



Technology Assessment Report

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Name of the Technology and DSM-IV Disorder of Focus:

PROMETA™ Protocol for the treatment of alcohol, cocaine and methamphetamine dependence.

Description of the Technology:

PROMETA™ protocols (formerly known as HANDS^R protocols) are proprietary pharmacotherapy and psychosocial treatment protocols designed for use by healthcare professionals to treat those diagnosed with dependence to alcohol, cocaine and methamphetamine, as well as combinations of these drugs. They have been patented by the company, Hythiam, who in turn is marketing them to professionals who may access these treatment protocols for a licensing fee. In addition to a proprietary medication regimen and therapy framework, Hythiam supports its clients with administrative services to assist physicians, provision of staff education, marketing/sales support and outcomes tracking for analysis.

Hythiam, Inc. (NASDAQ:HYTM), is a developmental stage healthcare services management company that delivers to treatment providers proprietary administrative services and physiological protocols designed to treat substance dependence. Hythiam describes their mission to research, develop, license and commercialize innovative physiological treatment protocols for substance dependence.

At this point in time, the PROMETA protocols are proprietary and there is no published scientific literature on their exact treatment components – dosage of drugs and type/amount of psychosocial therapy - except that they are administered in a “unique dosing algorithm.” However, there are two National Institutes of Health (NIH) funded studies that are currently recruiting patients in order to evaluate PROMETA protocols for both alcohol and methamphetamine dependence.

The information available on these studies lists the flumazenil (intravenous), gabapentin (oral), hydroxyzine and vitamins as the agents in a randomized, double-blind, placebo control, parallel assignment safety and efficacy study for alcohol dependence at the Medical University of South Carolina. It is noted that all subjects will receive Combined Behavioral Intervention Therapy once per week, or more, if required.

No drugs are listed for the PROMETA study for methamphetamine dependence. However, direct contact with the Principal Investigator at the University of California, Los Angeles for this study revealed that the same drugs will be evaluated as for the alcohol dependence study. There is no further specific information on the dosages or timing of the drug regimens for the PROMETA protocols.

The scientific basis for these protocols is targeting the receptor sites in the brain that regulate neurotransmitters implicated in the processes of substance dependence – specifically its GABAergic inhibitory effects and the withdrawal symptoms resulting from the removal of these inhibitory, anxiolytic effects. The protocol for psychostimulant dependence targets the impairment in dopaminergic brain function.

1. Technology must have final approval from the appropriate government regulatory bodies.

The PROMETA protocols do not have FDA approval. They are prescribed as an off-label usage of flumazenil (a benzodiazepine receptor agonist), gabapentin (anticonvulsant) and hydroxyzine (antihistamine) drugs.

2. The scientific evidence must permit conclusions about the effects of the technology on health outcomes. (Conclusive evidence in peer-reviewed medical literature to enable the evaluation of the effectiveness and efficacy of the procedure or drug.)

Levels of Evidence are defined as follows:

Level 1: Randomized trials that had enough power to demonstrate a statistically significant health outcome.

Level 2: Randomized trials with results that were not statistically significant but where a larger trial might have shown a clinically important difference.

Level 3: Nonrandomized concurrent cohort comparisons between contemporaneous patients.

Level 4: Nonrandomized historical cohort comparisons between current patients and former patients (from the same institution or from the literature).

Level 5: Case series without control subjects.

Alcohol Dependence Studies

Cedars-Sinai – (Level 1) – in process

This is an on-going Phase II, single site, randomized, controlled study (**N=80**) comparing the HANDS (previous name for the current PROMETA) protocol to standard medical treatment provided by primary care physicians to include acamprosate, naltrexone, Antabuse and antidepressants. Both groups of patients are admitted for two days of inpatient care and will not require abstinence prior to admission. The control group is subject to detoxification with benzodiazepines whereas the experimental group immediately receives the HANDS protocol. Outcome measures include self-report and biological measures of alcohol use, cravings for alcohol, health measures, cognitive function, Quality of Life measures and participation in recovery activities.

Medical University of South Carolina (MUSC) – (Level 1)- in process

This NIH funding study began recruiting patients in December 2005 with an expected enrollment of **60** subjects. The design is a randomized, double-blind, placebo control, parallel assignment safety/efficacy study. These 60 alcohol dependent patients who are drinking

heavily up to 72 hours or less, prior to study participation are randomized to receive either flumazenil (IV) on two successive days and gabapentin (orally) for 39 days or their matching placebos. All subjects receive hydroxyzine and vitamins. Individuals are evaluated for alcohol withdrawal, response to acoustic startle, cognitive ability, craving, mood, sleep and drinking during the first week. All are seen weekly for approximately 6 weeks during which they take gabapentin or placebo and are provided with Combined Behavioral Intervention Therapy (counseling) once a week or more, if required. Over this period they are evaluated weekly for alcohol consumption, craving, sleep, mood, and biological markers of alcohol consumption (%CDT and GGT). Blood is obtained on week 3 and 6 for general health (liver, blood count etc.) screening. After the end of treatment, subjects are followed-up at 4 weeks and 8 weeks after treatment to evaluate alcohol consumption, craving, sleep and mood. Subjects also undergo a functional MRI procedure sometime during the second or third week of study medication to assess cue induced regional brain activation to investigate the effect of medication on brain response to alcohol visual cues.

Methamphetamine Dependence Studies

UCLA - (Level 1) - in process

This randomized, double-blind, placebo-controlled study comparing the effectiveness of the PROMETA protocol for methamphetamine dependence as compared to a placebo condition began in January 2006 and is currently recruiting patients (**N=90**). It is expected to be completed in January 2008. The study procedure utilizes a combination of medications delivered both orally and by infusion (flumazemil, gabapentin, hydroxyzine) in a controlled medical setting for forty days, including two inpatient hospitalizations of three days each. All participants receive once-weekly psychosocial cognitive-behavioral therapy throughout the 106 day study duration. Throughout the study psychological, cognitive, medical and laboratory assessments will be collected.

Research Across America – 2006 (Level 5)

This was an open-label study of **50** people to evaluate the clinical effectiveness and safety of the PROMETA protocol in a methamphetamine-dependent population. All participants were long-term (5-10 year) users of methamphetamine with treatment being delivered in an outpatient setting. The medical and nutritional portions of the treatment were provided over a four-week period and all participants were followed for eight weeks after delivery of treatment. No psychosocial treatments were provided in this study. Thirty-six (36) of the fifty patients completed the study. Results were as follows: (1) frequency of use dropped from 80% of days during the 90 days prior to treatment to 28% of the 84 days following the first infusion – a reduction of self-reported used-days of 65% (2) 97% reported a decrease in frequency of cravings – including 4 patients who reported no cravings at the end of the study (3) Among the 30 subjects whose cravings decreased, the mean reduction in cravings from the first visit to study completion was 66%.

3. *The technology is as beneficial (safe and effective) as existing alternative treatments.*

There is currently only one study comparing PROMETA protocols to established alternatives to alcohol dependence treatment by primary care physicians to include acamprosate, naltrexone Antabuse and antidepressants. This study has not been completed. All other studies compare the PROMETA to a placebo medication. Therefore, due to lack of comparative data, PROMETA cannot be considered as beneficial as existing alternative treatments for alcohol or methamphetamine dependence.

4. *The technology improves the net health outcome, i.e., there is conclusive evidence that the benefits outweigh the risks.*

There is no conclusive evidence to date that the PROMETA protocol improves health outcome. One open-label trial did show positive results in reducing cravings and use of methamphetamines with only minor side effects. Currently, there is no empirical data published from well-designed and controlled studies that can determine whether benefits outweigh the risks.

5. *The improvement in health outcomes is reliably obtainable outside investigational settings.*

Improvement in health outcomes have not yet been established in an investigational setting and therefore cannot be determined to be useful outside of such a setting.

Conclusion (is the new technology proven or experimental, and summary of why):

The PROMETA patent has not had a controlled scientific review and approval process by the FDA. Hythiam is using the FDA's position regarding the use of approved medications for off-label purposes – in this case the detoxification from alcohol, cocaine and methamphetamine. This experimental protocol has potential safety risks and no data substantiating its usefulness. It is not understood why this procedure has been allowed to be sold commercially without the standard, unbiased FDA review.

The Technology Assessment Committee will review this technology again when the cited Level 1 studies have been completed and the finding published.

Determination: Experimental

Effective Date: 9/26/06

References:

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