Return to Work Randomized Controlled Trial: Counseling After Fatigue Treatment in HIV/AIDS

METHODS: Statistial Analyses – Grant submission 7/17/2013
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5. METHODS

5.8 Statistical Analyses

Estimated attrition: Combining armodafinil non-responders and those who decline counseling, we estimate that 80% of patients starting armodafinil treatment will enter counseling. Patients who are self-described as fatigued but who do not meet fatigue criteria will enter counseling without a medication phase, so 100% of these patients should enter counseling.

Estimated effect magnitude of armodafinil plus BA-PEP: In prior trials of modafinil and armodafinil, 27% achieved a specific work or training goal without counseling. In our current study combining armodafinil and counseling, 62% randomized to BA achieved their goal of work or training and 20% of SC patients did so. We expect patients not meeting fatigue criteria to follow the same percentages. We thus conservatively anticipate response rates of 60% for BA patients vs. 25% for SC patients.

5.8.2 Data Management. All research ratings and self-report scales are checked for accuracy and completeness before the patient leaves the clinic, and omissions or inconsistencies addressed. The data are double entered into a PC-based data management system. Data are analyzed using PC-based statistical packages.

Sample size and randomization: We propose to enroll a total of 140 patients (100 who are fatigued, and 40 who self-described as fatigue but do not meet fatigue criteria) seeking treatment to return to work with counseling, and armodafinil for those patients who are fatigued. The randomization will be carried out by the statistician. Individuals will be stratified by fatigue (two levels: those who will be given armodafinil for fatigue, and those who will not be given armodafinil). Stratification will ensure comparable representation of fatigued and non-fatigued patients across the treatment groups. The randomization sequences will be balanced in blocks of random size (2, 4) to prevent clinicians from guessing what the next patient's treatment might be.

Note #1: We will review baseline sociodemographic, psychiatric, medical history variables, HCV infection and HIV illness stage to determine whether there are significant differences between treatment groups on any relevant measure. If so, each measure will be studied in terms of their relationship to treatment outcome. If related to outcome, they will be entered as covariates in all outcome analyses. To distinguish between depression and fatigue, a depression measure (BDI [67]) will be used as a covariate in all analyses. In addition to standard scoring, the depression measures (BDI and HAM-D [67]) will be adjusted and scores prorated to exclude the fatigue items.

Missing Data. The pattern and distribution of missing data will be examined, and recourse taken to assess randomness and correlates as described in Cohen and Cohen [87, Chapter 7]. Assuming it is randomly distributed, appropriate estimates of missing values will be generated and used in analyses. For AIM 2 the examination of the secondary outcomes across the treatment period (i.e. BADS and EROS Scales), we will be using Linear Mixed Models for analyses. In the presence of missing data, Mixed Models uses all data, estimates parameters and test hypotheses about them but do not impute missing values [88], and Mixed Models can reduce bias due to dropouts [89]. For dichotomous outcomes, secondary

analyses will be performed that use alternative methods of imputation (e.g. last observation brought forward).

Attrition. We will deal with dropouts in 3 ways: excluding dropouts, counting dropouts as failures, and finally counting dropouts as responders, providing an idea of all possible outcomes are. As noted above, we will use Linear Mixed Models for analyses where appropriate, which can reduce bias due to dropouts.

Data Transformation. We will check all variables in terms of univariate and bivariate distributions to make sure any data analytic method we use appropriately reflects the relationship between the variables-- e.g. we will use nonlinear transformations and polynomial regression as necessary.

Definition of primary dependent variables:

Work: paid employment: 4+ hours/week including stipend jobs; volunteer work; Increased work hours: at least 20% increase with a minimum increase of 4 hours/week.

Training: Includes enrollment in GED classes, degree and vocational programs, computer classes, unpaid or stipend internships.

5.8.3: Analytic Strategies. (End points are final study visit and 3-month follow-up visit)

Specific Aim 1: to determine whether more patients in BA-PEP (N=70) return to work or start training compared to SC patients (N=70).

Hypothesis 1: Our primary outcome measure is success in work/training goal attainment using a modified GAS score; we hypothesize that 60% of BA-PEP patients will succeed as compared to 25% of SC patients. BA-PEP will significantly promote success in work goal attainment as compared to SC.

Analysis Plan: The effect of BA-PEP on the primary outcome (work goal attainment) will be examined using a logistic regression (PROC LOGISTIC in SAS®) adjusted for appropriate covariates (e.g., stratification variable, depression measure).

Specific Aim 2: Determine whether secondary outcomes, as measured from baseline to the end of treatment, differentiate between BA-PEP and SC. These include the Behavioral Activation Depression Scale, the Environmental Reward Observation Scale (EROS), Endicott Quality of Life, Role Function scale, and Mastery.

Hypothesis 2*:* Over time, the BA-PEP patients will show significantly more improvement compared to SC patients.

Analysis Plan*:* Hypothesis 2 will be analyzed using longitudinal mixed effect models (PROC GLIMMIX in SAS®) with main effect of time, treatment and interaction between treatment and time effect. The within subjects repeated measure across time will be the baseline session, session 4, and session 8 [end of treatment] assessments for the BADS Scales and the EROS, and the between subjects factor will be the two treatments (i.e. SC and BA-PEP counseling). Demographic measures and other characteristics that are significantly different between the two treatment groups at baseline, will be included as covariates. The main focus of the analysis will be on the interaction term of treatment and time, which addresses treatment group response over time. If the interaction term of treatment and time is found to be significant, we will test the contrast between treatment groups at session 8 [end of treatment].

Specific Aim 3: To identify predictors of success in goal attainment, including moderator variables such as concurrent Axis I depression, baseline BDI scores, health history and status, substance use history, time since last employed full-time and neuropsychological function. We will also examine mediating variables such as changes in apathy, mastery, coping style, motivation, mood (since starting counseling) and quality of life.

Hypothesis *3:* We expect several of these characteristics particularly depression, age, health status and neuropsychological function, to show significant association to successful goal attainment.

Analysis Plan*:* We will use Logistic Regression (LR) Analysis available in SAS® statistics package (PROC LOGISTIC). This LR procedure will be performed hierarchically within each treatment arm separately, as well as the combined treatments (BA-PEP + SC treatments). The dichotomous dependent outcome measure will be successful goal attainment or not. At the first analysis step, age sex and education and possibly other covariates will be entered into the model, followed by the measures mentioned above using the backward stepping procedure. We will also examine moderator variables by investigating the interaction of treatment arm with each variable listed above. We will examine as mediator variables the changes in apathy, mastery, coping style, motivation, mood, and quality of life from baseline to session 4. Change in baseline to session 4 will be used in order to have a reliable measurement before or closest to obtaining the goal for those that will obtain the goal, since obtaining the goal could also affect these potential mediator variables.

Power Considerations (Power calculations do not include Historical Control data.)
Pilot Data*:* In our pilot work, we have treated 31 patients with the BA-PEP; 19 (61%) achieved their goals. In the combined modafinil and armodafinil RCTs, about 28% who wished to do so returned to work.
Hypothesis 1: 60% of BA-PEP treated patients will attain their goal compared to 25% of the SC treated patients. We will enroll 70 patients into each treatment arm (50 who responded to armodafinil and 20 who self-described as fatigued but did not meet fatigue criteria). With expected rates of 60% and 25% goal attainment, a difference of 35%, power is over 95%. Differences as small as 23% can be detected with 80% power, for reasonable percentages of goal attainment in the SC treated patients, e.g., (48% BA-PEP vs. 25% SC), (53% BA-PEP vs. 30% SC), (63% BA-PEP vs. 40% SC).
Hypothesis 2*:* We predict that the secondary assessments will distinguish between the two treatment groups with BA-PEP patients showing more improvement by the end of the treatment period compared to SC patients. Using power estimates for three repeated measures (baseline session, session 4, and session 8 [end of treatment]), for 70 patients per group, alpha set at $p < .05$ for a two-tailed test and correlation between repeated measures estimated at .30: (Effect size/Power) .45 [medium]/80%, .48/85%, .52 /90%, .58/95%.

5.8.4. Additional Analyses (Examples)

1. The historical Control data will be added to all analyses described above.
2. Attainment of secondary goals (other than work/training): In addition to the simple dichotomous outcome for work/training, patients are asked to identify additional goals. We will analyze scores on the Goal Attainment Scale (GAS) which provides a more fine-grained description of progress made toward these other goals.

Analysis: We will use ANCOVA, first including only the highest ranked in priority, and then their combination, and any variables found to be unbalanced in the randomization or significantly predictive of outcome also will be used as covariates.