# Smart Capsules are a Promising Tool to Improve Medication Adherence in Clinical Trials

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# Adherence to pharmacotherapy in SUD clinical trials

Compliance with study medication in pharmacotherapy trials in individuals with substance use disorders is a significant problem as rates tend to be low (Baros et al. 2007; McRae et al., 2004; O'Brien et al., 1996; Somoza et al., 2010).

**Poor adherence can result in false negative results which delay the further development, increase costs and delay the use of potentially efficacious medications.**

# Current Methods and Their Limitations

| Method | Advantages | Disadvantages |
|---|---|---|
| Self report/Pill count | Inexpensive, minimal training of study personnel | No guarantee med taken, relies on bringing bottle to study visit |
| MEMS (medication event monitoring system) | Can detect medication bottle opening, more expensive | Cannot detect if medication consumed |
| Urinary riboflavin | Relatively inexpensive, need to train staff, ability to evaluate on site | Requires ultraviolet light, Ambiguous readings common, variability in absorption/metabolism |

# Comparison Between Methods

In pharmacotherapy trial for cocaine -dependent individuals multiple methods of measuring adherence were utilized (Mooney et al., 2004).

- The MEMS estimate of compliance was significantly lower (28%)
- Compared to Self-Report (87%) and
- Riboflavin (78%)

# ID-Cap® (EtectRx, Orlando, FL)

- Standard hard gelatin capsule containing an embedded ingestible wireless sensor – the ID-Tag.
- Once swallowed, the ID-Tag transmits a very low power digital message from within the patient's stomach (powered by stomach fluids).
- Ultra-thin flexible sensor is naturally eliminated through the GI tract.
- Small wearable reader device detects messages transmitted from ingested ID-Tags and forwards to the to the cloud-based Information Management Platform (IMP).
- IMP provides customizable reminders for to take medication at designated times, system status (e.g., reader battery status) and adherence history.

## ID-Capsule

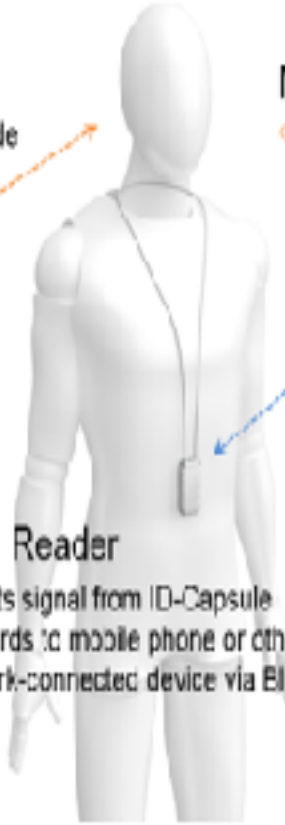
- Contains the study medication
- Ingested by the participant
- Powered by the participant's stomach fluid
- Emits low-power digital messages from inside the participant confirming ingestion

## Mobile Phone

- Communications portal for ID-Cap data, reader status, and participant messages

## Data & Management

- Verified, time-stamped, dose-level adherence events



## Reader

- Detects signal from ID-Capsule
- Forwards to mobile phone or other network-connected device via Bluetooth LE

# Methods

- **Healthy volunteers:** (aged 18-60) were recruited via media advertisements. Following informed consent mental health was assessed with the M.I.N.I. (Sheehan, et al., 1998). General health was evaluated with hx & PE, blood work, and UDS.

- **Exclusion criteria:** BMI < 18 or > 30, GI disorders that may impact capsule passage (e.g., gastroenteritis, Crohn's Disease, etc.), hypersensitive to riboflavin, adhesive or any capsule component, current or past psychotic disorder or bipolar disorder, moderate to severe SUDs (except nicotine and caffeine) within the past 60 days. Additional exclusion criteria included pregnancy, breast-feeding or not practicing an effective means of birth control.

# Randomization to Three Groups

**Group 1:** Standard Capsule with adherence measured by self-report and riboflavin measurement.

**Group 2:** ID-Cap with adherence measured by self-report, riboflavin, and data collected from the e-Tect reader.

**Group 3:** In addition to group 2 measures, participants received reminder calls and/or text messages if a signal was not sent from the e-Tect reader to the study team within one hour of the scheduled administration time.

# Methods continued

- 7 day supply of medication (compounded with 50mg of riboflavin powder) was dispensed each week for 4 weeks with instruction to take 1 cap every day at 9am.
  - Instructed not to take multivitamin with riboflavin during the study.

- Twice weekly study visits included: self-report of medication adherence, assessment of adverse effects, and a urine specimen for riboflavin measurement.

- Participants returned for a 1-week follow-up visit to assess adverse events and an abdominal x-ray in groups 2 and 3 to confirm passage of the capsule.

# Urinary Riboflavin

- Study personnel qualitatively assessed urine samples with a black light to assess for fluorescence.
  - Lack of fluorescence indicated that the participant likely did not take the previous day's dose.

- Quantified urine riboflavin level >900ng/ml was considered adherent consistent with previous research (Herron et al., 2013)

# Statistical Analysis

- Intent to treat analysis
- Baseline demographic differences compared using Wilcoxon Rank-Sum test for continuous characteristics and Chi-square test for categorical
- Medication adherence (data collected at each visit) defined as 100% of prescribed dose (self-report/pill count), 100% ID-Cap detected ingestions (including reported user error such as failure to charge reader)
- Percentage in agreement and kappa coefficients were calculated between ID-Cap and other measures of compliance
  - Due to a very high prevalence of medication compliance in the self-report and pill count measures, Kappa coefficients are calculated as the prevalence adjusted bias adjusted kappa (PABAK)
- Clustered logistic regression model using the methods of generalized estimating equations was utilized. Working correlation structures were independently compared. The primary main effects of measurement method and study week (visit) were examined for significance. Model results are reported as risk ratios and associated 95% confidence intervals (using the sandwich estimator for the variance estimate).

# PARTICIPANTS

- 69 individuals were consented
- 60 met eligibility criteria and were randomized
- 59 completed the 28 day study

- No significant differences in demographics was found between the three groups

# Differences in Compliance between ID-Cap groups vs. Riboflavin

| Outcome | OR (CI) | P Value | ID-Cap groups vs. Riboflavin group |
|---|---|---|---|
| **Self report** | 2.96 (1.13-7.79) | 0.027 | 90.6% vs. 76.3% |
| **Pill count** | 3.69 (1.49-9.14) | 0.005 | 89.4% vs. 69.7% |
| **Riboflavin** | 0.92 (0.37-2.30) | 0.85 | 83.4% vs. 84.2% |

# Agreement and kappa between ID-cap & other measures

| Visit | Self-report/ID-Cap | | Pill Count/ID-Cap | | Riboflavin/ID-Cap | |
|---|---|---|---|---|---|---|
| | % agree | κ | | κ | | κ |
| 1 | 92.3 | 0.85 | 92.3 | 0.85 | 71.8 | 0.44 |
| 2 | 92.5 | 0.85 | 90.0 | 0.80 | 71.1 | 0.43 |
| 3 | 82.5 | 0.65 | 82.5 | 0.65 | 69.2 | 0.39 |
| 4 | 84.6 | 0.69 | 84.6 | 0.69 | 66.7 | 0.33 |
| overall | 88.0 | 0.76 | 87.3 | 0.75 | 69.7 | 0.39 |

**Strong agreement between ID-Cap and self-report/pill count was found in week 1 & 2 with moderate agreement in week 3 & 4. Poor to weak agreement between ID-Cap and riboflavin was found throughout.**

# Adverse events

| | Overall | Standard Capsules (n=20) | ID-Cap (n=40) | P-value |
|---|---|---|---|---|
| # with any AE % (n) | 50.0 (30) | 50.0 (10) | 50.0 (20) | 0.99 |
| # AE Reported (all) | 0.5 (0-3) | 0.5 (0-3) | 0.5 (0-3) | 0.911 |

**Similar rates of adverse events were reported in individuals receiving the ID-Cap and individuals receiving standard capsules.**

# CONCLUSIONS

- Urinary riboflavin (one of the most commonly used compliance measures) had poor concordance with other measures of adherence.
- ID-Cap self-administration improved compliance measured by self-report and pill count.
- Taken together the use of smart capsules can more directly measure adherence in pharmacotherapy research.

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