# Post-hoc analysis of 2 clinical trials of customized adherence enhancement + long-acting injectable antipsychotic (LAI) for high-risk individuals with schizophrenia

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## Abstract

**Aims:** Long-acting injectable antipsychotic medication (LAI) can be a practical treatment option to optimize adherence for high-risk groups such as homeless individuals with serious mental illness (SMI). These investigators have developed a Customized Adherence Enhancement (CAE) approach that improves outcomes when added to LAI for homeless or recently homeless individuals with schizophrenia or schizoaffective disorder. For this analysis, data from 2 prospective, 6-month open-label, uncontrolled studies involving individuals with schizophrenia/schizoaffective disorder were pooled. Study design was nearly identical except that LAI used was haloperidol decanoate in study 1 and paliperidone palmitate in study 2. The CAE approach in study 2 was delivered by a licensed social worker and enhanced by more extensive outreach to community mental health clinics. This analysis investigated drop-out patterns, which are a significant problem in schizophrenia clinical trials.

**Methods:** Both trials combined CAE + LAI in 30 recently homeless individuals with schizophrenia or schizoaffective disorder for a total combined sample of 60. Clinical outcomes included medication adherence using the Tablets Routine Questionnaire (TRQ), LAI injection frequency and psychiatric symptoms measured by the Positive and Negative Syndrome Scale (PANSS), Brief Psychiatric Rating Scale (BPRS) and global psychopathology (Clinical Global Impressions /CGI). Social functioning was assessed via the Social and Occupational Functioning Assessment Scale (SOFAS).

**Results:** Mean combined age of the sample was 42.7 years (SD=9.0), mainly minorities (88.3% African-American), mainly single/never married (71.2%) with a mean of 11.4 years of education. Baseline rate of substance abuse within the past year was 25.0%, and rate of incarceration within the past 6 months was 21.6%. A total of 14 individuals (23.3%) terminated the study prematurely (prior to the 6-month endpoint). Demographic and clinical features did not predict drop out. Drop-out rate in study 1 (33.3%) trended higher compared to study 2 (13.3%) (p=.08). For both studies, most drop-outs occurred in the early portion of the clinical trial (mean of 58.8 (SD=36.0) and 56.0 days (SD=42.0), respectively). Completers had significant improvement in adherence, psychiatric symptoms, global psychopathology and functioning.

**Conclusion:** Highly symptomatic SMI is common in the homeless population and LAI combined with a targeted adherence enhancement approach may be a useful therapeutic approach in these high-risk individuals. Using an LAI that minimizes extrapyramidal burden and including social workers who are trained to interface with community mental health clinic staff in typical treatment settings may minimize trial drop-out. Additional intensive efforts may be needed early in the course of treatment, especially during the first 2 months, to help these individuals remain in treatment.

## Introduction

There is a direct correlation between non-adherence and relapse in schizophrenia. Non-adherent patients have a relapse risk 3.7 times greater than adherent patients. Long-acting injectable antipsychotic (LAI) medication can improve adherence (West 2008) but needs to be combined with a quality behavioral program to modify long-term attitudes and behaviors. Homeless individuals with schizophrenia are a particularly high-risk group prone to be poorly adherent with antipsychotic medication.

A novel customized psychosocial adherence enhancement intervention paired with LAI (CAE-L) (Sajatovic 2013) found reduced rates of homelessness, improved psychiatric symptoms and increased overall functioning in homeless, poorly adherent individuals with schizophrenia. CAE-L has been manualized and is highly acceptable to homeless people with serious mental illness. However, in spite of promising results, the CAE-L intervention had some important limitations that are barriers to scale-up. CAE-L used a PhD-level psychologist to deliver the behavioral part of the program and many public-sector clinical settings have a very limited number of such highly trained individuals. CAE-L also used the LAI haloperidol decanoate, which was associated with akathisia in 40% of people.

To address these obstacles, the CAE-L intervention was modified to 1) Use a social worker to deliver the intervention, 2) Use a second generation LAI (paliperidone palmitate), and 3) Include outreach to community mental health systems to help maintain engagement. For this analysis, data from the original CAE-L study (study 1/S1) and the modified CAE-L study (study 2/S2) were pooled. Other than the 3 modifications noted above, the study design was identical. This analysis focused on change in adherence, psychiatric symptoms and drop-out rates using the combined data.

## Introduction (continued)

## Methods

**Study Overview:** This was a post-hoc pooled data analysis combining results from 2 prospective 6-month, non-controlled trials of CAE-L in 60 recently homeless individuals with schizophrenia or schizoaffective disorder. CAE-L combines an adherence-enhancement psychosocial intervention + LAI. Research assessments were conducted at screening, baseline, 3-month, and 6-month follow-up. Primary outcome was treatment adherence as measured with the Tablets Routine Questionnaire (TRQ) and LAI injection frequency. Additional outcomes included housing status, psychiatric symptoms, global psychopathology, functional status, reported side effects, health resource use and satisfaction with treatment.

### Inclusion Criteria

1. Individuals age 18 and older with schizophrenia or schizoaffective disorder as confirmed by the Mini International Psychiatric Inventory (MINI)
2. Currently or have been recently homeless (within the past 12 months)
3. Poor adherence defined as TRQ indicating ≥20% or more missed medication

### Exclusion Criteria

Individuals on LAI immediately prior to enrollment, those with current/past clozapine use, significant medical conditions and/or substance dependence were excluded.

### Intervention:

**LAI:** Haloperidol decanoate (S1) or Paliperidone palmitate (S2) were dosed as per package insert.

**Customized Adherence Enhancement (CAE):** CAE targets key areas relevant to non-adherence in schizophrenia (psychoeducation, assistance with medication routines, coaching in communication with providers, and modified motivational interviewing for substance use). CAE-L combines CAE + LAI. The interventionist was a PhD-level psychologist in S1 and a masters-level social worker in S2.

### Measures:

- **Treatment adherence:** Self-reported Tablets Routine Questionnaire (TRQ), LAI injection frequency (within 7 days of scheduled time)
- **Symptoms:** Positive and negative syndrome scale (PANSS), Brief Psychiatric Rating Scale (BPRS), and Clinical Global Impressions (CGI)
- **Functioning:** Social and Occupational Functioning Scale (SOFAS), Global Assessment of Functioning (GAF)

## Results

**Sample:** Table 1 illustrates baseline demographic and clinical variables of the pooled sample

**LAI:**

Mean end-point dose of haloperidol decanoate was 68.0 mg, SD 21.1, range 50-100 mg/monthly injection (S1)

Mean end-point dose of paliperidone palmitate was 122.57 mg, SD 30.04, range 78-156 (S2)

**Table 1: Baseline clinical characteristics of 60 non-adherent homeless/recently homeless individuals with schizophrenia or schizoaffective disorder**

| Variable | Screening Value | Baseline |
|---|---|---|
| Age in yrs Mean (SD - Range) | 42.7 (9.0 - 21-60) | - |
| Female N (%) | 26 (43.30%) | - |
| Race N (%)<br>White<br>Black | <br>6 (10.0%)<br>53 (88.3%) | - |
| Hispanic Ethnicity N (%) | 4 (6.8%) | - |
| Education in yrs Mean (SD - Range) | 11.4 (1.9 - 7-16) | - |
| Marital Status N (%)<br>Single, never married<br>Divorced/Separated<br>Married<br>Widowed | <br>42 (71.2%)<br>13 (22.1%)<br>2 (3.4%)<br>2 (3.4%) | - |
| Type of illness N (%)<br>Schizophrenia<br>Schizoaffective | <br>16 (26.7%)<br>44 (73.3%) | - |
| Age of onset of illness in yrs<br>Mean (SD)<br>Range (Median) | <br>21.8 (10.2)<br>41.0 (20.0) | - |
| TRQ Mean (SD)<br>Past Week<br>Past Month | <br>56.7 (33.1)<br>47.3 (32.6) | <br>34.6 (36.7) (n=57)<br>38.4 (33.7) (n=56) |
| Housing status as a proportion of the previous 180 days %(SD)<br>Outdoors<br>Short-term/emergency shelter<br>Transitional housing<br>Permanent housing with assistance<br>Permanent housing without assistance<br>Incarceration | - | <br>3.9% (12.7)<br>29.4% (38.1)<br>11.8% (24.5)<br>21.1% (35.0)<br>21.9% (40.4)<br>6.4% (19.5) |
| Past or current substance abuse N (%) | -16 (26.7%) | - |
| History of incarceration N (%) | 9 (32.1%) | - |
| BMI Mean (SD) | - | 32.1 (7.1) |

TRQ: Tablets Routine Questionnaire; BMI: Body Mass Index

## Results (continued)

### Drop-Outs/Safety:

**Study 1:** Ten individuals (33%) terminated S1 prematurely. Reasons for drop out included: 4 (40%) lost to follow-up, 3 (30%) incarcerated, 2 (20%) re-located, and 1 (10%) due to akathisia. After 168 days, 66.7% of individuals completed treatment.

**Study 2:** Four individuals (13.3%) terminated S2 prematurely. Reasons for drop out included 3 (75%) lost to follow-up and 1 withdrew consent (25%).

**Combined sample:** 14 (23.3%) terminated the study prematurely. Time-to-event data for the dropout from injection treatments were modeled using Kaplan-Meier estimation (Figure 1). Two-sided log-rank test was close to significant (p=.074). For both studies, most drop-outs occurred in the early portion of the clinical trial. Mean days to drop-out was 58.8 (SD=36.0) in S1 and 56.0 days (SD=42.0) for S2.

## Conclusions

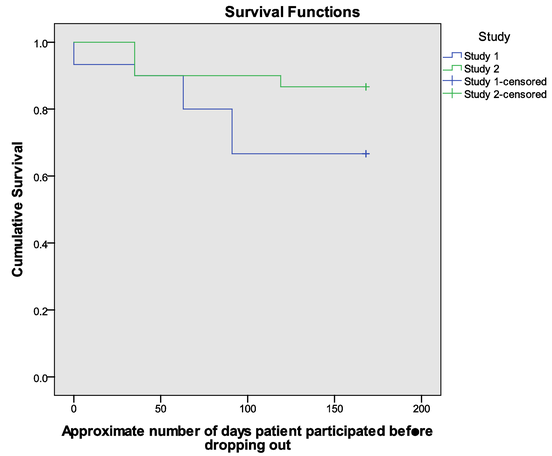
Individuals with schizophrenia/schizoaffective disorder who are homeless and poorly adherent may be engaged with an approach that combines LAI and a behavioral adherence intervention program. Use of a second-generation antipsychotic and providing support to community mental health clinic staff may help to maximize treatment engagement although some individuals will still drop out of clinical trial participation, particularly early-on in the trial.

**Table 2: Changes in Medication Adherence, Symptoms, Global Psychopathology and Social Functioning in 60 non-adherent homeless/recently homeless individuals with schizophrenia or schizoaffective disorder**

| Variable | Screen[a] | Baseline[a] | Wk 13 | Wk 25 | N | Statistic* |
|---|---|---|---|---|---|---|
| TRQ Mean (SD)[b]<br>Past Week<br>Past Month | <br>50.4% (32.4)<br>45.2% (33.6) | <br>26.7% (29.3)<br>32.5% (30.4) | <br>16.8% (29.5)<br>16.2% (24.9) | <br>17.1%(30.6)<br>13.8%(23.2) | <br>26<br>25 | <br>**.001**<br>**.002** |
| Injection frequency | - | - | 86.1 (32.8) | 90.5 (30.1) | 50 | .060 |
| BPRS Mean (SD) | - | 44.1 (8.3) | 33.9 (7.9) | 30.8 (8.3) | 41 | **< .001** |
| PANSS Mean (SD)<br>Positive Symptoms Scale<br>Negative Symptoms Scale<br>Composite Scale (Pos-Neg)<br>Gen. Psychopathology Scale | <br>-<br>-<br>-<br>- | <br>16.7 (6.3)<br>28.5 (10.9)<br>14.9 (10.3)<br>19.9 (18.9) | <br>-<br>-<br>-<br>- | <br>12.4 (5.8)<br>20.8 (7.9)<br>7.8 (8.2)<br>9.8 (14.1) | <br>36<br>35<br>36<br>36 | <br>**.001**<br>**<.001**<br>**<.001**<br>**<.001** |
| CGI Severity Mean (SD) | - | 4.6 (0.9) | 3.4 (0.7) | 3.1 (0.8) | 38 | **<.001** |
| SOFAS Mean (SD) | - | 51.1 (8.1) | - | 61.3 (9.7) | 40 | **<.001** |

***Statistic reported is the p-value from a matched-pairs t-test run with data from the earliest point in time (screen or baseline) and data from the last visit (week 25).**

**Figure 1: Kaplan-Meier Estimates of Attrition during a 25-Week (168 Day) Regimen of Long-Acting Injectable Antipsychotic Among 60 Homeless/Recently Homeless Individuals with Schizophrenia or Schizoaffective Disorder**

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