

Synopsis of CTN0044 Publications

Primary Analysis (Campbell et al., AJP 2014)

Compared to treatment-as-usual, those receiving Therapeutic Education System reduced dropout from treatment (Hazard Ratio=0.72 [95% CI, 0.57-0.92], P=.010), and increased abstinence (Odds Ratio=1.62 [95% CI: 1.12-2.35], P=.010), an effect that was more pronounced among patients with a positive urine drug and/or breath alcohol screen at the point of study entry (n=228) (Odds Ratio=2.18 [95% CI: 1.30-3.68], P=.003).

Secondary Outcomes

SMOKING (McClure et al., 2015, JSAT): Participants generally did not reduce or quit smoking throughout the course of the study. Among a sub-set of participants with higher baseline nicotine dependence scores randomized to the control arm, scores at the end of treatment were lower compared to the experimental arm, though measures of smoking quantity did not appear to decrease. Further, being a smoker was associated with poorer treatment outcomes compared to non-smokers enrolled in the trial.

CONTINGENCY MANAGEMENT COSTS (Cunningham et al., 2015, JSAT): Distribution of draws earned (median = 119 vs 17; $p < .0001$) and prizes redeemed (median = 54 vs 9; $p < .001$) for drug abstinence differed significantly for baseline negative compared to baseline positive participants. Baseline negative earned on average twice as much in prizes as BL positive participants (\$245 vs \$125). Median value of prizes earned was 5.4 times greater for baseline negative compared to baseline positives participants (\$237 vs \$44; $p < .001$). Two-thirds of expenditures in an abstinence incentive program were paid to baseline negative participants. These individuals had high rates of drug abstinence during treatment and did not show improved abstinence outcomes with TES versus usual care (Campbell et al., 2014). Effectiveness of the abstinence-focused CM intervention included in TES may be enhanced by tailoring delivery based on patients' drug use status at treatment entry.

ECONOMIC ANALYSIS (Murphy et al., Drug and Alcohol Dependence, 2016): From the provider's perspective, TES+TAU as it was implemented in this study costs \$278 (SE=87) more than TAU alone after 12 weeks. The quality-adjusted life years gained by TES+TAU and TAU were similar; however, TES+TAU has at least a 95% chance of being considered cost-effective for providers and payers with willingness-to-pay thresholds as low as \$20,000 per abstinent year. Findings for the subgroup not abstinent at study entry are slightly more favorable. TES+TAU has a high probability of being considered cost-effective, based on the clinical outcome of abstinence, for most willingness-to-pay thresholds. The analyses performed here serve as an initial economic framework for future studies integrating technology into SUD therapy.

Moderator Analyses

PRIMARY SUBSTANCE (Cochran et al., 2015, Addictive Behaviors): Adjusted odds ratios (AOR) demonstrated primary stimulant users receiving TES were more likely to be abstinent in the final four weeks of treatment compared to stimulant users receiving TAU (AOR=3.59, 95% CI=1.25-10.27). Adjusted odds ratios for alcohol (AOR=3.15, 95% CI=0.85–11.65) and cannabis (AOR=2.64, 95% CI=0.73-9.52) also were of similar magnitude to stimulants but did not reach significance. Abstinence among primary opioid users was not improved by the TES intervention.

Synopsis of CTN0044 Publications

GENDER (Campbell et al., 2015, JSAT): Gender did not moderate the effect of treatment on the outcomes of abstinence, retention, social functioning, and craving. Women reported higher acceptability scores at week 4 ($p=.02$), but no gender differences were detected at weeks 8 or 12. Acceptability was positively associated with abstinence, but only among women ($p=.01$).

RACE/ETHNICITY (Campbell et al., under review): Racial/ethnic subgroups differed by age (Black participants were older [$M=38$] than White [$M=33$] or Hispanic [$M=36$] participants) and education (Black and Hispanic participants were more likely to have less than a high school education [33%] compared to Whites [20%]). Whites were more likely to report opioids (33%) as their primary substance while Blacks were more likely to report cocaine (41%) and Hispanics were more likely to report alcohol (29%) and cannabis (29%). Findings demonstrated that race/ethnicity did not moderate the effect of TES vs TAU on abstinence or retention; there was also no main effect of race/ethnicity on abstinence ($p=.78$) or retention ($p=.83$). Acceptability of the TES intervention did differ by race/ethnicity subgroup. White participants reported lower acceptability of TES compared to African American/Black ($p=.006$) and Hispanic/Latino ($p=.008$) participants. However, acceptability overall was relatively high with a mean average of 8.0 (on a scale of 0-10) or higher.

AGE (Evans et al., under review): No significant difference of treatment effect among three age categories on abstinence or retention at week 12. There was also no significant association between categorized age and abstinence; however young adults dropped out of the treatment significantly more quickly than the oldest group ($X^2(2)=7.70$, $p=.02$), irrespective of treatment arm. Findings suggest that TES is a viable treatment intervention among younger, middle and older patients. Dropout remains a significant problem particularly among young adults; further research is needed to determine ways in which technology-assisted treatments may further be customized to most effectively treat different age groups.

INTERNET USE (Tofighi et al., under review): Internet use was common among respondents (74%), and was more likely among younger (18-49 years old) participants and those who completed high school ($p<.001$). There was a significant interaction between treatment, baseline abstinence and internet access on time to dropout ($X^2(1)=3.8089$, $p=.051$). Only non-abstinent participants at baseline with internet access randomized to TES had significantly lower rates of loss-to-follow-up than TAU ($Z=-2.67$, $p=.0075$).

CRIMINAL JUSTICE (Lee et al., under review): CJS-mandated/recommended ($n=176$) participants were more likely to be younger, male, and unmarried vs. CJS-none ($n=206$) participants. CJS-mandated/recommended participants reported higher rates of marijuana as their substance of choice vs. CJS-none (30% vs. 20%); CJS-risk participants reported more opiate use (30% vs. 21% [CJS-none] and 15% [CJS-mandated/recommended]). CJS-mandated/recommended and CJS-risk reported more internet use than CJS-none (83% [CJS-risk], 76% [CJS-mandated/recommended], 66% [CJS-none]). CJS-mandated/recommended participants had lower propensity for depressive disorders and lower addiction severity ratings vs. CJS-none. The three-way interaction of treatment, baseline abstinence and CJS status was marginally significant ($p=.07$). CJS-risk participants not abstinent at baseline responded significantly greater abstinence in TES treatment, compared to treatment-as-usual ($p=.008$).

Mediation

COPING STRATEGIES (Levesque et al., under review): The average baseline coping strategies scores were not significantly different between the two treatment arms. TES intervention was associated with better coping strategies scores (Mean = 19.30, SD = 4.31) compared to TAU (Mean = 17.91, SD = 4.74) ($P = .0007$), and higher coping strategies scores were associated with an increased likelihood of abstinence at the end of treatment. The effect of TES on abstinence was no longer significant after controlling for coping strategies scores.

Synopsis of CTN0044 Publications

Baseline Descriptive

CLINICAL CHARACTERISTICS BY ABSTINENCE STATUS (Cochran et al., 2014, *Addiction Science and Clinical Practice*): Participants classified as abstinent from the primary drug were 84% (opioid), 76% (stimulant), 62% (alcohol) and 33% (marijuana). Drug positive versus negative patients did not differ on demographics or rates of substance abuse/dependence diagnoses. However, those negative at baseline had better physical and mental health profiles, were less likely to be using a secondary drug, and more likely to be attending 12-step self-help meetings. Those who are actively using at treatment entry have worse health and mental health outcomes, as well fewer days of 12-step attendance.

SAMPLE CHARACTERISTICS BY PRIMARY SUBSTANCE (Campbell et al., 2013, *Journal of Addiction Medicine*): Few participants expressed disinterest in the study at screening due to the computer-assisted intervention. A diverse sample of substance users completed baseline and were enrolled: 22.9% marijuana; 21.7% opiates; 20.9% alcohol; 20.5% cocaine; and 13.9% stimulants. Marijuana users were younger, less likely to be married or attend 12-step meetings, and more likely to be in treatment as a result of criminal justice involvement. All patients, even marijuana users, reported comparable rates of co-occurring mental health disorders and sexual risk, as well as substantial rates of polysubstance use disorders. Primary substance of abuse may be a less important indicator of overall severity compared to co-occurring disorders and other factors common across treatment seekers, further demonstrating the need for integrated treatment services and care, as well as comprehensive pre-treatment assessment.

AGE (Kalapatapu et al., 2013, *Journal of Addiction Medicine*): Middle-aged adults (45+) were more likely to be non-Caucasian and have a marital status other than single/never married. Significant association between years of education and the age group, and between frequency of Internet use and the age group. 45% of middle-aged adults versus 21% of younger adults reported no Internet use in the prior 90 days. A greater percentage of middle-aged adults used cocaine, and a greater percentage of younger adults used marijuana and opioids. Clinically significant cognitive impairment was found for the average middle-aged substance abusing adult on immediate memory and for the average participant in both groups on logical association of familiar concepts.

MENTAL HEALTH (Sanchez et al., 2015, *Substance Abuse*): 21%; n=106 of the sample screened positive for depression; those positive for depression were significantly more likely to screen positive for anxiety (66.9%) and PTSD (42.9%). After controlling for anxiety and PTSD symptoms, presence of depressive symptoms remained significantly associated with fewer coping strategies ($p = .001$), greater impairment in social adjustment ($p < .001$), and poorer health status, ($p < .001$), but not to days of drug use in the last 90 days ($p = .14$). Coping skills are a significant predictor of treatment outcomes and it may be especially important to screen for and enhance coping among depressed patients.

Methods

DESIGN AND METHODOLOGICAL CONSIDERATIONS (Campbell et al., 2012, *Contemporary clinical Trials*): Describes the methodological considerations of WEB-TX including potential effectiveness trial designs that were considered and the rationale for the final choice of design: a randomized controlled design (with independent treatment arm allocation), intention-to-treat primary outcome analysis, biological markers for the primary outcome of abstinence, long-term follow-up assessments, precise measurement of intervention dose, and a cost-effectiveness analysis.

GENERALIZABILITY (Blanco et al., in press, *Journal of Clinical Psychiatry*): Prior to reweighting the sample, the Odds Ratio (OR) of response to TES versus treatment-as-usual

Synopsis of CTN0044 Publications

was 1.62 (95% CI=1.12-2.35). After reweighting the sample (using data from the nationally representative National Epidemiological Survey on Alcohol and Related Conditions [NESARC]), the ORs were 1.33 (95% CI=0.34-5.26) for the representative sample with any substance use and 1.64 (95% CI=0.82-3.27) for the representative sample who were receiving treatment. The point estimates of the treatment effects for the representative samples both fell within the confidence interval of the original clinical trial results. Applying propensity score weighting to clinical trial results provides a method for estimating the population generalizability of clinical trial findings and informing the potential for treatment effectiveness in later dissemination efforts.