from middle-class families. The subjects and controls were similar except that ADHD subjects were significantly more likely to have a parental history of alcohol use disorders ($p<0.001$) and drug use disorders ($p=0.003$).

Investigators found that children with ADHD were 1.5 times more likely to develop a SUD compared with controls. Within ADHD, comorbid oppositional defiant disorder and conduct disorder were significant predictors of any SUD, after adjusting for gender (hazard ratio [HR], 2.31; $p<0.001$) and parental history of SUD (HR, 3.0; $p<0.001$).

Within the population of ADHD youths who developed drug use disorders, comorbid major depressive disorder was a further significant predictor, essentially doubling the risk ($p=0.006$). Analysis showed that boys who received extra help in school were approximately half as likely to develop a SUD ($p=0.02$).

"In general, gender did not predict risk for SUD, and we found no significant associations between baseline cognitive or academic dysfunction and later SUD in our ADHD youth," Dr. Wilens said. "No significant results were found for social or family environment factors, cognitive factors, or any school functioning factors."

"Dr. Wilens and colleagues showed that there are children with ADHD that are at risk for substance abuse, but most of them have a diagnosis of conduct disorder, which translates into juvenile delinquency later. Many ADHD children want to be good. For the child with conduct disorder, 'being good' is not a priority. This work says that ADHD plus conduct disorder equals a very serious problem," commented R. Scott Benson, MD, APA Council on Communications.

The study suggests that the vast majority of ADHD children will not abuse drugs later, but if a child has more severe, oppositional behavior, that child may be at risk of developing serious substance abuse issues. The challenge for psychiatrists is to find ways to treat these comorbidities.

## Prescription Opioid Dependence: Relapses Associated with Shorter Treatment Course

The National Drug Abuse Treatment Clinical Trials Network Prescription Opioid Addiction Treatment Study found that patients who tapered off prescription opioids using buprenorphine during a 9-month period, whether initially or after a period of improvement, almost universally relapsed. "There has been virtually no research on the treatment of persons dependent on prescription opioids, in spite of the major increase in prescription opioid abuse and in the numbers of persons entering treatment for addiction to prescription opioids," said Roger D. Weiss, MD, Harvard Medical School, Boston, and McLean Hospital, Belmont, MA.

The study, which is the largest treatment study ever conducted for prescription opioid dependence (POD), sought to determine the optimal length of pharmacotherapy and the value of intense counseling.

The study investigated whether adding intense counseling to buprenorphine-naloxone plus standard medical management improved patient outcomes, what duration of buprenorphine is best, and whether chronic pain influenced outcomes.

The study enrolled 653 persons at 10 sites with POD and offered them standard medical management, which included buprenorphine (12-16 mg maximum, adjusted for addiction), an initial 1-hour visit, and weekly 20-minute sessions with a physician who counseled them and monitored for drug side effects. Half of the group remained in this standard medical management (SMM) arm while half received enhanced medical management (EMM) that included twice-weekly 60-minute individualized drug counseling sessions that were focused on interpersonal issues, coping with triggers, and high-risk situations.

Patients were evaluated after periods of individualized buprenorphine tapering and maintenance and were assessed for abstinence from opioids at various periods.

All patients had a DSM-IV diagnosis of opioid dependence and had used opioids for at least 20 of the past 30 days. The average subject was 33 years old and had been using opioids for 4.5 years, including sustained-release oxycodone (35%), hydrocodone (32%), immediate-release oxycodone (19%), methadone (6%), and others (8%). For 70% of subjects, this was the first treatment for opioid dependence.

Patients reported current chronic pain (42%), a history of heroin use (23%), alcohol abuse (60%) or dependence (27%), cannabis abuse (47%) or dependence (15%), and cocaine abuse (32%) or dependence (18%).

Treatment success was defined as ≤ 4 days of opioid use per month, no positive urine screens for opioids for 2 consecutive weeks, no other formal substance abuse treatment, and no opioid injections.

Phase 1 included 1 month of tapering and 2 months of stabilization. At the end of this period, few patients were successfully treated, and enhanced management did not influence the results. In the SMM group, only 7% met the criteria for success, as did just 6% of the EMM group ($p=0.45$). "Nearly all patients relapsed after a 4-week taper," Dr. Weiss reported.

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.