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A 6-month prospective trial of a personalized behavioral intervention + long-acting injectable antipsychotic in individuals with schizophrenia at risk for treatment non-adherence and homelessness

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Abstract

Purpose—Long-acting injectable antipsychotic medication (LAI) can optimize adherence for high-risk serious mental illness (SMI). This Customized Adherence Enhancement approach delivered by social worker interventionists was combined with LAI (CAE-L) of paliperidone palmitate for homeless, poorly-adherent individuals with SMI.

Methods—This 6-month prospective, uncontrolled trial of CAE-L in 30 recently homeless individuals with SMI assessed adherence using the Tablets Routine Questionnaire (TRQ), injection frequency, and SMI symptoms measured by the Positive and Negative Syndrome Scale (PANSS), Brief Psychiatric Rating Scale (BPRS) and Clinical Global Impressions (CGI). The Social and Occupational Functioning Assessment Scale (SOFAS) measured social function. Standardized scales assessed extrapyramidal effects.

Findings—Mean age was 43.6 years (SD=9.53), mainly minorities (86.7% African-American), mainly single/never married (72.4%). Rate of substance abuse within the past year was 40.0% and rate of incarceration within the past 6 months was 32.1%. Four (13.3 %) participants terminated the study prematurely. CAE-L was associated with good adherence to LAI (92.9%) and improved adherence with oral drug as measured by TRQ ($p=.02$). There were significant improvements in PANSS ($p<.01$), BPRS ($p<.001$), CGI ($p=.003$) and SOFAS ($p=.005$). There were no significant extrapyramidal effects.

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Implications—While findings must be tempered by the methodological limitations, CAE-L appears associated with multiple domains of improvement in homeless / recently homeless individuals with SMI. Side effects limit tolerability in some individuals and not all will remain engaged. However, LAI combined with a patient-centered behavioral approach can improve outcomes for some high-risk individuals with SMI.

Keywords

schizophrenia; schizoaffective disorder; antipsychotic medication; adherence; homelessness

1. Introduction

Recovery of individuals with serious mental illness (SMI) may be complicated by problems such as homelessness, substance use and poor adherence (1, 2). Long-acting injectable antipsychotic (LAI) medication may improve adherence (3), however, recovery comprises more than just medication-taking. Whitley and Drake (4) noted 5 key SMI recovery domains that include clinical recovery (reducing symptoms), existential recovery (hope and empowerment), functional recovery (housing, employment), physical recovery (medical health), and social recovery (social connections, community).

In homeless and poorly-adherent persons with SMI, a treatment approach combining Customized Adherence Enhancement + LAI (CAE-L) may reduce homelessness, improve SMI symptoms and increase functioning (5). CAE-L is a manualized intervention that is highly acceptable to homeless people with SMI (5). However, in spite of promising preliminary results, previous versions of CAE-L had barriers to scale-up. While delivery by a PhD-level psychologist is effective, many public-sector clinical settings have a very limited number of such highly trained individuals. Additionally, CAE-L used first-generation LAI (haloperidol deaconate), which while affordable, is associated with akathisia in 40% of people. To increase potential generalizability, the CAE-L intervention was modified to be delivered by social workers and featured a second-generation LAI (paliperidone palmitate) (6–8). This prospective 6-month, non-controlled trial of modified CAE-L assessed multiple domains of recovery outcomes in 30 homeless or recently homeless individuals with schizophrenia or schizoaffective disorder.

2. Materials and Methods

2.1. Overview

CAE-L combined an adherence-enhancement psychosocial intervention + LAI delivered prospectively over 6 months. Once intolerance to antipsychotic drug was ruled out, individuals received monthly LAI delivered concurrently with 30–60 minute interactive individual sessions based on cognitive-behavioral principles delivered by a trained social worker. Research assessments were conducted at screening, baseline, 13 and 25-week follow-up. Primary outcome was change in adherence as measured with the Tablets Routine Questionnaire (TRQ) and LAI injection frequency. Additional outcomes included housing status, SMI symptoms, global psychopathology, general and social functioning,

hospitalization counts, satisfaction with treatment, extrapyramidal symptoms and reported side effects.

2.2. Participants

Individuals, recruited from the community, were all age 18 with schizophrenia or schizoaffective disorder as confirmed by the Mini International Psychiatric Inventory (MINI) version 6.0 (9). Participants had been homeless within the past 12 months and had poor adherence with oral antipsychotics defined as missing 20% of medication in the last week or month on the TRQ (10, 11). Individuals on LAI immediately prior to enrollment, those with clozapine use, significant medical conditions and/or substance dependence were excluded. The study was approved by the local Institutional Review Board (IRB). Individuals were compensated for research assessments. Individuals were encouraged to continue care in their standard setting, mainly community mental health clinics (CMHCs).

2.3. CAE-L Intervention

2.3.1. LAI—Paliperidone palmitate was dosed as per manufacturer's package insert (<https://www.invegasustenna.com>). After the initial loading dose, paliperidone palmitate was administered every 4 weeks in the deltoid muscle for a total of 6 months. Individuals not on any antipsychotic or on antipsychotics other than paliperidone or risperidone at screening were given oral paliperidone (3 mg daily) for 3 days as an oral tolerance test (OTT). The LAI dosing was based on clinical judgement of the treating research psychiatrist.

2.3.2. Customized adherence enhancement—Customized Adherence Enhancement (CAE), originally designed for non-adherent bipolar patients (12), targets key areas relevant to non-adherent individuals with SMI broadly and includes 4 flexibly administered modules based upon baseline evaluation of 4 key adherence barriers: 1.) psychoeducation focused on the role of medication in SMI recovery, 2.) developing medication and lifestyle routines, 3.) communicating with providers, and 4.) managing adherence in the context of substance abuse. The CAE interventionist was a social worker who also reached out and worked with CMHCs to enhance adherence and help facilitate LAI continuation as clinically indicated over the long-term. One social worker interventionist was trained and supervised by one PhD level clinical psychologist on CAE administration. Training included videotaping intervention sessions with the psychologist reviewing the recordings and providing input to the social worker in addition to regular research review meetings approximately weekly.

2.4. Concomitant treatments

Antipsychotic drugs other than LAI were discontinued with the exception of low-dose bedtime oral antipsychotic (i.e. quetiapine 50–100 mg) for insomnia in a small number of individuals unable to be weaned off these drugs. Stable doses of psychotropic drugs other than antipsychotics were continued through the course of the study. New psychotropic medications were strongly discouraged. Medications for extrapyramidal side effects were given at the discretion of the treating psychiatrist.

2.5. Study Assessments

Participants were assessed at screening, baseline (first administration of LAI or first CAE session) and at 13 and 25 weeks follow-up. The primary study outcome was adherence behavior assessed via the TRQ and LAI injection frequency. Raters trained to pre-set acceptability standards who were not involved in the study intervention performed assessments.

2.6. Primary outcomes

The TRQ (10, 11) determines proportion of prescribed medication missed, and ranges from 0 (no medication missed/100% adherent) to 100 (no medication taken/0% adherent). For this trial, the TRQ captured an exact proportion (%) of days with a missed medication dose for each maintenance oral psychotropic drug and derived an average combined TRQ. Full LAI adherence was defined as receiving an injection within 7 days of scheduled time.

2.7. Secondary Outcomes

Secondary outcomes included self-reported housing status, adherence attitudes, hospitalization count, SMI symptoms, social functioning, treatment satisfaction, side effects and biological/safety measures. Sub-optimal housing was defined as incarceration, outside, transitional housing, homeless shelter, or temporary/overnight stays with individuals in their social network. Days in sub-optimal housing were assessed in the 6-months prior to study enrollment and during the 6-month study. The 10-item Drug Attitude Inventory (DAI) measured attitudes towards medication (13). The Attitudes toward Mood Stabilizers Questionnaire (AMSQ), adapted from the Lithium Attitudes Questionnaire (14), measured medication attitudes. Use of emergency care and hospitalization resources in the 6-months pre and post study enrollment were evaluated. SMI symptoms were measured with the Positive and Negative Syndrome Scale (PANSS) (15), Brief Psychiatric Rating Scale (BPRS) (16) and the Clinical Global Impressions (CGI) (17). Functional status was evaluated with the Social and Occupational Functioning Scale (SOFAS) (18). The Alcohol, Smoking and Substance Involvement Screening Test (ASSIST) measured drug use (19).

Safety evaluations included baseline and Week 25 (or end of study) comprehensive metabolic panel, lipid profile, CBC with differential and pregnancy testing for women. EKG was conducted at baseline and Week 25 (or end of study). Vital signs and weight were collected at each study visit. Measures of involuntary movements were the Simpson Angus Scale (SAS) (20), Barnes Akathisia Rating Scale (BARS) (21), Abnormal Involuntary Movement Scale (AIMS) (17) and the Extrapyramidal Symptoms Scale-Abbreviated version (ESRS-A) (22). Reported side effects were evaluated at each study visit. To assess generalizability of CAE-L, we assessed regular clinical care retention and patient satisfaction post-study assessed via telephone 3 months after the last study in-person visit.

2.8. Data analysis

Descriptive statistics were calculated for baseline characteristics. Change was measured by taking differences in scores across time points. Hypothesis tests for assessing whether or not the median difference scores are zero were conducted using Wilcoxon signed rank test. Statistical analyses were performed using SPSS software version 20.

3. Results

3.1. Study Flow and Sample

Figure 1 shows study flow. The average time between screening and baseline was 7.37 (SD=5.67) days. Mean sample age was 43.6 years (SD=9.53), 86.7% African-American, 72.4% single/never married, with a mean of 11.55 years of education. Baseline rate of substance abuse within the past year was 40.0%, and rate of incarceration within the 6 months prior to enrollment was 32.1%. In the 6 months prior to study enrollment, participants spent 40 % of their time in sub-optimal housing. On average, individuals missed approximately 58% of prescribed oral medication.

3.2. Medication

At baseline, individuals were predominantly prescribed second-generation antipsychotics (N=22, 73.3%) with just one individual (3.3%) prescribed a first-generation antipsychotic drug. Mean end-point dose of paliperidone palmitate was 122.57 mg, SD 30.04, range 78–156 mg. Modal dose was 117 mg. Additional concomitant (non-antipsychotic) medications included mood stabilizing drugs (lithium, anticonvulsants) prescribed to 5 individuals (16.7 %) and antidepressants prescribed to 16 (53.3 %) of individuals.

3.3. Drop-Outs and Safety

Four individuals (13.3%) terminated prematurely. Reasons for drop out included 2 (50%) lost to follow-up, 1 relocated (25%), and 1 withdrew consent (25%). There were 7 Serious Adverse Events (SAEs) that occurred in 5 individuals: 1 psychiatric hospitalization, 5 medical hospitalizations (hernia, respiratory/COPD exacerbation, frostbite, spider bite, and elevated liver function and QTc prolongation on EKG in the context of acute alcoholic hepatitis), and 1 emergency room visit due to falls. Two SAEs were possibly related to study drug (falls, worsened alcoholic hepatitis).

3.4. Efficacy and Side Effects

As shown in Table 1, CAE-L was associated with good LAI adherence (90.5%) and improved oral drug adherence ($p=0.02$). There were improvements in AMSQ ($p=0.01$), BPRS ($p=0.01$), PANSS ($p<0.001$), CGI ($p<0.001$) SOFAS ($p<0.001$), and psychiatric hospitalizations ($p=0.03$). There was a trend for reduced days in sub-optimal housing ($p=0.05$). The most common side effect (57%) was injection site complaints. There were no serious or sustained injection site reactions. Thirteen individuals (33%) experienced at least mild akathisia at some point during the trial, but only 1 akathisia case persisted at 6 months. One individual was discontinued due to adverse effects, a reported dystonic reaction after first LAI injection. There were no significant changes on AIMS, SAS, BARS, ESRS-A. Mean weight gain was 5.85 (SD 9.35) kg and median gain was 4.99 kg, range -10.43 to 31.30 kgs, with 9 (30%) individuals gaining more than 7% of body weight. There was no significant change in laboratory testing.

Of individuals who completed 25 weeks of CAE-L, 21 (80.8%) provided post-study information. Nineteen (90.5%) were still in CMHC care. Overall, 17 (81.0%) were very satisfied and 4 (19.0%) were satisfied with CAE-L, and felt it was worth the time and effort.

Nine (42.9%) said they missed injections since the study ended: 5 (62.5%) chose to end their injections due to side effects, 2 (28.6%) missed due to either lack of transportation or inconvenience in getting the injection, 1 (14.3%) was incarcerated, and one individual (14.3%) missed due to medication access problems.

4. Discussion

Combining LAI with a psychosocial intervention that targets individual barriers to adherence may improve multiple outcomes in homeless individuals with SMI. Findings from this trial generally replicated findings from an earlier pilot study (5). Refinements of the CAE-L approach which are intended to facilitate broad scale-up included use of social workers to deliver the intervention and the use of a second-generation antipsychotic drug as LAI.

Paliperidone palmitate was generally well-tolerated, with injection site complaints the most common problem. Weight gain was relatively common with approximately 30% of individuals gaining >7% of body weight. Although many second-generation antipsychotic drugs are associated with weight gain (23), some of the weight gain in this sample could have been related to life-style issues seen in those residing in shelters or transitional housing. The formulation of paliperidone palmitate used in this study was the monthly injection version. Recently, a formulation of paliperidone palmitate that appears safe and effective when given every 3 months has become available (24). It is possible that this strategy could further protect against future adherence-related relapse and could be an approach that might help retain individuals on LAI for longer periods of time.

Future implementation considerations might include embedding CAE-L directly into settings where homeless individuals present for crisis services such as temporary or homeless shelters. Another target might be prior to release from correctional settings. Notably, approximately one-third of our sample had been incarcerated in the 6 months prior to study entry.

There are few established treatments for homeless people with SMI (25), and it is perhaps not surprising that their prognosis is often poor (26). A literature review by Zhornitsky and colleagues (27) suggested that LAIs reduce risk of relapse when combined with psychosocial interventions in some patients. While CAE-L was designed as an intervention to get very high-risk patients stabilized and on the road to recovery, it is encouraging that observed improvements in this trial suggests progress in several of the key recovery domains articulated by Whitley and Drake (4). Clinical recovery was demonstrated by SMI symptomatic improvement (PANSS, BPRS, CGI), while functional recovery was demonstrated by reduced use of hospital services and a trend for improvement in housing status. Other domains of improvement included dramatic reduction in missed medication from 57.7% missed medication at screening vs. 22% at 6-month follow-up, and improved attitudes towards treatment and medication. Adherence behavior and attitudinal change could be indicators of empowerment and health ownership although these constructs were not measured explicitly. Lastly, social functioning was improved in the sample. A recent qualitative analysis of trajectories of recovery among formerly homeless adults with SMI (2) noted that significant-other relationships were a top contributor to recovery change.

This study had a number of limitations including small sample size, an observational/non-controlled design, un-blinded assignment and assessment as well as the single-site setting. However, findings are similar to a nearly-identical trial conducted by this study team which used haloperidol decanoate as LAI. It seems reasonable to cautiously conclude that a personalized intervention to address adherence barriers combined with LAI can improve adherence and selected recovery outcomes in high risk individuals with SMI (28). A pooled analysis of the two CAE-L studies conducted by this team found that drop-out rate trended lower in the modified version which featured social worker interventionists and second-generation LAI (13.3%) vs. the original version which used a PhD psychologist interventionist and first-generation LAI (33.3%) ($p=.08$) (28). Demographic and clinical features did not predict drop out and most drop-outs occurred in the early portion of the original trial (mean of 58.8 days ($SD = 36.0$) and 56.0 days ($SD = 42.0$) in the modified CAE-L trial. Completers had significant improvement in adherence, psychiatric symptoms, global psychopathology and functioning.

In conclusion, a manualized adherence enhancement approach that targets adherence barriers, uses social workers as interventionists, and is appropriate for both first and second-generation LAIs may help recovery in some high-risk individuals with SMI. Controlled and larger studies which include additional assessments such as LAI drug levels are needed to confirm preliminary findings.

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Figure 1.

CONSORT Diagram of participation in a study of customized adherence enhancement plus long-acting injectable antipsychotic (LAI).

*One patient's psychiatrist did not recommend enrolling the patient due to the patient having newly identified medical problems.

Table 1

Change in Primary and Secondary Study Outcomes

Variable	Screen			Baseline			Wk 13			Wk 25			Change	N	Statistic*
	Mean (SD)	Median, range	Mean (SD)	Median, range	Mean (SD)	Median, range	Mean (SD)	Median, range	Mean (SD)	Median, range	Mean (SD)	Median, range			
TRQ ^{a,b}															
Past Week	56.2% (33.6)	42.9%, 0–100%	46.5% (35.6)	28.6%, 0–100%	26.5% (38.8)	4.8%, 0–100%	19.2% (30.9)	0.0%, 0–100%					–37.0%	16	Z= –2.41, p=0.02
Past Month	48.7% (34.8)	33.3%, 0–100%	43.9% (32.9)	35.0%, 0–100%	21.9% (28.2)	10.0%, 0–100%	15.2% (26.3)	8.3%, 0–100%					–33.5%	15	Z= –2.07, p=0.04
Injection Frequency	-	-	-	-	91.3% (28.8)	100%, 0–100%	90.5% (30.1)	100%, 0–100%					---	21	Z= –1.41, p=0.16
DAI ^c	7.6 (1.6)	8.0, 3 – 10	-	-	8.3 (1.6)	8.0, 4–10	8.4 (1.4)	9.0, 6 – 10					+0.8	23	Z= –1.72, p=0.09
AMSQ ^d	6.3 (3.4)	6.0, 0 – 16	-	-	-	-	4.0 (2.9)	3.0, 0 – 9					–2.3	26	Z= –2.69, p=0.01
BPRS ^e	-	-	43.5 (8.9)	43.0, 29–71	34.3 (7.4)	34.0, 21–52	29.8 (8.1)	29.0, 20–55					–13.7	24	Z= 2.45, p=0.01
PANSS ^f															
Positive Symptoms	-	-	21.2 (5.3)	21.0, 11–32	14.7 (3.9)	14.0, 9 – 23	12.9 (4.0)	12.5, 7 – 24					–8.3	24	Z= –4.03, p<0.001
Negative Symptoms			13.7 (4.0)	13.0, 8 – 23	13.0 (5.5)	11.0, 7 – 26	12.1 (6.1)	10.0, 7 – 30					–1.6	24	Z= –1.37, p=0.17
Composite Scale			7.5 (5.9)	8.5, –2 – 20	1.7 (6.1)	3.0, –13 – 12	0.8 (6.6)	1.5, –21 – 9					–6.7	24	Z= –3.73, p<0.001
General Psych.			35.2 (7.2)	34.0, 24 – 49	27.6 (6.5)	26.0, 16 – 41	24.7 (6.4)	24.0, 16 – 38					–10.5	22	Z= –3.67, p<0.001
CGI ^g	-	-	4.6 (0.9)	5.0, 3 – 6	3.3 (0.7)	3.0, 2 – 5	2.9 (0.8)	3.0, 2 – 5					–1.7	22	Z= –3.73, p<0.001
ASSIST ^h	-	-	3.3 (2.7)	3.0, 0 – 10	2.4 (2.0)	2.0, 0 – 7	2.0 (2.5)	0.0, 0 – 7					–0.9	20	Z= –1.87, p=0.06
SOFAS ⁱ	-	-	53.2 (8.8)	51.5, 34 – 70	-	-	63.1 (8.7)	62.0, 31 – 72					+9.9	26	Z= –3.48, p<0.001
Hospitalizations past 6 mos															
Psychiatric	-	-	0.6 (1.0)	0.0, 0 – 3	-	-	0.2 (0.4)	0.0, 0 – 1					0.4	26	Z= –2.12, p=0.03

Variable	Screen			Baseline			Wk 13			Wk 25			Change	N	Statistic*
	Mean (SD)	Median, range		Mean (SD)	Median, range		Mean (SD)	Median, range		Mean (SD)	Median, range				
Medical				0.4 (0.9)	0.0, 0 – 4					0.2 (0.4)	0.0, 0 – 1		-0.2	26	Z= -1.61, p= 0.11
% days sub-optimal housing (past 6 mo.)	52.1% (39.2)	35.6%, 1–100%		44.9% (41.8)	34.4%, 0–100%		-	-		29.0% (38.2)	3.1%, 0–100%		-15.9%	20	Z= -1.94, p= 0.05
AIMS ^j	2.3 (3.2)	0.0, 0 – 7		1.9 (2.9)	0.0, 0 – 9		-	-		1.5 (2.5)	0.0, 0 – 7		-0.4	23	Z= -0.36, p= 0.72
SAS ^k	0.2 (0.5)	0.0, 0 – 2		0.3 (0.9)	0.0, 0 – 5		0.1 (0.3)	0.0, 0 – 1		0.0 (0.2)	0.0, 0 – 1		-0.3	20	Z= -0.58, p= 0.56
BARS ^l	0.1 (0.4)	0.0, 0 – 2		0.1 (0.5)	0.0, 0 – 3		0.4 (1.1)	0.0, 0 – 4		0.3 (1.3)	0.0, 0 – 6		+0.2	20	Z= -1.00, p= 0.32
ESRS-A ^m															
Parkinsonism	0.2 (1.0)	0.0, 0 to 5		0.2 (1.0)	0.0, 0 to 5		0.0 (0.0)	0.0, 0 to 0		0.0 (0.2)	0.0, 0 to 1		-0.2	20	Z= -0.45, p= 0.66
Dystonia	0.0 (0.2)	0.0, 0 to 1		0.0 (0.2)	0.0, 0 to 1		0.0 (0.0)	0.0, 0 to 0		0.0 (0.0)	0.0, 0 to 0		---	20	Z= 0.00, p= 1.00
Dyskinesia	1.3 (2.3)	0.0, 0 to 7		1.4 (2.2)	0.0, 0 to 7		0.3 (1.2)	0.0, 0 to 6		1.4 (2.2)	0.0, 0 to 6		---	20	Z= -0.18, p= 0.86
Akathisia	0.0 (0.2)	0.0, 0 to 1		0.0 (0.0)	0.0, 0 to 0		0.2 (0.6)	0.0, 0 to 2		0.2 (0.9)	0.0, 0 to 4		+0.2	20	Z= -1.00, p= 0.32

* Statistic is Wilcoxon signed-rank test.

^a Mean TRQ for oral BD medications in addition to LAI;

^b TRQ: Tablet Routines Questionnaire, lower % indicates better adherence;

^c DAI : Drug Attitudes Inventory: Higher scores indicate better attitudes;

^d AMSQ: Attitudes toward Mood Stabilizers Questionnaire, higher scores indicate worse attitudes;

^e BPRS: Brief Psychiatric Rating Scale: Higher scores indicate more severe symptoms;

^f PANSS: Positive and Negative Syndrome Scale, higher scores indicate more severe symptoms;

^g CGI: Clinical Global Impression; higher scores indicate more severe illness;

^h ASSIST: Alcohol, Smoking and Substance Involvement Screening Test, higher scores indicate more problems;

ⁱ SOFAS: Social and Occupational Functioning Assessment Scale; higher scores indicate higher functioning;

^j AIMS: Abnormal Involuntary Movement Scale, higher scores indicate more severity;

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k_{SAS} : Simpson Angus Scale; higher scores indicate more severity;
 I_{BARS} : Barnes Akathisia Rating Scale, higher scores indicate more severity;
 m_{ESRS-A} : Extrapyramidal Symptoms Scale-Abbreviated version, higher scores indicate more severity