of insulin and susceptibility to hypoglycemia: oral antidiabetic drugs, ACE inhibitors, disopyramide, fibrates, fluoxetine, MAO inhibitors, propoxyphene, salicylates, somatostatin analog (e.g., octreotide), and sulfonamide antibiotics. Beta-blockers, clonidine, lithium salts, and alcohol may either potentiate or weaken the

blood-glucose-lowering effect of insulin. Pentamidine may cause hypoglycemia, which may sometimes be followed by hyperglycemia. In addition, under the influence of sympatholytic medicinal products such as beta-blockers, clonidine, guanethidine, and reserpine, the signs of hypoglycemia may be reduced or absent. The results of *in-vitro* and *in-vivo* protein binding studies demonstrate that there is no clinically relevant interaction between insulin detemir and fatty acids or other protein bound drugs. **Mixing of Insulins:** If LEVEMIR® is mixed with other insulin preparations, the profile of action of one or both individual components may change. Mixing LEVEMIR® with insulin aspart, a rapid acting insulin analog, resulted in about 40% reduction in AUC<sub>(0-2h)</sub> and C<sub>max</sub> for insulin aspart compared to separate injections when the ratio of insulin aspart to LEVEMIR® was less than 50%. LEVEMIR® should NOT be mixed or diluted with any other insulin preparations. **Carcinogenicity, Mutagenicity, Impairment of Fertility:** Standard 2-year carcinogenicity studies in animals have not been performed. Insulin detemir tested negative for genotoxic potential in the *in-vitro* reverse mutation study in bacteria, human peripheral blood lymphocyte chromosome aberration test, and the *in-vivo* mouse micronucleus test. **Pregnancy: Teratogenic Effects: Pregnancy Category C:** In a fertility and embryonic development study, insulin detemir was administered to female rats before mating, during mating, and throughout pregnancy at doses up to 300 nmol/kg/day (3 times the recommended human dose, based on plasma Area Under the Curve (AUC) ratio). Doses of 150 and 300 nmol/kg/day produced numbers of litters with visceral anomalies. Doses up to 900 nmol/kg/day (approximately 135 times the recommended human dose based on AUC ratio) were given to rabbits during organogenesis. Drug-dose related increases in the incidence of fetuses with gall bladder abnormalities such as small, bilobed, bifurcated and missing gall bladders were observed at a dose of 900 nmol/kg/day. The rat and rabbit embryofetal development studies that included concurrent human insulin control groups indicated that insulin detemir and human insulin had similar effects regarding embryotoxicity and teratogenicity. **Nursing mothers:** It is unknown whether LEVEMIR® is excreted in significant amounts in human milk. For this reason, caution should be exercised when LEVEMIR® is administered to a nursing mother. Patients with diabetes who are lactating may require adjustments in insulin dose, meal plan, or both. **Pediatric use:** In a controlled clinical study, HbA<sub>1c</sub> concentrations and rates of hypoglycemia were similar among patients treated with LEVEMIR® and patients treated with NPH human insulin. **Geriatric use:** Of the total number of subjects in intermediate and long-term clinical studies of LEVEMIR®, 85 (type 1 studies) and 363 (type 2 studies) were 65 years and older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. In elderly patients with diabetes, the initial dosing, dose increments, and maintenance dosage should be conservative to avoid hypoglycemic reactions. Hypoglycemia may be difficult to recognize in the elderly.

**ADVERSE REACTIONS:** Adverse events commonly associated with human insulin therapy include the following: **Body as Whole:** allergic reactions (see PRECAUTIONS, Allergy). **Skin and Appendages:** lipodystrophy, pruritus, rash. Mild injection site reactions occurred more frequently with LEVEMIR® than with NPH human insulin and usually resolved in a few days to a few weeks (see PRECAUTIONS, Allergy). **Other: Hypoglycemia:** (see WARNINGS and PRECAUTIONS). In trials of up to 6 months duration in patients with type 1 and type 2 diabetes, the incidence of severe hypoglycemia with LEVEMIR® was comparable to the incidence with NPH, and, as expected, greater overall in patients with type 1 diabetes (Table 4). **Weight gain:** In trials of up to 6 months duration in patients with type 1 and type 2 diabetes, LEVEMIR® was associated with somewhat less weight gain than NPH (Table 4). Whether these observed differences represent true differences in the effects of LEVEMIR® and NPH insulin is not known, since these trials were not blinded and the protocols (e.g., diet and exercise instructions and monitoring) were not specifically directed at exploring hypotheses related to weight effects of the treatments compared. The clinical significance of the observed differences has not been established.

Table 4: Safety Information on Clinical Studies\*

| Treatment            | # of subjects | Weight (kg) |                  | Hypoglycemia (events/subject/month) |          |       |
|----------------------|---------------|-------------|------------------|-------------------------------------|----------|-------|
|                      |               | Baseline    | End of treatment | Major**                             | Minor*** |       |
| Type 1<br>Study A    | LEVEMIR®      | N=276       | 75.0             | 75.1                                | 0.045    | 2.184 |
|                      | NPH           | N=133       | 75.7             | 76.4                                | 0.035    | 3.063 |
| Study C              | LEVEMIR®      | N=492       | 76.5             | 76.3                                | 0.029    | 2.397 |
|                      | NPH           | N=257       | 76.1             | 76.5                                | 0.027    | 2.564 |
| Study D<br>Pediatric | LEVEMIR®      | N=232       | N/A              | N/A                                 | 0.076    | 2.677 |
|                      | NPH           | N=115       | N/A              | N/A                                 | 0.083    | 3.203 |
| Type 2<br>Study E    | LEVEMIR®      | N=237       | 82.7             | 83.7                                | 0.001    | 0.306 |
|                      | NPH           | N=239       | 82.4             | 85.2                                | 0.006    | 0.595 |
| Study F              | LEVEMIR®      | N=195       | 81.8             | 82.3                                | 0.003    | 0.193 |
|                      | NPH           | N=200       | 79.6             | 80.9                                | 0.006    | 0.235 |

\* See CLINICAL STUDIES section for description of individual studies

\*\* Major = requires assistance of another individual because of neurologic impairment

\*\*\* Minor = plasma glucose <56 mg/dl, subject able to deal with the episode him/herself

**OVERDOSAGE:** Hypoglycemia may occur as a result of an excess of insulin relative to food intake, energy expenditure, or both. Mild episodes of hypoglycemia usually can be treated with oral glucose. Adjustments in drug dosage, meal patterns, or exercise may be needed. More severe episodes with coma, seizure, or neurologic impairment may be treated with intramuscular/subcutaneous glucagon or concentrated intravenous glucose. After apparent clinical recovery from hypoglycemia, continued observation and additional carbohydrate intake may be necessary to avoid recurrence of hypoglycemia.

**More detailed information is available upon request.**

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47% were classified in the pain-persistence group.

Patients in both active-treatment arms received 16 twice-weekly treatment sessions in eight-patient groups, each session 4 hours in length, plus homework assignments. The first half of each session was devoted to cognitive-behavioral therapy (CBT), the second half to exercise training, which included aerobic exercises, either strength or flexibility training, and relaxation techniques. The patient's significant other attended the 3rd, 9th, and 15th sessions. A booster session was held 3 months after completion of the 8-week program.

The CBT was delivered by therapists with experience in CBT for rheumatologic conditions. Therapy was guided by a written manual. The exercise training was provided by physical therapists.

The pain-avoidance treatment regimen was tailored toward achieving in-

**In all, 60% of patients in the tailored-therapy arms experienced a clinically significant reduction in the impact of fibromyalgia on daily life, vs. 24% of controls.**

creased daily activities, reduced fear of pain and pain-avoidance behaviors through titrated exposure, and a gradual gain in physical condition. The emphasis in the pain-persistence group was on learning to improve pacing and regulation of activities of daily life and physical exercise, along with altering pain-persistence cognitions.

Five of the six primary outcome end points in the study were changes from baseline in pain, fatigue, functional disability, negative mood, and anxiety as measured on the Impact of Rheumatic Diseases on General Health and Lifestyle scale, which is derived from the Arthritis Impact Measurement Scales. The sixth measure was change in the impact of fibromyalgia on daily life, as assessed by the 10-item Fibromyalgia Impact Questionnaire (FIQ).

The results were striking: In all, 60% of patients in the tailored-therapy arms experienced a clinically significant reduction in the impact of fibromyalgia on daily life, vs. 24% of controls.

Of the tailored-therapy patients, 67% had a clinically significant improvement in the physical function domain combining pain, fatigue, and functional disability, vs. 33% of controls.

And 62% of tailored-therapy patients demonstrated a clinically significant improvement in psychological function as reflected in reduced scores for negative mood and anxiety, compared with 33% of controls.

The improvements in the end points were consistently numerically greater in the pain-avoidance group than in the pain-persistence arm, but not significantly so.

Pain scores (which have a theoretical range of 6-25) went from a mean base-

line of 20 in the pain-avoidance treatment arm to 16 at the end of treatment and 17 at 6 months of follow-up. In the pain-persistence arm, pain scores went from a baseline of 19 to 16, then 16 at follow-up. Pain scores were unchanged over time in the control arm.

Similarly, the impact of fibromyalgia on daily life as assessed by the FIQ (with a theoretical range of 0-100 points) went from a baseline of 66 to 48 at the end of pain-avoidance therapy, with a modest rebound to 50 at 6 months of follow-up.

In the pain-persistence arm, scores improved from a baseline of 57 to 47 at

treatment's end and 43 at follow-up. Again, scores were flat over time in the control arms.

The encouraging results with tailored therapy in this study are particularly welcome because of the dearth of effective treatment options for fibromyalgia, Ms. Van Koulik said. ■

**Disclosures:** The study was financially supported by the Dutch Arthritis Association and the Netherlands Organization for Health Research. Ms. van Koulik reported having no conflicts of interest.

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- Outline the clinical course of SLE and cutaneous lupus; explain the importance and benefit of early treatment.
- Identify the aspects of care, treatment, and overall outcomes that are important in the management of pediatric patients with rheumatic diseases.
- Develop a strategy for a diagnostic workup to accurately establish (or rule out) fibromyalgia as a cause of a patient's symptoms.
- Apply the most current information regarding the risk factors for, the clinical manifestations of, and the cutting-edge treatments for hyperuricemia and gout.
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