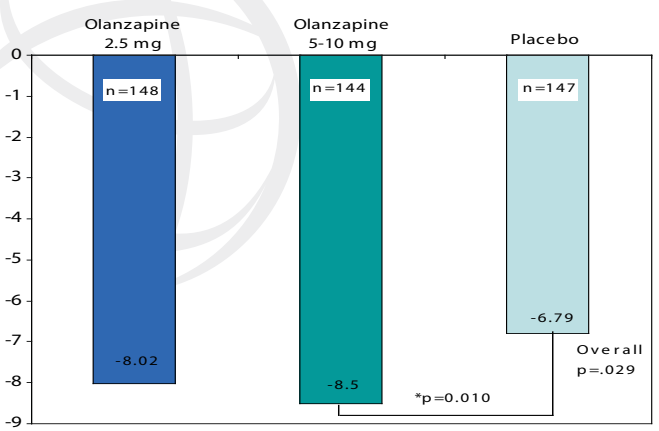
approximately 20% being unemployed due to their BPD. This study also had an impressive retention rate, with over 60% in each treatment group completing the trial. The OLZ 5-10 mg group was superior to placebo in change from baseline to final in ZAN-BPD score (p=0.010; Figure 2). The safety profiles in both studies were consistent with previous trials of OLZ in adults, and results from these studies led the presenters to conclude that a 5-10mg/day dose of OLZ may be effective in the treatment of BPD. "The high proportion of subjects completing this study demonstrate the feasibility, especially considering the length of the study," reiterated Dr. Zanarini. However, due to the high placebo response to study procedures, future trial designs in this population should consider the placebo arm as an active comparator.

Figure 2. ZAN-BPD Total Change from Baseline to Endpoint (LOCF) – Primary Efficacy Analysis.



Effect size:	OLZ 2.5 mg	0.19 (95% CI -.04, .42)
	OLZ 5-10 mg	0.29 (95% CI .06, .52)

The COMBINE Trial: Treatment of Alcohol Dependence from Bench to Bedside

In the latest update on the COMBINE Trial, a multi-center, treatment comparison study funded by the National Institute on Alcohol and Alcohol Abuse (NIAAA), leading alcohol researchers gathered to present the most recent findings from this collaborative project.

Briefly, the purpose of the COMBINE Trial has been to evaluate the effectiveness of behavioral management techniques, pharmacological interventions, and combinations of the two methods in the treatment of alcoholism. The rationale for which was the mounting evidence suggesting that these modes of treatment may actually enhance one another, thus, decreasing the likelihood of relapse in the recovering alcoholic. The behavioral treatment conditions included Medical Management Therapy (a brief motivational-based treatment), Combined Behavioral Intervention (CBI; a combination of Cognitive Behavioral Therapy, Motivational Enhancement Therapy and Twelve-Step Facilitation) plus Medical Management Therapy, as well as CBI alone. The drugs evaluated alone or in combination with these therapies were naltrexone and acamprosate. Treatment lasted for 16 weeks. The primary outcome measures utilized were "percent days abstinent" and "time to relapse".

Summarizing the latest findings (Anton et al. *JAMA* 2007; 297:2003-2017), Robert Swift, MD, PhD, Brown University, not only noted small attrition rates, but indicated that, in the context of abstinence, most participants did well independent of the particular treatment condition to which they were randomly assigned. In fact, Dr. Swift noted a 45% mean increase in days abstinent over the course of the trial. Looking at the particular treatments, there appeared to be no significant difference in days abstinent between those patients who were on either acamprosate or naltrexone versus placebo. For "time to relapse", patients on naltrexone fared better than those taking acamprosate or placebo. In the context of therapy, no benefit was apparent in participants undergoing CBI plus Medical Management Therapy versus Medical Management Therapy alone. When looking at the particular combination of treatments, no benefit was reported in those groups taking naltrexone in combination with acamprosate, or undergoing CBI while taking acamprosate. There was however, an increase in percent days abstinent in those patients taking naltrexone in combination with Medical Management Therapy only. Dr. Swift notes, these patients "did the best", although the treatment effects were modest.

Allen Zweben, PhD, Columbia University, noted that treatment effects seen in the COMBINE trial could not be accounted for strictly based on treatment adherence rates, though 12-step program participation was higher with patients undergoing Medical Management Therapy. Still, patients taking

acamprosate showed lower adherence rates than those individuals taking naltrexone only.

Overall, the Director of NIAAA's Treatment and Recovery Research unit, Mark Willenbring, MD, was encouraged by the latest round of findings. Medical Management Therapy in conjunction with naltrexone is has shown to be an effective practice when treating individuals with alcohol problems. The clinical utility of this mode of treatment is that it is more accessible than traditional mental health service to many individuals. It can not only be used by the mental health professional, but the general practitioner as well. NIAAA has now published a step-by-step guide for the general practitioner to treat alcoholics using Medical Management Therapy. This guide is available on their website at www.niaaa.nih.gov.

Bifeprunox: Efficacy with Minimal Metabolic Concerns

Bifeprunox, a partial dopamine agonist, is being developed as a possible treatment for schizophrenia. The results of a 6-month randomized, double-blind, placebo-controlled study of 497 patients with schizophrenia were presented by Michel Bourin, MD, of the University of Nantes, France.

In order to be included in the study, patients were required to have had a diagnosis of schizophrenia for at least 2 years, a Positive and Negative Syndrome Scale (PANSS) score of at least 60, scores of ≤ 4 on PANSS items of Hostility and/or Uncooperativeness, and either could not tolerate side effects of their current antipsychotic medications or were experiencing residual symptoms. Patients were randomized to treatment with either bifeprunox 20 mg/day, bifeprunox 30 mg/day, or placebo. Patients were washed off their current medications over a period of 3-6 days. Bifeprunox doses were initiated at 0.25 mg on day 1, and were doubled each day until the target doses of 20 mg or 30 mg were reached. The primary efficacy measure was time to deterioration from the date randomization. Deterioration was defined as one or more of the following criteria: a Clinical Global Impression-Improvement score of ≥5, a PANSS Hostility and/or Uncooperativeness score ≥5 for two consecutive days, or a ≥20% increase in PANSS baseline score.

There were no statistically significant differences between treatment groups in age, gender, baseline weight, or baseline body mass index (BMI).

Both doses of bifeprunox were superior to placebo in the primary efficacy measure, with 41% of the 20 mg group, 38% of the 30 mg group, and 59% of the placebo group reaching deterioration criteria by 6 months (p=0.008 and p=0.006 vs placebo, respectively). The most common adverse events (≥5% and at least double that of placebo) were nausea, vomiting, anorexia, dizziness, dyskinesia, asthenia, and akathisia.

Patients taking bifeprunox 30 mg had a significant decrease in body weight and BMI compared with placebo (-1.5 kg vs -0.8 kg, respectively; p=0.027; Figure 1). Patients in all groups lost weight, regardless of whether or not they experienced adverse events of nausea and/or vomiting, but patients experiencing adverse events of nausea and/or vomiting experienced greater weight loss. Treatment with bifeprunox 30 mg also decreased fasting triglyceride levels compared to placebo (p=0.006); prolactin levels increased in all groups. This compares favorably with many of the currently available antipsychotic medications which are associated with hyperprolactinaemia (Meaney AM et al. *Life Sci* 2002;71(9):979-92), weight gain, and increases in lipid levels (Newcomer JW. *CNS Drugs* 2005;19 Suppl 1:1-93). The authors concluded that this agent may be a well-tolerated and efficacious option for stable schizophrenia patients.

Figure 1. Adjusted Mean Weight Change from Baseline to Last Assessment.