

APPROACH: Assessing Pain, Patient Reported Outcomes and
Complementary and integrative Health (A National VA Demonstration
Project)

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Principal Investigators

Stephanie L. Taylor, PhD, MPH

Steven B. Zeliadt, PhD, MPH

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APPROACH Statistical Analysis Plan

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Study Summary and Aims

Brief summary of study purpose

The APPROACH Study (Assessing Pain, Patient-Reported Outcomes and Complementary and Integrative Health) will assess the value of Veterans participating in practitioner-delivered complementary and integrative health (CIH) therapies or self-care therapies compared to a combination of self-care and practitioner-delivered care (dual care).

Study Design

This is a pragmatic, prospective longitudinal study utilizing quasi-experimental causal inference methods.

Primary Aims

Aim 1a Evaluate the causal effect of receiving self-care CIH therapies only compared to receiving dual care on pain outcomes.

Aim 1b Evaluate the causal effect of receiving practitioner-delivered CIH therapies only compared to receiving dual care on pain outcomes.

Secondary Aims

Aim2 Evaluate the effect of individual CIH therapies on pain outcomes.

Aim3 (?) Evaluate the mediating effect of “mechanism of action” variables on pain outcomes.

Data Sources

Data for this study will come from three sources: the OPCCCT CIH Experience Survey, the VA’s Electronic Health Record (EHR) system, and interviews/visits with study sites. The CIH Experience Survey is a longitudinal survey administered at 4 time points: a baseline timepoint intended to occur around the time of CIH initiation followed by follow-up surveys at 1 month, 3 months and 6 months post-baseline.

Study Population

The primary study population consists of Veterans with moderate to severe chronic musculoskeletal pain who initiate at least one of the six CIH therapies at one of the 18 sites designated as Whole Health flagship sites during the three-year study period.

To be classified as having moderate to severe chronic musculoskeletal pain, a Veteran must have

- a history of at least one of several musculoskeletal pain-related ICD10 diagnoses AND

- at least two scores recorded in the EHR of on the 0-10 numeric rating scale (NRS) which are separated by at least 30 days in the year prior to the index CIH visit.

Veterans who have used any of the six CIH therapies in the six months prior to their index visit will be excluded. Determination of prior CIH therapy use will be based on evidence from the EHR as well as self-reported use from the baseline survey.

Other exclusion criteria are

- patients older than 90 years of age at the time of their index visit
- patients with any of the following severe behavioral disorders:
 - schizophrenic/delusional disorders
 - manic/bipolar disorder (severe)
 - dissociative/conversion disorders
 - paranoid/unstable personality disorder
 - cognitive impairment
 - dementia

Study Measurement Time Periods

There are four study time points: baseline (index CIH visit), 1 month post-baseline, 3 months post-baseline, and 6 months post-baseline. Each time point corresponds to when a survey will be administered.

In addition, data on business practices and nudges to CIH will be collected directly from the sites during site calls held quarterly.

Study Outcomes

Primary Outcomes

The primary outcomes are

- the Brief Pain Inventory (BPI) pain severity score
- the BPI pain interference score

The BPI pain severity score is a self-reported rating on a scale from 0 (“no pain”) to 10 (“pain as bad as you can imagine”) of the participant’s average pain in the previous week. The BPI pain interference score is a self-reported rating on a scale from 0 (“does not interfere”) to 10 (“completely interferes”) of the degree to which pain has interfered with the participant’s life.

Pain outcomes will be measured through the CIH Experience Survey at Baseline, 1 month, 3 months, and 6 months.

Secondary Outcomes

Outcomes that will be analyzed in secondary analyses are

- Global Health (PROMIS10)
- Global Mental Health (PROMIS10 subscale)
- Global Physical Health (PROMIS10 subscale)
- Opioid Use

Tertiary Outcomes

Outcomes that will be analyzed in tertiary or exploratory analyses are

- Mental Health (PGIC)
- Depression (PHQ2)
- Global Social Health
- Purpose of Life (LET)
- Stress (PSS)
- Quality of Life (item in PROMIS10)
- Fatigue (PROMIS10 item)
- Fatigue (PGIC variant)
- Perceived improvements from CIH Use

All outcome measures except for opioid use are measured as self-reported outcomes on the survey at all survey timepoints. Opioid use will be measured via the EHR system.

Study Covariates

Covariate(s) of Interest

Among those Veterans who initiate with self-care CIH therapy, the covariate of interest is a binary exposure variable indicating whether that Veteran received self-care CIH therapy only or received both self-care and practitioner-based CIH therapies.

Among those Veterans who initiate with practitioner-based CIH therapy, the covariate of interest is a binary exposure variable indicating whether that Veteran received practitioner-based CIH therapy only or received both practitioner-based and self-care CIH therapies.

Confounders/precision variables for Adjustment

Adjustment variables that are available from the survey are

- current relationship status (categorical, nominative)

- employment status (categorical, multiple responses allowed)
- financial security (categorical, ordinal)
- education level (categorical)
- service in combat or war zone (binary)
- impact of COVID-19 on healthcare access (ordinal)
- impact of COVID-19 on mental and emotional health
- format of delivery of therapy
- recent injury or acute cause of pain

Adjustment variables that are available from EHR data are

Mechanisms of Action

Hypothesized mechanisms of action are health competency (perceived ability to manage one's health), ownership (perceived role in and responsibility for one's health), and self-efficacy (confidence in managing one's health condition). Health competency is measured by the Perceived Health Competency Scale (PHCS-2). Ownership is measured by the Altarum Consumer Engagement (ACE). Self-efficacy is measured by Self-Efficacy for Managing Chronic Disease.

Instruments

Data will be collected on variables that could serve as instruments in instrumental variable models. Specifically, we will work with sites to identify business practices related to CIH use that nudge individuals towards dual use of CIH therapies.

Coding of CIH Use, Exposure Status, and Outcomes

Coding CIH Use and Exposure Status

Exposure status will be coded through a combination of CIH use captured in the EHR system and self-reported CIH use captured in the survey. The criteria for being considered exposed to each CIH modality are listed below:

CIH Modality	Delivery mechanism (Practitioner or self-care)	Dose Criteria	Data Source (survey, EHR, or both)
Chiropractic	Practitioner		
Acupuncture	Practitioner		
Therapeutic massage	Practitioner		

Mindfulness	Self-care		
Yoga	Self-care		
Tai Chi	Self-care		

- chiropractic:
- acupuncture:
- therapeutic massage:
- mindfulness:
- yoga:
- Tai Chi:

Coding of Primary Outcomes

The BPI Pain Intensity outcome measure will be computed from survey items 17-20.

The BPI Pain Interference outcome measure will be computed from survey items 21 - 27. Pain interference will be defined as the mean of the seven interference items. Pain interference will be scored as long as four of the seven items have answers. Otherwise it will be coded as missing.

Coding of Secondary Outcomes

Statistical Analyses and Description of Main Tables

Descriptive Analyses

In descriptive analyses of the data, we will examine characteristics of the distributions of the variables measured from our three data sources. We will create tables of summary statistics of the instruments, exposure and adjustment variables at each of the survey timepoints. Summary statistics will also be displayed graphically.

In descriptive analyses, we will examine the in-sample balance between exposure groups on baseline variables. We will additionally examine the in-sample balance between nudged and non-nudged individuals on baseline variables.

Aim 1 Statistical Analyses

In Aims 1a and 1b, we propose to estimate the causal effect of dual use of CIH therapies compared to practitioner-delivered therapies alone and self-care therapies alone. We have identified two analytic strategies to answer these questions. One analytic strategy is based on

using the variation in business practice nudges as an instrument in an instrumental variables model to identify the causal effect of receiving dual care within the 6-month follow-up window on the outcomes measured at 6-month follow-up (Strategy 1). The other analytic strategy is based on treating dual use status as a time-varying exposure within the 6-month follow-up period (Strategy 2).

These strategies should not be seen as mutually exclusive competing analyses, but rather as complementary analyses that address different underlying questions. The IV analysis addresses the question of the average causal effect of dual use of self-care and practitioner-based CIH on pain at 6 months post-index visit in a population where actual dual usage of CIH therapies during the 6-month follow-up period follows the distribution seen in our sample. The analysis approach based on marginal structural models, on the other hand, is useful for estimating causal effects under more hypothetical interventions in which individuals utilize dual usage of CIH therapies during each of the study timepoints.

Strategy 1

Our first analysis strategy is based on identifying from the EHR and through our connections with the study sites possible nudges that can serve as instruments for the relationship between dual use of CIH and pain in instrumental variable (IV) analyses.

Our instrumental variable model will be fit as follows.

Let $\mathbf{Z}_i = (Z_{i1}, Z_{i2}, \dots, Z_{iq})$ be the vector of instrumental variables for the i^{th} individual in the study. Let D_i be the indicator variable for whether the i^{th} individual was a dual user of CIH strategies during the follow-up period. Let $\mathbf{X}_i = (X_{i1}, X_{i2}, \dots, X_{ip})$ be the vector of available covariates for the i^{th} individual in the study. Finally, let Y_i be the outcome measured at the end of follow-up. To estimate the causal parameter of interest, we use a two-stages least-squares regression approach. The first stage model regresses the observed dual use variable D_i on the instruments and covariates

$$\text{Stage 1: } D_i = \alpha_Z \mathbf{Z}_i + \alpha_X \mathbf{X}_i + \epsilon_i.$$

Let \hat{D}_i be the fitted value from this first stage regression. The second stage model regresses the observed outcome Y_i on \hat{D}_i and the covariates \mathbf{X}_i

$$\text{Stage 2: } Y_i = \beta_D \hat{D}_i + \beta_X \mathbf{X}_i + \epsilon_i$$

We will report results from both the first stage and second stage regression models. For the first stage model, we will especially focus on the explanatory power of the instruments \mathbf{Z}_i , as represented by the F-statistic for the instruments. If the F-statistic is judged to be too low, we will consider alternative estimation procedures such as Limited Information Maximum Likelihood.

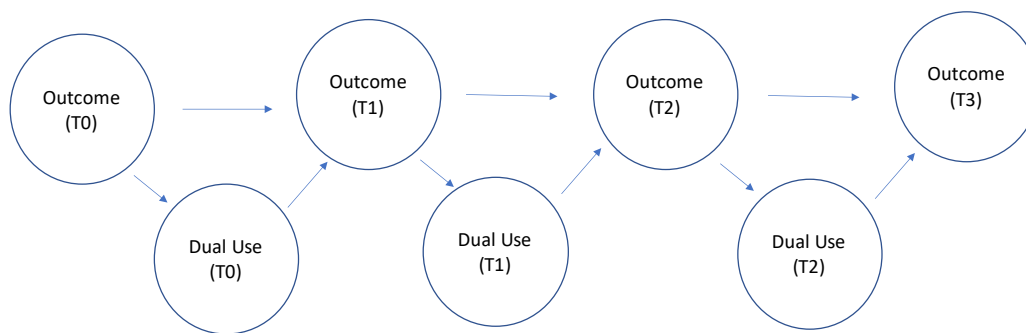
For the second stage model, we will report point estimates and 95% confidence intervals for model coefficients. The coefficient estimate $\hat{\beta}_D$ will serve as our estimate of the causal effect of receiving dual care compared to practitioner-only care on the outcome of interest.

Strategy 2

Strategy 2 is based on directly adjusting for measured covariates that confound the relationship between dual use of CIH therapies and pain while accounting for the time-varying nature of the exposure through the use of marginal structural modeling.

The marginal structural model will take the form

Our marginal structural model is guided by the following DAG:



This DAG illustrates two important features of the data generating process that we wish to account for with the marginal structural model: (1) dual use of CIH may vary within individuals over the course of the study and (2) intermediate outcomes may influence both subsequent use of CIH and subsequent outcomes. Hence, there is a feedback mechanism in which intermediate outcomes function as both confounders and mediators. Marginal structural models only us to correctly account for this when treating dual use as time-varying.

Aim 2 Statistical Analyses

Proposed Timeline

outline of proposed timeline of analysis-related tasks, potentially in the form of a Gantt chart

Project Links

links or folder/file locations for related project documents, e.g. project proposal, project descriptions, data dictionaries, etc.

Appendix: Shell Tables and Figures

any shell tables or figures referenced in Section 7 should be included here.