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Concordance of Direct and Indirect Measures of Medication Adherence in A Treatment Trial for Cannabis Dependence☆

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ABSTRACT

The current study compared adherence rates as measured by two indirect measurement methods (pill count and daily medication diary) to two direct measurement methods (urine riboflavin and serum 6-OH-buspirone level measurement) among participants (n = 109) in a medication treatment trial for cannabis dependence. Pill count and diary data showed high levels of percent agreement and strong kappa coefficients throughout the study. Riboflavin levels indicated lower level of percent in adherence during the study as compared to both pill count and self-report. In the subset of participants with 6-OH-buspirone levels (n = 58), the kappa coefficient also showed low to moderate agreement between the pill count and medication diaries with 6-OH-buspirone levels. In contrast to pill count and medication diaries, adherence as measured by riboflavin and 6-OH-buspirone significantly decreased over time. The findings from this study support previous work demonstrating that pill count and patient self-report of medication taking likely overestimate rates of medication adherence, and may become less reliable as the duration of a clinical trial increases.

1. Introduction

Medication adherence is of critical importance in clinical trials, as poor medication adherence in research studies may obscure potential effects of a pharmacologic intervention (Farmer, 1999; Spilker, 1991; Williams, Amico, Bova, & Womack, 2013). Adherence can be a particular challenge for researchers in the addiction field, as substance use can directly impair judgment, which may negatively impact treatment adherence. There can also be ambivalence surrounding the use of medications in this population, which could further reduce adherence (Sowers & Golden, 1999).

Both direct and indirect methods to measure medication adherence are commonly utilized in substance use clinical trials. Direct methods of adherence measurement include directly observed medication administration, detection of the drug or drug metabolite in a biologic fluid, and detection of a biological marker administered with the drug. Indirect methods of adherence measurement can be objective, such as pill counts and electronic medication event monitoring systems (MEMS), or subjective, such as participant or collateral self-report. Each method has advantages and limitations. Directly observing participant ingestion of a medication should ensure adherence, but places significant burden on both participants and research staff. Measurement of a drug, metabolite, or biological marker in a biological fluid provides objective confirmation that a dose of medication has been ingested by an individual; however, such "spot" levels may not be reflective of steady state drug confirmation. Advantages of pill counts include low burden and costs. However, pill counts may be inaccurate due to participants not returning all medication as directed. Further, although a total number of medication ingestions may be estimated from pill counts, it is not possible to confirm an individual took the medication as prescribed. Although MEMS are widely regarded as the gold standard measure of participant adherence, a potential shortcoming of this approach is that actual medication ingestion is not measured; rather, the system is limited to registering times when the medication container is opened and when it is closed. Cost is also a consideration with use of MEMS, as the product components and software required for data retrieval can be expensive. Participant self-report is the most common method used to assess medication adherence. Advantages of self-report include low participant and provider burden and essentially no cost. Disadvantages of self-report include recall bias and potential inaccuracy in reporting.

Given the critical importance of accurate adherence measurement in interpretation of medication trial results, data on validity of measurement methods are needed to inform clinical trial design. The current study expands on limited previous research in this area by comparing adherence rates as measured by two indirect measurement methods (pill count and daily medication diary) to two direct measurement methods (urine riboflavin and serum metabolite level measurement).

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Further, as clinical trials commonly exceed four to eight weeks in length, evaluations of reliability of measurement methods over an extended time period are needed. It was hypothesized that indirect methods of adherence would overestimate adherence as compared to direct methods, and that all adherence measurements would demonstrate a reduction in adherence over the course of the study.

2. Methods

2.1. Design and procedures

Participants were primarily recruited through media and internet advertisements between November, 2009, and March, 2014, to participate in a 12-week, double-blind, placebo-controlled trial of a medication and behavioral intervention in cannabis-dependent individuals. All procedures were conducted in accordance with Good Clinical Practice Guidelines and the Declaration of Helsinki and received approval from the Medical University of South Carolina Institutional Review Board. All participants gave written, informed consent prior to study participation.

Following assessment to determine study eligibility, participants were randomized to receive either buspirone (flexible dose of up to 60 mg/day) or a matching placebo. Medication was dosed twice daily, with each dose containing 25 mg of riboflavin. Participants also completed three sessions of motivational enhancement therapy focused on cannabis use. Escalating contingency management compensation was used to reinforce study visit attendance and retention; compensation was not contingent on cannabis abstinence. Participants attended weekly clinic visits.

2.2. Adherence measures

Medication adherence was assessed using (1) pill counts, (2) patient self-report, (3) quantitative urine riboflavin levels, and (4) serum measurement of 6-OH-buspirone, a major metabolite of buspirone. At each study visit, participants were provided with a supply of medication and a diary to record medication intake. Returned pills were then counted by study staff to determine the proportion of pills taken from what was prescribed at each previous visit, and diaries were also collected weekly. Participants received $10 weekly compensation for returned medication diaries, pill bottles, and unused pills. Urine samples were collected for riboflavin analysis at every other visit (visits 2, 4, 6, 8, 10, and 12). Analysis was conducted using a TECAN microplate reader. Samples were exposed to light at a wavelength of 444 nm, and emission fluorescence of riboflavin measured at 515 nm. A standard curve was established by measuring the intensity of emitted light of known amounts of riboflavin (concentrations ranging from 250 ng/ml to 8000 ng/ml); study samples were run against this standard curve. Serum samples were also obtained at every other visit (visits 2, 4, 6, 8, 10, and 12) for determination of 6-OH-buspirone concentrations. A liquid–liquid extraction procedure was developed following a previously described method (Dockens, Salazar, Fulmor, et al., 2006) and samples analyzed using a Waters 2695 HPLC (Waters Corp., Milford, MA) equipped with a photo diode array (PDA) detector capable of spectral analysis for peak purity and identity confirmation.

Adherence was defined as having reported ≥80% of doses taken (pill count / diary), riboflavin ≥ 900 ng/ml, and 6-OH-buspirone > 0 (in the active treatment group only). The riboflavin cut-off was based on recommendations by Herron, Mariani, Pavlicova, et al. (2013). Since riboflavin was considered the gold standard of adherence measurement in this study, adherence was calculated at each visit where riboflavin data and at least one other measure were present. Participants taking a multivitamin containing riboflavin were excluded from the analysis.

2.3. Statistical analysis

Baseline demographics and clinical characteristics were calculated as means and associated 95% confidence intervals for continuous variables and percentages (n) for categorical variables. A t-test was used to evaluate continuous baseline demographic and clinical measures while the normal Pearson Chi-Square test was used to assess the relationship for categorical and ordinal variables (Fisher's exact test was used where appropriate) between the analysis cohort and the cohort of participants excluded from the analysis.

Various methods of measuring medication adherence were assessed across several visits during the treatment phase of the study (weeks 2, 4, 6, 8, 10, 12). Percentages in agreement and kappa coefficients were calculated between each measurement method. Due to very high prevalence of self-reported adherence in the study population, kappa coefficients are calculated as the prevalence adjusted bias adjusted kappa (PABAK) (Byrt, Bishop, & Carlin, 1993). Using riboflavin determined adherence as the reference marker, a clustered logistic regression model using the methods of generalized estimating equations (Zeger & Liang, 1986) was applied to assess the differences in measurement methods on binary adherence outcomes over time. Working correlation structures were independently compared and the final model structure was chosen using the quasilikelihood under the independence model criterion statistic (Pan, 2001). The main effects of adherence measurement method and visit as well as the interaction between method and visit were examined for significance. Additionally, demographic and clinical characteristics were individually added to the primary analysis model to assess possible predictors of treatment adherence. All statistical analyses were conducted using SAS version 9.3 (SAS Institute Inc. Cary, NC, USA).

3. Results

3.1. Participant characteristics

The present study included all participants from the parent study (n = 175) with at least one riboflavin adherence measure, either a concurrent pill count or medication diary measure, and those not taking multivitamins that contain riboflavin (n = 109). The cohort was primarily Caucasian (n = 69, 63.3%) and male (n = 82, 75.2 %). The average age was 23.1 years (SD = 5.3) with an average age of cannabis dependence onset of 19.3 years (SD = 3.5). Participants excluded from the analysis (n = 66) were slightly older than those included (25.6 ± 7.6 vs. 23.1 ± 5.3. p = 0.017); however the excluded participants were otherwise clinically and demographically similar to those included in the analysis (Table 1). Demographic and clinical characteristics collected at the baseline visit were assessed for univariate associations with both direct and indirect measures of medication

Table 1
Demographic and clinical characteristics of the study cohort and those excluded from the study analysis.

Characteristic	Study Cohort n = 109	Excluded N = 66
Age (yrs)	23.1 (22.0–24.1)*	25.6 (23.7–27.5)
Male % (n)	75.2 (82)	78.8 (52)
Caucasian % (n)	63.3 (69)	65.2 (43)
Graduated HS % (n)	90.8 (99)	89.4 (59)
Buspirone Treatment % (n)	53.2 (58)	45.5 (30)
Age of Onset of Cannabis Dependence	19.3 (18.7–20.0)	20.6 (19.1–22.1)
Ounces used per week	5.2 (4.8–5.7)	5.3 (4.6–6.0)
Sessions Per Day	3.1 (2.7–3.5)	3.2 (2.8–3.7)

Continuous characteristics are shown as their mean and associated 95% confidence interval while categorical characteristics are shown as percent (n). Continuous characteristics are compared using a t-test statistic while categorical characteristics are compared using a Pearson chi-square test statistic.

* Age (p = 0.017).