Patients (n=360) who relapsed entered Phase 2, were randomized again to SMM or EMM and received 3 months of buprenorphine stabilization, and then had treatment tapered for 1 month, with a 2-month follow-up.

At the end of stabilization (Week 12), substantial improvement (abstinence for ≥ 3 of the final 4 weeks of buprenorphine stabilization by urine-confirmed self-report) was noted for 52% of the EMM group and 47% of the SMM group, though there was no additional benefit to enhanced management (p=0.3).

"We went from an average success rate of 49% to 26% at Week 16," Dr. Weiss reported. At Week 24 (8 weeks post-taper), only 9% of patients remained successfully treated. "At the end of the study, 7 of 8 patients doing well on buprenorphine maintenance had relapsed."

The only predictor of outcome was lifetime use of heroin. At Week 12, improvement was noted for 37% of those who reported lifetime heroin use, compared with 54% of those without a history (p=0.003); at Week 24, this was 5% and 10%, respectively (p=0.13). The presence of chronic pain did not influence outcomes. Chronic pain patients were equally likely to have early treatment failure and equally likely to be substantially improved at Week 12 of phase 2 (53% vs 47% for those without chronic pain).

Over half of the subjects reported at least moderate reduction of pain from baseline (≥30%), and one-third had a substantial improvement (≥50%).

Milnacipran for the Treatment of Fatigue Associated with Fibromyalgia

Milnacipran may be an effective treatment for the fatigue that is associated with fibromyalgia (FM). FM is a chronic disorder with symptoms, including musculoskeletal pain and allodynia, as well as debilitating fatigue. Milnacipran is a dual reuptake inhibitor of serotonin and norepinephrine that is used for the treatment of FM. Allan Spera, MD, Forest Pharmaceuticals, Jersey City, NJ, and colleagues evaluated the effect of milnacipran on fatigue in patients with FM (as determined by American College of Rheumatology criteria) in a pooled analysis of three Phase III trials.

In these three trials, patients were randomized to receive milnacipran 100 mg daily (n=1139), milnacipran 200 mg daily (n=837), or placebo (n=1133) for 12 weeks following a dose escalation phase. The mean age was 49 years, and the majority of patients (~94%) was female. The three groups were well matched at baseline. Patients with severe psychiatric illness or medical condition or who were experiencing a current major depressive episode (determined by Mini-International Neuropsychiatric Interview [MINI] and Beck Depression Inventory ≥4) were excluded from participation in the study. Efficacy measures were change from baseline on Multidimensional Fatigue Inventory (MFI) total and subscale scores and Fibromyalgia Impact Questionnaire (FIQ) fatigue-related questions 6 and 7 (question 6: "How tired have you been?" and question 7: "How have you felt when you get up in the morning?") at 3 months.

Patients in both milnacipran treatment arms demonstrated significant improvement in MFI total score and FIQ items 6 and 7 compared with placebo at 3 months (p<0.01). There was a significant reduction in fatigue at all study visits among patients who were taking milnacipran (p<0.01 for both doses). Significant improvement in all MFI subscale scores was observed in those who were treated with milnacipran 200 mg daily compared with placebo (p<0.05). Those who were treated with milnacipran 100 mg daily demonstrated significant improvement in the general fatigue, physical fatigue, and reduced motivation subscale categories compared with placebo (p<0.05).

Overall, treatment with milnacipran resulted in favorable outcomes that were related to fatigue in patients with FM. This benefit was observed in the MFI total scores and FIQ (questions 6 and 7) scores, as well as several of the MFI fatigue-related subscale categories. A modest correlation was found between MFI total score and pain and Patient Global Impression of Change (PGIC) scores at endpoint. However, similar correlations were found among the placebo-treated patients. While milnacipran is currently being used for the treatment of pain that is associated with FM, it may also be an effective treatment for fatigue in patients with FM. Further studies that focus on the fatigue aspect of FM are needed to establish the efficacy of milnacipran for the treatment of fatigue symptoms in patients with FM.

Risk of Low Bone Mineral Density with Psychotropic Drugs

The use of certain psychotropic medications may be enhancing an already high underlying risk for osteoporosis, according to several studies that were presented at the American Psychiatric Association 2010 Annual Meeting.

Psychotropic agents have been linked to fractures, and antidepressants have been associated with low bone mineral density (BMD). The studies that were presented validate these earlier findings and suggest that many patients may already be at high risk for bone disease.

In a large study from Canada, osteoporosis was found to be associated with the use of selective serotonin reuptake inhibitors (SSRIs), mood stabilizers other than lithium, and benzodiazepines but that the use of tricyclic antidepressants was protective.

A 40% increased risk for low BMD with SSRIs and a 37% reduced risk with tricyclic antidepressants were reported by James Bolton, MD, University of Manitoba, Winnipeg, Canada.

Data were derived from Manitoba's health care database, which captures all physician contacts and diagnoses, all prescribed medications, all hospitalizations, and census data, which were then linked to data from the Manitoba Bone Density Program, a clinical database of information from dual-energy X-ray absorptiometry scans (DXA).

Investigators were able to identify 7994 osteoporosis cases from database records covering the period 2000 to 2007. Cases were defined as persons with a T-score of -2.5 or lower at one of four sites (trochanter, femoral neck, total hip, or lumbar spine). Controls were 23,928 subjects who were matched for gender, age, and ethnicity. Three controls were matched for each osteoporosis case.

Dr. Bolton and colleagues assessed all psychotropic medications that were prescribed, all mental disorders that were diagnosed, and nearly 20 confounders (eg, body mass index, medical comorbidity, estrogen use, and bisphosphonate use).

The adjusted odds ratio was 1.39 for SSRIs (95% CI, 1.21 to 1.59), 1.35 for nonlithium mood stabilizers (eg, anticonvulsants) (95% CI, 1.10 to 1.66), 1.10 for benzodiazepines (95% CI, 1.01 to 1.20), and 0.63 for tricyclic antidepressants (95% CI, 0.56 to 0.72). Dr. Bolton suggested that perhaps because sample sizes were smaller, the odds ratio for lithium was 0.57, but the confidence interval crossed 1.0 (95% CI, 0.29 to 1.12). The same was true for typical antipsychotics (OR, 1.20; 95% CI, 0.81 to 1.77) and for atypical antipsychotics (OR, 1.55; 95% CI, 0.87 to 1.97). Other antidepressants had an odds ratio of 1.08 (95% CI, 0.91to 1.27).

Mental disorders themselves also had statistically significant osteoporotic effects, including dementia (HR, 1.34; 95% CI, 1.04 to 1.72), schizophrenia (HR, 1.92; 95% CI, 1.11 to 3.33), and alcohol dependence (HR, 1.53; 95% CI, 1.01 to 2.32). Risk was reduced, interestingly, with depression, which carried an odds ratio of 0.85 (95% CI, 0.75 to 0.95). Bipolar disorder and drug abuse or dependence was not significantly associated with osteoporosis.

Dr. Bolton concluded, "SSRIs, anticonvulsant mood stabilizers, and benzodiazepines are associated with osteoporotic changes in bone, independent of the effects of mental disorders and other confounders, and tricyclic antidepressants appear to be protective."

A study by Barbara Gracious, MD, University of Rochester Medical Center, Rochester, NY, suggested that women who are treated for depression—and presumably are receiving SSRIs—have an underlying risk for osteoporosis that may be neglected.

The majority of study subjects was disabled by depression and had been on maintenance therapy with SSRIs for many years. They also had exposure to prolactin-elevating antipsychotic medications (associated with reduced estrogen and testosterone). "We found the risk factor burden of these patients was huge," said Barbara Gracious, MD.

This study systematically examined osteoporosis risk factors via personalized screening to determine if osteoporosis prevention is warranted in midlife mood-disordered patients. Nineteen patients, mean age 47 years and 94% female, were recruited from a university psychiatric partial hospitalization program and an urban university neighborhood family medical center. The Mini-International Neuropsychiatric Interview (MINI) confirmed the Primary Axis 1 diagnosis of major depression and captured comorbid mental disorders. Structured interviews provided demographics, history, lifestyle, and medication risk.

The average patient was found to have 19 risk factors for osteoporosis. The most prevalent iatrogenic risk factors were history of SSRI use (89%), history of major surgery (89%), and history of prolactin-elevating antipsychotic exposure (68%). Prevalent lifestyle factors were decreased weight-bearing exercise (76%), low vitamin D levels (64%), alcohol use (59%), cigarette smoking (53%), and excess salt intake (41%).

Many had a family history of fractures (53%) or osteoporosis (29%) and irregular menstruation cycles (35%). Only about 50% of subjects were postmenopausal.

Investigators concluded that midlife patients who are treated for major depression have many lifestyle, iatrogenic, and historical risk factors that raise the likelihood of poor bone quality and osteoporotic fractures at younger ages.

"We believe that lifestyle interventions are appropriate for this population, including calcium and vitamin D supplementation and enhanced weight-bearing physical activity. In addition, coordinated primary care follow-up should be a priority, and heavy smokers and alcohol abusers should receive substance abuse treatment," concluded Dr. Gracious.