

Naltrexone and Bupropion Combination on Obese, Smoking
Patients With Schizophrenia

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Subjects: A total number of 60 subjects will be recruited for the study with 30 of them to complete the imaging assessment. The major inclusion criteria are: 1) diagnosis of schizophrenia; 2) age between 18 and 65 years; 3) on stable antipsychotic medication regimen for at least one month; 4) BMI \geq 28 kg/m² using the BMI criterion for obesity in the Chinese population; 5) smoking at least 10 cigarettes daily for a minimum of 1 year; 6) desire to lose weight and quit smoking. The exclusion criteria are: 1) binge eating or other eating disorders; 2) current use of weight loss medications; 3) current substance use (except nicotine or caffeine); 4) elevated hepatic transaminase levels (>2.5x normal range); 5) clinically significant TSH and/or T4 abnormalities; 6) history of seizure disorder; 7) history of unstable cardiac problems or other unstable medication conditions; 8) being pregnant or nursing (for women).

Screening visit: After written informed consent is obtained, a diagnosis of schizophrenia will be determined by the International Classification of Diseases 10th Revision (ICD-10) by a research psychiatrist. A medical history and physical examination will be obtained by a research psychiatrist to assess inclusionary and exclusionary criteria, including current medications, substance use and number of cigarettes smoked daily. A urine pregnancy test will

be performed for women of childbearing potential. In addition, a urine drug screen, and a 12-lead EKG will be performed.

Baseline visit: Eligible subjects will come to the clinic for the baseline assessment including: 1) height, weight and waist circumference; 2) Fasting blood samples for glucose, insulin, leptin, ghrelin, HbA1c, lipid profile, comprehensive metabolic profile, CBC, high sensitivity CRP, IL-6 and TNF- α ; 3) breath CO level; 4) smoking craving using the Visual Analogue Scale; 5) number of cigarettes smoked in the past week; 6) the Positive and Negative Syndrome Scale (PANSS), 7) the side effects questionnaire. On a separate day, subjects who participate in the imaging assessment will complete the brain MRI scans. Subjects will then receive the study drug (either combination medication or placebo). The randomization is based on a 1:1 ratio using permuted block randomization, stratified by imaging assessment participation. In addition, subjects will receive the first session lifestyle counseling.

Follow-up visits: Subjects will be followed at weeks 2, 4, then every 4 weeks to receive the study drug and the lifestyle counseling. Weight, breath CO, and possible side effects will be assessed during each visit. Waist circumference, scales, the clinical

symptoms assessment will be repeated every 4 weeks. Fasting blood samples for glucose, insulin, leptin, ghrelin, HbA1c, lipid profile, comprehensive metabolic profile, CBC, high sensitivity CRP, IL-6 and TNF- α will be repeated at weeks 12, 24. Those subjects who participate in the imaging assessment, will repeat the brain MRI scans at week 24.

Intervention: This is a randomized, double-blind, placebo-controlled study. Following screening and confirmation that inclusion and exclusion criteria are met, subjects will be treated with naltrexone sustained release 15mg once per day and bupropion sustained release 150mg once per day in the first two weeks. Then subjects take naltrexone 15mg twice per day and bupropion 150mg twice per day during the rest of the study. The dosing choice of NB is based on the efficacy and side effects of various dosing strategies reported in previous NB trials as well as the supply availability of both naltrexone and bupropion in China. Subjects will be maintained on the same antipsychotic at the same dose whenever possible during the study; however the subject's clinical well-being will determine antipsychotic dosing. Subjects will return to meet with an investigator every 2 weeks for the first 4 weeks, then every 4 weeks to review medical and psychiatric status. Compliance will be

assessed by pill counts at each meeting. Subjects also receive culturally sensitive lifestyle counseling during each visit.