Role of Patient Adherence in the Treatment and Prevention of Depression

John F. Dickerson

A dissertation submitted in partial fulfillment of the
requirements for degree of

Doctor of Philosophy
University of Washington

2014

Reading Committee:
Anirban Basu, Chair
Gary Chan
Chuan-Fen Liu

Program Authorized to Offer Degree:
Public Health-Health Services
University of Washington

Abstract

University of Washington

Abstract

Role of Patient Adherence in the Treatment and Prevention of Depression

John F. Dickerson

Chair of the Supervisory Committee

Anirban Basu, Associate Professor

Departments of Health Services, Pharmacy, and Economics

Patient adherence to treatment and prevention guidelines as part of depression care is complex process. Major depression is a common disorder that can cause substantial morbidity, increase risks of mortality, negatively impact social relationships, and influence long term trajectories of education attainment and labor market outcome. Adherence is an important aspect of depression care because variability in compliance with prescribed treatments contributes to treatment effect heterogeneity and thus can decrease the effectiveness of viable treatments. This dissertation provides research to better understand barriers to pharmacotherapy and effects of patient adherence on health services use and health outcomes. Results from this project provide important information about characteristics of adherence and demonstrate the potential benefit

allocating resources towards improving patient adherence for depression treatment and prevention.

This dissertation examined determinants and consequences of adherence from different perspectives using observational data extracted from electronic medical records of a large integrated managed care maintenance organization as well as clinical trial data from a large multisite study. In the first aim of the dissertation, we studied the effects of industry-level unemployment on antidepressant pharmacotherapy using methods to control multiple channels of bias. We used medication persistence as our dependent variable, which measures the amount of time a patient accumulates medication from the beginning of therapy to discontinuation. We found empirical evidence that industry-level economic contraction interfered with optimal antidepressant therapy. In addition, we found the effect to be most pronounced during periods of economic shock and among mid-career employees.

The second aim of this dissertation, we examined the effects of antidepressant adherence and persistence on medical care expenditures, also controlling for multiple sources of bias. We found a small but significant effect of antidepressant persistence on total costs excluding medications and on the costs of outpatient services. As persistence increased, our measures of medical care expenditures decreased. We conducted a longer-term economic evaluation of a clinical trial testing clinical- and cost-effectiveness of a depression prevention program and examined the effect of intervention dose on economic outcomes as part of the third and final aim of this dissertation. We demonstrated longer-term cost-effectiveness of the depression prevention program and showed higher doses of the intervention resulted in more favorable measures of cost-effectiveness. Our research signals the potential benefit of additional adherence promotion as part of an existing intervention program.

Each aim in this dissertation project contributed policy-relevant research about barriers to patient adherence or about the effects of adherence on important patient outcomes. We applied rigorous quantitative methods to establish causality in our analyses, and applied these methods rich datasets from multiple sources. Our research findings provided meaningful contributions to the research literature in comparative effectiveness research, health economics, patient adherence, and mental health. In additional, we identified important areas of future research to be built on this dissertation project.

Table of Contents

List of Figures

List of Tables

Chapter 1 – Introduction

This dissertation examines the role of patient adherence in the treatment and prevention of depression. Depression is a common disorder affecting about 1 in 5 people during their lifetime[1]. In addition to reduced health-related quality of life, people in a depressive episode are at elevated risk for other health problems as well as for adverse events, including suicide attempts and accidents[2], [3]. Depression also carries a high societal burden through absenteeism and reductions in work productivity[3], [4]. Despite efficacious treatment options for depression, patient adherence to treatment tends to be poor. For example, only 20% of patients who begin antidepressant therapy for depression receive the recommended minimum therapeutic dose, and about 50% discontinue their medication following their first dispense[5], [6].

Patients' adherence to treatment guidelines for most medical interventions is a primary factor in differences in treatment response. How well patients follow prescribed instructions is often interrelated with the targeted health outcomes. For example, how well a person adheres to prescribed antidepressant therapy is influenced by how much their depressive symptomology is changing. This phenomenon is often referred to endogeneity or unobserved confounding. Modelling the effects of treatment adherence without consideration for the problem of endogeneity will likely introduce substantial bias, which can lead to erroneous conclusions. This is true in analyses using observational data as well as analyses related to intervention adherence as part of controlled experimental trials.

The Gelberg-Andersen Behavioral Model for Vulnerable Populations (G-A), an expansion of the most recent version of the Andersen behavioral model, is used as part of this dissertation to explain the conceptual framework of how we explore the role of patient adherence

in the treatment and prevention of depression[7], [8]. Three important characteristics of the G-A conceptual model make it an ideal framework for this research study. First, it incorporates community-level factors into the model. Second, it identifies improvements in health status as outcomes along with changes in health services use. Third, it recognizes feedback loops across the model, which is particularly important in the context of the endogeneity.

The three aims of this dissertation help provide clearer understanding of why consideration of patient adherence is an important component of depression treatment and prevention. We began the research project by exploring community level environmental factors that may affect patients through their work environment. We hypothesized that increasing levels of economic stress, as proxied through increasing unemployment, could disrupt optimal antidepressant therapy[9]. We applied dynamic panel models to control multiple sources of bias to a rich dataset of employed adults who were medical members of a large integrated managed care organization (MCO). Monthly unemployment rates by industry were matched to patients' employment records during the first six months of a new course of antidepressant treatment.

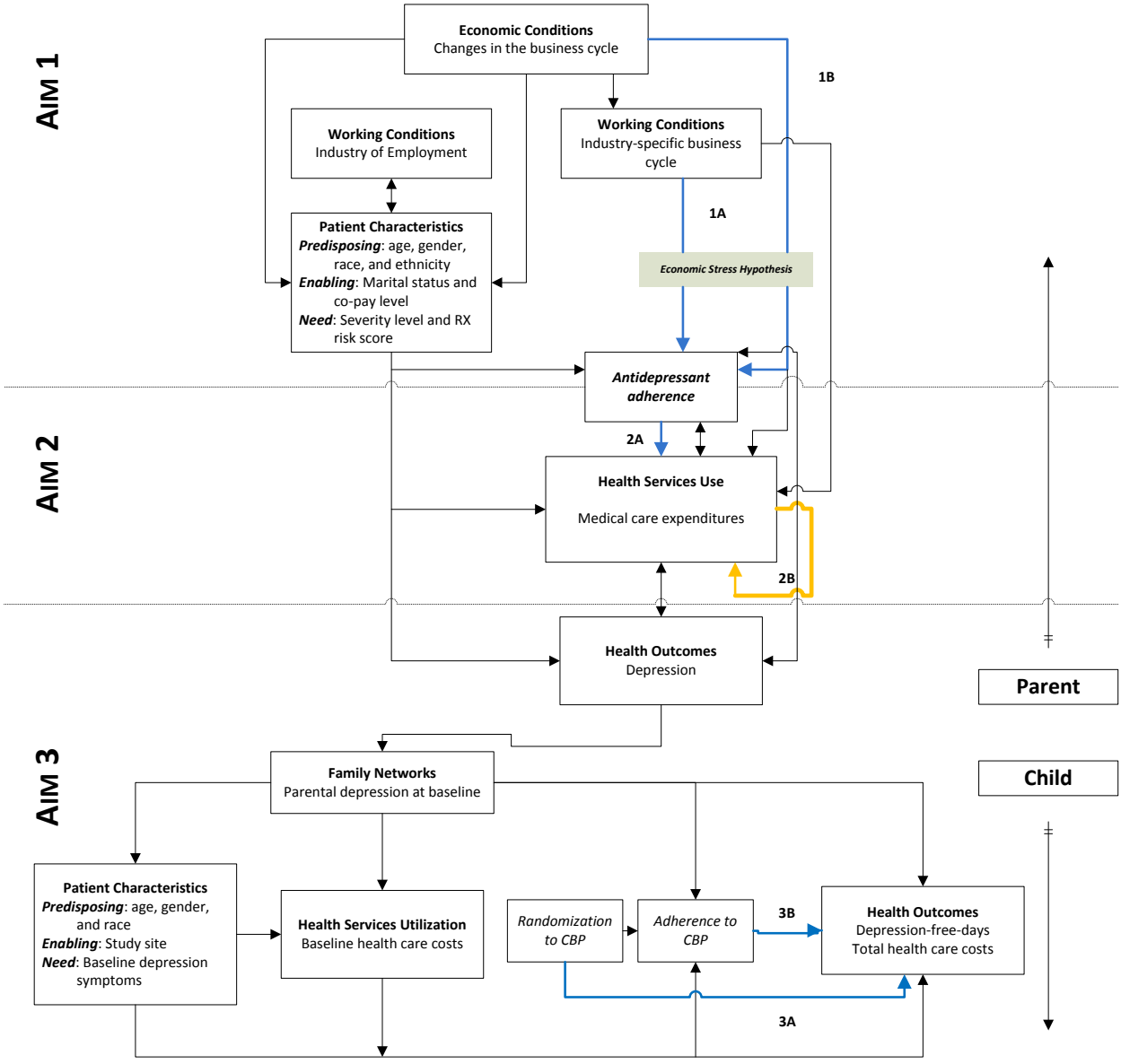
After exploring factors that affect antidepressant adherence, we turned to examining the effects of antidepressant adherence on medical care expenditures using observational data from a large integrated MCO. The majority of studies on antidepressant adherence and medical care expenditures using observational data have been unable to interpret their results from a causal perspective because of the problem of endogeneity[10], [11]. We expanded on previous research by quantifying the causal effect of antidepressant adherence on medical care expenditures using dynamic panel estimators[12]. We hypothesized that better adherence would lead to lower medical care expenditures. The analytic model in this aim of the dissertation conceptualized one health behavior (health services use as measured by expenditures) as a function of another health

behavior (adherence to antidepressant treatment), highlighting the importance of feedback looks in the conceptual model.

The analytic challenges of studying adherence with observational data are also present in randomized gold trials, typically thought of as the gold-standard for causal inference. While causal relationship can be identified, on average, between those people offered treatment and those who were not, disentangling the causal relationship of participation in the intervention, or "dose", on outcome is also vulnerable bias. The third aim of this project addressed this issue as part of a long-term cost-effectiveness analysis of a clinical trial designed to prevent depressive episodes in children who were at an elevated risk of depression[13]. This aim evaluated the cost-effectiveness of the intervention over three years and explored whether the results vary based on levels of adherence to study protocol. Instrumental variable methods were used to account endogeneity, and we hypothesized better adherence (higher dose) would result in more favorable outcomes.

The three aims of the project provide important information about the role of adherence in depression treatment and prevention in the fields of health economics and comparative effectiveness research. Results from the first aim identify groups of people at elevated risk for premature antidepressant discontinuation who may benefit from adherence promotion interventions. The second aim provides evidence of the monetary benefits of antidepressant adherence, which may provide further support to decisions makers about the value of adherence promotion programs. Finally, the third aim demonstrates the value of improved adherence within an existing intervention. This dissertation provides valuable research about factors influencing adherence and about the effects of adherence on important outcomes.

Figure 1-1. Unified Conceptual Framework



Adapted from Gelberg-Andersen behavioral model

A. Intention-to-treat effect
B. Treatment effect

References for Chapter 1

[1] M. Olfson, S. C. Marcus, B. Druss, L. Elinson, T. Tanielian, and H. A. Pincus, "National trends in the outpatient treatment of depression.," *JAMA*, vol. 287, no. 2, pp. 203–9, Jan. 2002.

[2] M. Jellinek and J. Snyder, "Depression and suicide in children and adolescents," *Pediatr Rev.*, vol. 19, no. 255, 1998.

[3] G. E. Simon, "Social and economic burden of mood disorders.," *Biol. Psychiatry*, vol. 54, no. 3, pp. 208–15, Aug. 2003.

[4] P. S. Wang, G. Simon, and R. C. Kessler, "The economic burden of depression and the cost-effectiveness of treatment.," *Int. J. Methods Psychiatr. Res.*, vol. 12, no. 1, pp. 22–33, Jan. 2003.

[5] S. H. Simpson, D. T. Eurich, S. R. Majumdar, R. S. Padwal, R. T. Tsuyuki, J. Varney, and J. a Johnson, "A meta-analysis of the association between adherence to drug therapy and mortality.," *BMJ*, vol. 333, no. 7557, p. 15, Jul. 2006.

[6] E. Vermeire, H. Hearnshaw, P. Van Royen, and J. Denekens, "Patient adherence to treatment: three decades of research. A comprehensive review," *J. Clin. Pharm. Ther.*, vol. 26, pp. 331–342, 2001.

[7] L. Gelberg, R. M. Andersen, and B. D. Leake, "Healthcare Access and Utilization The Behavioral Model for Vulnerable Populations : Application to Medical Care Use and Outcomes for Homeless People," *Heal. Serv Res*, vol. 34, no. 6, pp. 1273–302, 2000.

[8] R. M. Andersen, "Revisiting the behavioral model and access to medical care: does it matter?," *J. Health Soc. Behav.*, vol. 36, no. 1, pp. 1–10, Mar. 1995.

[9] R. Catalano, D. Dooley, and D. Charles, "A Test of Economic Instability : of Economic Health Effects Stress Hypothesis," vol. 24, no. 1, pp. 46–60, 1983.

[10] W. Katon, C. R. Cantrell, M. C. Sokol, E. Chiao, and J. M. Gdovin, "Impact of antidepressant drug adherence on comorbid medication use and resource utilization.," *Arch. Intern. Med.*, vol. 165, no. 21, pp. 2497–503, Nov. 2005.

[11] L. von Knorring, A.-C. Akerblad, F. Bengtsson, A. Carlsson, and L. Ekselius, "Cost of depression: effect of adherence and treatment response.," *Eur. Psychiatry*, vol. 21, no. 6, pp. 349–54, Sep. 2006.

[12] R. Blundell and S. Bond, "Initial conditions and moment restrictions in dynamic panel data models," *J. Econom.*, vol. 87, no. 1, pp. 115–143, Nov. 1998.

[13] J. Garber, G. N. Clarke, V. R. Weersing, W. R. Beardslee, D. A. Brent, T. R. G. Gladstone, L. L. DeBar, F. L. Lynch, E. D'Angelo, S. D. Hollon, W. Shamseddeen, and S. Iyengar, "Prevention of depression in at-risk adolescents: a randomized controlled trial.," *JAMA*, vol. 301, no. 21, pp. 2215–24, Jun. 2009.

Chapter 2 – The impact of economic stress on antidepressant medication persistence across industry-specific business cycles

Abstract

This paper examines the effect of economic stress on antidepressant (AD) medication persistence among employed adults, and separately their spouses, who begin a new course of AD therapy. Data spanning calendar years 2000-2010 come from a large, integrated medical care organization located in the Pacific Northwest and from Bureau of Labor Statistics. We apply dynamic panel models to control multiple sources of confounding. We find a significant inverse relationship between economic stress and AD persistence. The effect is most pronounced during periods of negative economic shocks. Subgroup analyses reveal that the effect only appears among mid-career employees. We find no evidence of spousal spillover effects and no evidence of differential effects by gender or union coverage.

Keywords: Persistence; Adherence; Pharmacotherapy; Economic stress; Dynamic panel data; Antidepressant

JEL classification:

I18

J64

Introduction

The status of the economy has been a significant area of concern for US households over the late 2000's and early 2010's as unemployment rose to levels not seen in decades and chaotic markets substantially eroded household wealth (Angus & Deaton, 2011). US voters named the weak economy as the most important issue in the 2008 and 2012 US presidential and congressional elections (Fair, 2012). While the effects of the business cycle are relatively transparent to individuals' employment prospects, income, and wealth, it is less clear how changes in the macroeconomy may adversely impact peoples' health and health-related behaviors. Extensive research has found countercyclical correlations between indicators of macroeconomic growth and physical-health (Catalano, 1991, 2009; Perrewé et al., 2012). Prevailing theories posit that detrimental health behaviors, such as excessive drinking or smoking, become more expensive during economic contractions, and people react as would be expected by economic theory (Catalano, 2009)—that is, they engage in lower levels of unhealthy behaviors. In contrast, several research studies have demonstrated a consistent procyclical association between macroeconomic indicators and mental health (Brand et al., 2008; Mandal & Roe, 2008; Ruhm, 2005; Tefft, 2011) How macroeconomic change affects patient health and health-related behavior is not well understood.

In our study, we explore the possibility that some of the procyclical association found between mental health morbidity and macroeconomic change could be attributable to interference with mental-health related treatments. We believe this inference manifests through changing levels of economic stress (as proxied by unemployment) from contracting industries and increasing economic uncertainty. Specifically, we examine whether monthly unemployment rates by industry affect persistence with antidepressant (AD) medication therapy among

employed adults who began a new course of AD therapy and were concurrently diagnosed with a mood disorder. While we are unable to test all steps along the full causal chain between unemployment, economic stress, changes in AD persistence, and mental health morbidity, we are able to viably test whether industry-level unemployment rates affect AD persistence. Our conceptual model describes the mechanism from unemployment to economic stress. And the efficacy and effectiveness of AD therapy for the treatment of mental health morbidity has been shown in multiple clinical trials (Keller, 2001; Mundt, 2001), providing a plausible pathway from economic stress to mental health morbidity.

Examining a portion of the pathway from business cycle variation to mental health morbidity in this paper provides an important contribution to the literature for several reasons. First, it utilizes rich micro data that allow for consideration of industry-specific variation in unemployment. Second, it models the effect of economic stress, as proxied by unemployment, on AD persistence, a health-related behavior, controlling for multiple sources of bias. This will help enrich knowledge about the effects of business cycle changes on health behaviors at the individual level. And third, findings from this study have clear policy implications. Groups of employees affected by higher levels of economic stress may benefit from novel interventions or existing resources designed to manage stress, particularly resulting from contractions in the business cycle.

The economic-stress-hypothesis was originally developed to explain the link between short term community economic change and illness and injury (Catalano et al., 1983). The research considered multiple hypotheses about the link between the macroeconomy and health, considering both the type of economic change and the type of job and financial events that were affected. Empirical analyses supported the hypothesis that economic contraction associated with

an increase in the incidence of undesirable job and financial events and an increase in the incidence of illness and injury (Catalano et al., 1983). We extend this hypothesis to argue that increases in economic stress related to undesirable job and financial events may interfere with patients' persistence to AD treatment. This papers solely focuses on the effects of economic stress among people who remain employed during seven months following an incident AD dispense. We choose to focus on employed individuals because of their continued access to AD medications[1], whereas job loss likely introduces significant barriers to medication acquisition.

We find that higher industry-specific unemployment rates, our proxy for economic stress, are significantly associated with lower AD persistence among employed adult medical members of a large MCO after controlling for patient-level effects. In addition, we find a small but significant effect of unemployment on AD persistence after controlling for time-varying confounding through application of Arellano-Bond dynamic panel models. The effect is most pronounced during periods of negative economic shocks. Subgroup analyses reveal that effect is only present among mid-career patients. In addition, we find evidence that AD persistence improves during periods of mild to moderate economic growth. We find no evidence of a spillover effect to spouses nor do we detect differential effects by gender or by the level union coverage within an industry. Results are robust to a variety to sensitivity analyses.

The remainder of the paper is organized as follows. Section 2 discusses background and prior research related to health and the macroeconomy. Section 3 describes data sources and presents sample characteristics. Section 4 defines the econometric methodology. Section 5 summarizes analytic results and presents robustness tests. Section 6 shows results from

[1] Firms may respond to contracting business cycles by reducing employer-sponsored health benefits. We control for this time-varying heterogeneity in our analytic models. However, firms' response to changes in the business cycle is a legitimate channel of economic stress.

subgroup analyses, and section 7 discusses interpretation of estimated effects. Section 8 concludes the paper.

Background and prior research

Conceptual Framework

Patient engagement with recommended medical care treatments is a major factor influencing heterogeneity of targeted health outcomes (Vermeire et al., 2001). Multiple factors, whether patient-specific or external, affect whether patients engage with prescribed treatment recommendations, and at what level. This is true across most types of treatment options, including behavioral health and pharmacotherapy. Overall patient compliance with prescribed pharmacotherapy is typically evaluated through measures of medication adherence and persistence. While similar, there are important distinctions between the two. Adherence has generally replaced the global term compliance as the overall descriptor of patient behavior around adherence to care because it better describes the role of patient-engagement in the treatment process (Cramer et al., 2008) Measures of medication adherence, however, quantify medication in possession over a fixed interval (Cramer et al., 2008) Measures of persistence, on the other hand, incorporate timing of refills to estimate the overall exposure of a medication as well as the continuity of its dose (Cramer et al., 2008). The purpose of this study is to evaluate the effects of economic stress, as proxied with industry-specific unemployment rates, on AD *persistence*. We also examine the effect of economic stress on *adherence* as part of our robustness tests.

The Andersen conceptual model of health services use, along with the Gelberg-Andersen behavioral model for vulnerable populations, provide the theoretical foundation for our study and

help clarify our analytic models (Andersen, 1995; Gelberg et al., 2000). These conceptual models describe health services use as being predicted by predisposing, enabling, and need characteristics. Predisposing characteristics include factors such as marital status and social structure; enabling factors include household income and health insurance; and need factors include the severity of illness and comorbidities (Andersen, 1995). We are interested in explicitly modeling the effects of changes to employment-related predisposing factors on changes to personal health practices, as quantified through AD persistence. Holding constant patient-level and time-varying confounding, we hypothesize the burden of stress related to a contracting business cycle interferes with optimal AD treatment, consistent with the economic stress hypothesis (Catalano et al., 1983).

The Gelberg-Andersen behavioral model for vulnerable populations provides further detail on how this mechanism behaves. While employed adults are not considered vulnerable in general, the model highlights factors that may become relevant during economic contractions within an industry. In addition to increased uncertainty about continued employment and increased work burden to employees who remain employed following layoffs, studies have found that social networks deteriorate (Perrewé et al., 2012) and task-related bullying, which is a form of work-place bullying that takes the form of being assigned unmanageable workloads or given unobtainable timelines, increases during economic contractions (Skogstad et al., 2007). Families may find also themselves more likely to need social services during contracting phases of the business cycle, which in turn are also more likely to be underfunded during difficult economic times. There may also be anticipatory stress among those individuals who remain employed following lay-offs, wondering if they are targeted for future rounds of downsizing.

These changes stress the psychological resources of individuals on AD therapy, and we posit interfere with AD persistence.

Prior research tested the economic stress hypothesis and showed that economic contraction affects the incidence of undesirable economic and financial events, which in turn lead to illness and injury (Catalano et al., 1983). We expand this hypothesis to include the effect of undesirable events to personal health practices, specifically AD persistence. We use industry-specific unemployment rates to proxy employees' level of economic stress. Quantifying the effect of economic stress on AD persistence is not a precise process. Our estimates provide ranges for the effect of economic stress on AD persistence. Our models, discussed in Section 4, hold constant time-variant and –invariant heterogeneity. This process controls away stress channels from firms' responses to a contracting business cycle, such as reductions in benefit packages, mandatory reductions in work hours, and increased management oversight to reduce shirking. Therefore, our estimates provide a bound around the true effect of economic stress on AD persistence.

Prior empirical evidence

Many studies have examined the role of the macroeconomy on both physical- and mental-health over the past several decades (Catalano, 1991, 2009; Perrewé et al., 2012; Ruhm, 2005; Tefft, 2011). While findings have been mixed, several consistent themes have emerged from previous research. Job loss is associated with increased incidence of both mental and physical disorders, however, temporal patterns of which precedes which are not clear (R Catalano, 2009). Evidence typically shows job loss precedes mental-health disorders, for example, those who lose their jobs are more likely to experience a psychiatric break; but the

temporal order between physical health and job loss has been shown to go both ways (Catalano, 2009).

Among those who remain employed during economic contractions, correlations between physical and mental health and unemployment move in opposite directions, with physical health following a countercyclical relationship and mental health following a procyclical relationship (Ruhm, 2005). Researchers hypothesize that physical health improves as the macroeconomy worsens for a variety of reasons. During a contraction, unhealthy behaviors, such as excessive drinking or smoking, become more expensive, and people consume less of those goods (Ruhm, 2005). In addition, downward pressure on wages and employment prospects reduce the opportunity cost of healthy activities, such as exercise, and people undertake more of those activities because of the reduced cost (Ruhm, 2005).

Increased rates and severity of mental health disorders during economic contractions are thought to be caused by multiple factors as well. Studies have shown decreased tolerance for people demonstrating severe symptoms of mental health disorders, with non-cooperative psychological confinement (e.g., involuntary psychiatric hospitalization) increasing during economic downturns (Catalano, 1991). In addition, studies have shown psychological treatment is deferred due to cost or potential stigma, leading to the eventual onset of acute symptoms (Charles & Decicca, 2008). Employees have real or perceived incentives to reduce medical and pharmacy claims during tightening labor markets to avoid targeted layoffs during downsizing campaigns (Charles & Decicca, 2008).

While there are no studies we know of that examine psychotropic medication adherence among employed individuals during economic contractions, there are several studies that found associations between unemployment and medication adherence for hypertensive agents (Bone et

al., 2000; Saounatsou et al., 2001). Similarly, we not aware of any studies that have applied the economic stress hypothesis in the context of medication adherence. Other researchers have built on the seminal work by Catalano and applied economic stress hypothesis in the context of accumulation of economic stress over the life cycle (Lindström, et al., 2012). Our study provides a novel contribution to the existing literature by showing a clear effect of industry-level unemployment on AD persistence, which is most pronounced during economic shocks and for mid-career employees. We argue this effect manifests through changing levels of economic stress that follow the business cycle.

Data and sample characteristics

Data

Data used in this study is comprised of patient-level measures of AD medication use, demographics, and employment status and industry-level macroeconomic indicators. Patient data spans 2000 through 2010, inclusive and comes from Kaiser Permanente Northwest's (KPNW) electronic medical record (EMR). KPNW is an integrated, group-model, not-for-profit medical care organization (MCO) serving more than 470,000 members in northwest Oregon and southwest Washington with a single hospital and 26 outpatient medical offices during the study time period. Every health plan member has a unique, permanent health record number. Every contact an individual makes with the medical care system and all referrals to outside services are recorded in a comprehensive EMR under the patient's health record number. This EMR system stores information, such as patient demographics, medical history, and visit summaries.

Inclusion criteria for this study includes being working age at study entry (18-64); receiving health plan benefits through an employer; receiving an indent dispense of AD

medication associated with a mood disorder; and having continuous health plan enrollment with medication benefits for 12 months prior to and 7 months following an incident AD medication dispense, implying continued employment during the follow-up period. We define an incident AD dispense as having no EMR record of an AD medication dispenses in the previous 12 months. Exclusion criteria includes patient registry in a health plan database opting out of inclusion in data only research studies and switching of employment industry during the 7 months after an incident AD dispense. Application of these criteria result in a primary analysis sample of 21,365 patients in our analyses of employees, and 10,498 patients in our analyses of potential spillover effects to spouses.

Patients enter into the panel at the time of an incident AD medication dispense and are followed for at least seven consecutive months after study entry. At the month of study entry, we collect patient data on demographics, industry of employment, and type of medical plan membership (e.g., primary subscriber, spouse, dependent). Patients' employers are categorized into industry classifications using numeric codes from the North American Industry Classification System (NAICS). Follow-up data on medication use is indexed to the date of the incident dispense and aggregated in monthly periods.

Measures of economic stress

We proxy economic stress using monthly unemployment rates drawn from the Bureau of Labor Statistics (BLS, 2013). The BLS of the U.S. Department of Labor is the principal Federal agency responsible for measuring labor market activity, working conditions, and price changes in the economy and disseminates essential economic information to the public domain. Measures of unemployment from the BLS have the advantage of being industry specific. We use NAICS

codes to match unemployment rates to patients' industry of employment and index to their incident AD dispense. For example, a patient who is employed in manufacturing and receives their incident AD dispense in October 2008 will be matched to the manufacturing unemployment rate in October 2008 during period one, to the unemployment rate for November 2008 for period two, and so forth.

We also select and additional regional, employment metric from the Federal Reserve Economic Data (FRED, 2011) data series as a robustness check. The FRED is an online database consisting of more than 61,000 economic data time series from 49 national, international, public, and private sources and was created and maintained by Research Department at the Federal Reserve Bank of St. Louis. The selected measure of macroeconomic change from the FRED is the monthly number of individuals employed within an industry in Oregon. While we are unable to collect an appropriate denominator, this measure provides an opportunity to establish consistency of results. We log transform all measures used to proxy economic stress to ease interpretation.

Measures of AD persistence

We use monthly Estimated Level of Persistence with Therapy (ELPT) as our dependent variable. ELPT provides an estimate of continuous medication persistence and is calculated as the number of days until exhausting one's supply of medication, allowing for gaps in medication supply. For example, a person who accumulates 45 days' supply of medication prior to discontinuing is considered persistent for the entire first month (30 of 30 days) and half of the second month (15 of 30 days) at a minimum. The maximum allowable gap used in the calculation further extends our measure of persistence. Applying a maximum gap of 30 days in

the previous example results in full persistence in the first and second months but half in the third month. All monthly measures of persistence range from 0 to 30 days. We chose persistence as our dependent variable because of the importance of continuity in AD treatment (Cantrell et al., 2006). We calculate ELPT using a maximum cumulative gap of 30-days. We explore the effect of our choice by running sensitivity analyses using a more conservative gap of 15-days and a less conservative gap of 60-days. We also examine the effect of unemployment on medication adherence as a robustness test. We measure AD adherence using Proportion of Days covered (PDC), the number of days of medication in possession divided by the number of days under observation (Cantrell, et al., 2006). The principal difference between medication persistence and adherence is that persistence measures how well a patient continuously complies with treatment whereas adherence does not explicitly include consideration for continuity.

Sample characteristics

Table 2-1 explains the demographic characteristics at study entry of analytic groups comprised of primary subscribers and spouses, which are mutually exclusive. The average (SD) age for primary subscribers is 42.9 (11.0) and 43.3 (10.6) for spouses. Consistent with epidemiologic studies of depression and AD use, the samples are predominantly female, 60.3% of primary subscribers and 73.2% of spouses. Based on EMR records, 6.8% of the primary subscriber sample is from a racial minority and 4.2% is Hispanic, and 6.0% of the spouse sample is from a racial minority and 3.7% is Hispanic.

Table 2-2 shows the descriptive statistics of monthly unemployment rates by major industry categories. Marked heterogeneity exists with average unemployment ranging from 2.7% for local government to 10.3% for unemployment for real estate and construction. The

extremes tails reside in the same industries. Local government shows the lowest minimum level of unemployment, 1.3%, whereas real estate and construction show the maximum monthly unemployment. Figure 2-1 shows the average and range of month-to-month unemployment by calendar month over the study period. Clearly, not all industries had similar experiences during national expansions and contractions.

Table 2-3 shows medication persistence and adherence for primary subscribers and spouses. The column labeled "30-day" under "Estimated Level of Persistence with Therapy" parallels the outcome of principal interest in the remaining analyses. Other measures of persistence and adherence are included for interested readers, and are analyzed as part of robustness tests. The measures of persistence from Table 2-3 are the percentage of people who have not discontinued within a specific month. For example, a person persistent for only 90 days is included in the numerator of the first 3 months. The measure of adherence in Table 2-3 is the proportion of days covered in a specific month regardless of previous gaps in medication coverage. For example, a person with dispenses of 30 days' supply at the beginning of months 1 and 6 will have values of 1 for those months and 0 for all other months. Consistent with other studies, about one-third to half of the sample remain persistent with AD treatment after seven months. Clearly, the operational choice of how to define persistence in terms allowable gaps has a non-trivial impact on measurement patient persistence. The decay in persistence (and adherence) is remarkably similar between the primary subscriber and spouses.

Empirical approach

Overview

The purpose of this paper is to model the effect of economic stress on AD medication persistence among employed adults who begin an incident course of AD medication treatment. We use monthly industry-specific unemployment rates as a proxy for economic stress and apply our empirical models to patient-level data from a large integrated MCO. Estimating the true effect of economic stress on AD medication persistence requires control of multiple sources of bias. Time-invariant patient characteristics, such as gender and educational attainment, will likely lead to omitted variable bias, favoring models that include patient fixed effects.

Time-varying factors that influence AD medication persistence and correlate with unemployment introduce potential for further confounding. For example, expected future income decreases during economic contractions as does average household size. Firms' responses to changes in the business cycle also introduce a potential source of bias. Contracting business cycles may incent firms to reduced employee benefit packages, institute mandatory reduction in work hours, or increase management oversight to reduce employee shirking.

We undertake a stepped analytic approach to examine the relationship between unemployment and AD medication persistence and to better understand the influence of multiple sources of bias. As the first stage of our analysis**,** we begin by regressing AD medication persistence on log-transformed unemployment with a naïve OLS model, which does not account for patient-specific or time-varying confounding and takes the following form:

$$Y_{i,t} = \beta_0 + \beta_1 (\log \text{Unemp}_{j,t}) + \eta_i + \delta_t + e_{i,t} \qquad (1)$$

for $i = 1, \ldots N$; $t = 1, \ldots T$, where i is the patient and t is the time indicator. t=1 represents the month during which patient i had their incident AD medication dispense. $Y_{i,t}$ is the monthly level of AD medication persistence for patient i during month t. Log $\text{Unemp}_{i,t}$ is the

natural log of industry-specific unemployment rates for patient *i* during month *t*. We log transform unemployment rates to ease interpretation. η_i and δ_t are time- and patient-specific effects, respectively; and $e_{i,t}$ is a disturbance term.

The model specified in Eq. (1) does not adjust for time-invariant patient characteristics or time-varying confounding. In order to remove the influence of time-invariant patient characteristics, we first difference Eq. (1), which can be written as

$$\Delta Y_{i,t} = \beta_1 (\Delta \log \text{Unemp}_{j,t}) + \Delta\delta_t + \Delta e_{i,t} \quad (2)$$

for $i = 1, \ldots N$; $t = 2, \ldots T$, where Δ is the difference operator ($\Delta Y_{i,t} = Y_{i,t} - Y_{i,t-1}$, etc.). The remaining notation holds from above. First differencing removes the confounding effect of time-invariant patient characteristics but does not affect time-varying biases.

Next, we turn to the A-B dynamic panel estimator to control time-varying confounding (Arellano & Bond, 1991; Blundell & Bond, 2000). The A-B framework relies on lagged values of variables specified in the models as instruments and estimates a system of moment equations using Generalized Method of Moments (GMM). The regression equations estimated in the system GMM are as follows:

$$Y_{i,t} = \beta_1 (\log \text{Unemp}_{j,t}) + \beta_2 (Y_{i,t-1}) + \eta_i + \delta_t + e_{i,t} \quad (3)$$

$$\Delta Y_{i,t} = \beta_3 (\Delta \log \text{Unemp}_{j,t}) + \beta_4 (\Delta Y_{i,t-1}) + \Delta\delta_t + \Delta e_{i,t} \quad (4)$$

Prior to discussing the process of obtaining moment conditions, it is worth noting the impact of inclusion of a one-period lag of the dependent variable as a regressor. The inclusion of

$\Delta Y_{i,t-1}$ as an explanatory variable in these models allows for a dynamic process between past and current realizations of the dependent variable. While we believe this dynamic process likely exists in our data, we did not include it in previous equations as part of our stepped analysis plan because it would produce inconsistent estimates in the first-differenced model (Eq. [2]). Specifically, the error term, $\Delta e_{i,t} = \Delta e_{i,t} - \Delta e_{i,t-1}$, would be correlated with the lagged dependent variable, $\Delta Y_{i,t-1} = \Delta Y_{i,t-1} - \Delta Y_{i,t-2}$. In order to address this problem, and to remove time-varying biases, the A-B estimator utilizes lagged values of the dependent variable and other explanatory values as instruments. Lags are chosen far enough back in periods to avoid error correlation, making them valid instruments.

We estimate the A-B estimator as a fully augmented system GMM as defined in Eqs. 3 and 4. An alternative would be to estimate just Eq. 4, often referred to as first difference or difference GMM (Arellano & Bond, 1991). However, the system GMM specification has been shown to provide substantially more accurate estimates when the outcome is persistent by utilizing the additional moment conditions in the levels equation (Blundell & Bond, 2000). Our initial set of moment conditions come from both the levels and difference equations. Taking the standard assumption that $E[X_{i,t}e_{it}] = 0$ for $t = 2, \ldots, T$ results in the following initial moment conditions:

$$E[X_{i,t-s}\Delta e_{i,t}] \text{ where } X_{i,t} = (\log \text{unemp}_{i,t}; Y_{i,t}) \qquad (5)$$

for $s = 2, \ldots S$, where s is the lag operator. Only using values of $s \geq 2$ allows the use of suitably lagged levels of the variables as instruments, after the equation has been first-differenced to eliminate the patient-specific effects (Arellano & Bond, 1991). These moments

could be used to estimate the difference GMM as described above. However, the parameter estimates likely have poor finite sample properties if the lagged levels are not strongly correlated with current first differences (Blundell & Bond, 2000). We are able address this potential weakness by adding further restrictions from the levels equation. Assuming log unemployment and unobserved patient fixed effects are uncorrelated, $E[X_{i,t}\eta_i] = 0$, and that the initial conditions satisfy $E[\Delta Y_{i,2}\eta_i] = 0$ results in the following initial moment conditions:

$$E[\Delta X_{i,t-s}(\eta_i + e_{i,t})] \text{ where } X_{i,t} = (\log \text{unemp}_{i,t};\ Y_{i,t}) \qquad (6)$$

for $s = 1$. We are now able to use suitably lagged first differences of the variables as instruments for the equation in levels (Blundell & Bond, 2000). Both sets of moments are used in the GMM estimation of the system of system of equations defined above. The Stata command xtabond2 is used in A-B types of analyses (Roodman, 2009).

The identification assumptions underlying the system GMM are strong (Mishra & Newhouse, 2009). In addition, our panel is well suited for the underlying asymptotic properties to hold. We have a large number and a relatively short time dimension. Our choice of methods control for multiple sources of bias, in important issue rarely addressed in earlier studies. Given the lack of convincing external instruments, the choice of using system GMM estimators likely produces the most accurate estimates with available data (Mishra & Newhouse, 2009).

Assuming appropriate model specification, the A-B model can provide an unbiased estimate of the effect of economic stress (as proxied by unemployment) on AD medication persistence holding constant time-variant and invariant confounding factors. However, as part of the control process, an important channel of economic stress is controlled away. Specifically,

firms' reactions to changes in the business cycle likely have influence on employees' economic stress. For example, reduction in employer-sponsored benefits (whether real or perceived) likely induce higher levels of economic stress. We do not believe our model estimates provide true point estimates of the effect of economic stress on AD medication persistence, but rather provide bounds around the true effects. The true effect of economic stress lays somewhere between the parameter estimates from Eq. (2) and Eq. (3).

Nonlinear effects

In order to explore nonlinear effects of economic stress on AD medication persistence, we replace $Unemp_{j,t}$ in Eq. (3) with set of linear spline variables. We construct the set of linear spline levels in two ways. First, we rely on the empirical distribution of unemployment rates by industry to select knots based on quartile values. Second, we use theoretical guidance to select meaningful location of knots (Stock & Watson, 2001). Previous research on the effect of economic shocks defines a shock as greater than or equal to one standard deviation from the mean of unemployment rates. We therefore select knots at the average minus one standard deviation, average, and average plus one standard deviation of unemployment rates. The empirically and theoretically derived model specifications are estimated separately. Both methods take the following form:

$$\Delta Y_{i,t} = \beta_1 (\Delta S1_{i,t}) + \beta_2 (\Delta S2_{i,t}) + \beta_3 (\Delta S3_{i,t}) + \beta_4 (\Delta S4_{i,t}) + \beta_5 (\Delta Y_{i,t-1}) + \Delta\delta_t + \Delta e_{i,t} \quad (6)$$

The variables S_1-S_4 represent the four splines. One would expect differences in the magnitude, direction, or statistical significance between β_1, β_2, β_3, and β_4 if the effects are not linear across the spectrum of unemployment rates.

Spillover effects

The effects of economic stress could easily spillover to other members of a household. We apply our modelling framework to data on patients who are designated as spousal beneficiaries to explore potential spillover effects of economic stress on spouses' AD persistence. Notation and model specification carry over from Section 4.1 except for one important distinction -- models examining spillover effects include industry-specific unemployment rates for the household's primary subscriber rather than the patient under study. To illustrate this distinction, we rewrite Eq. (3) from the spousal perspective.

$$\Delta Y_{i,t} = \beta_1 (\Delta \log \text{Unemp}_{i,t}) + \beta_2 (\Delta Y_{i,t-1}) + \Delta\delta_t + \Delta e_{i,t} \qquad (7)$$

for $i = 1, \ldots N$; $t = 1, \ldots T$, where i is the patient under study, and t is the time indicator. In this model $\Delta \log \text{Unemp}_{i,t}$ measure unemployment in the primary subscriber's industry of employment, not the unemployment rate for patient i.

Results

We present results in the following order. First, we report empirical results from our stepped analytic plan for primary subscribers. Estimates come from OLS, fixed effects, and A-B system GMM regression models. We also report estimates of non-linear effects of

unemployment on AD persistence among primary subscribers. Second, we test for spillover effects of unemployment to spouses' AD persistence using the same framework. Third and finally, we subject our findings to a series of robustness tests to examine the consistency of our estimates. Section 5 presents subgroups analyses.

Primary subscriber

Table 2-4 shows parameter estimates and model statistics from OLS, patient fixed effects, and system GMM regression models using data on primary subscribers. The estimated coefficient is consistently negative and statistically significant across all three models, suggesting an inverse relationship between economic stress and AD persistence. That is, as economic stress increases (ergo, unemployment increases) AD persistence decreases. The magnitude of the log unemployment estimates is highest of the three estimates in the uncontrolled, naïve OLS regression. After removing patient-level fixed effects, the estimates decreases by about a third, suggesting substantial confounding from time-invariant patient-characteristics. The change in the parameter estimate is small, only about 3%, after controlling for time-varying confounding and the dynamic process in AD persistence. This is not particularly surprising because patients are only observed for seven months. This is a short time frame during which firms could respond to a contracting business cycle or patients' health change markedly. Regardless, our estimates show a clear effect that increases in economic stress interferes with AD persistence.

Table 2-5 shows the A-B system GMM estimates from our analyses of possible non-linear effects of economic stress on AD persistence. The left-hand column of results show estimates from a model using empirically derived linear spline variables, and the right-hand column presents results from a model using theoretically derived linear spline variables as

discussed previously in section 4.2. We do not find evidence of non-linear effects using empirically derived spline variables. We do find that log unemployment has nearly a four times larger effect in periods of economic shock (greater than one standard deviation from the mean) than in our previous linear model. Specifically, we find the estimated effect of log unemployment to be -2.15 in the spline depicting economic shock in Table 2-5 compared to the estimated linear effect of log unemployment, -0.55, in the linear model from Table 2-4.
The estimates presented in the right-hand column follow an intuitive pattern; with non-significant positive results in periods of lower unemployment, a non-significant but negative result in periods of higher unemployment, and a significant negative result in periods of high unemployment considered to be an economic shock. There appears to be no effect of economic stress on AD persistence during periods of economic growth. While non-significant, the direction of the estimate changes to negative in periods of mild to moderate economic decline. And highly significant effect is shown during negative economic shocks. The results provide further empirical evidence of the inverse relationship between economic stress on AD persistence, and that AD persistence is most disrupted during periods of rapid economic decline.

Spouses

Table 2-6 shows parameter estimates and model statistics from OLS, patient fixed effects, and system GMM regression models using data on spouses. In these models we test the effect of economic stress, as its manifests as a spillover from unemployment in the primary subscribers' industry of employment to the spouse, on AD persistence for the spouse. We found neither statically significant spillover associations nor effects between economic stress and AD persistence. Despite no empirical evidence of a linear relationship, we proceed with an analysis of potential nonlinear effect because the spillover effect may appear during periods of economic

shock similar to our findings in section 4.1. Table 2-7 shows the A-B system GMM models of possible non-linear effects. We find no evidence of non-linear spillover effects. However, the estimates follow a similar pattern to those found among primary subscribers.

Robustness checks

In order to evaluate the robustness of our findings, we conduct three separate sensitivity analyses using data on primary subscribers. First, we examine if persistence to other, non-mental health medications follow similar patterns. Specifically, we analyze antihypertensives, the largest category of non-mental health medications dispense in our samples. Second, we use the seasonally adjusted number of individuals employed within an industry as an alternate proxy of economic stress as an explanatory variable in our models. Third and finally, we model multiple constructs of patient compliance with prescribed AD therapy, modelling separately both measures of medication persistence and adherence.

Other medications

An important consideration is whether or not the effects we find are being driven by people who enter our cohort during contracting phases of the businesses and are suffering from lesser, or somehow different, forms of mental or physical illnesses. One could argue that people who begin a new course of AD treatment during a recessionary period are different than a typical case requiring AD treatment during stable economic times and are less committed to persisting with treatment. While we do not believe this to be the case, we empirically test the possibility by examining persistence to non-mental health medications, specifically antihypertensives, within our sample of primary subscribers. We choose antihypertensives because it is the largest class of

medications in our sample for which some level of continued persistence is recommended (Staessen et al., 1997). If this process was influencing our results, we would expect to see no effect of unemployment on non-mental health medication persistence.

A total of 4,999 (23.4%) within our sample filled at least one prescription for an antihypertensive following entry into our panel and had at least seven months of continuous medical plan coverage subsequently. It is worth noting that this sample is a combination of incident and prevalent users, and we are unable to adjust for the duration of prior pharmacotherapy. We found marginal evidence of a similar effect (β=-1.129, p=.061) in a well specified model[2]. Given the significant reduction in sample size, we find this result reassuring despite not reaching a more conservative level of statistical significance (i.e., p<.05). The consistency in magnitude and direction of the estimate provide support that our findings are not being driven by a bias introduced from our panel selection process.

Other definitions of Unemployment

We use an alternate proxy for economic stress by modelling the effect of employment changes on AD persistence using data from the FRED. The explanatory variable in this model is the monthly, log-transformed number employees in an industry in the state of Oregon. We find a significant effect (β=1.601, p=.011) consistent with earlier findings. This model uses a measure of *employment* rather than *unemployment*, so the expected direction of the estimate is reversed. A positive finding here corresponds to a negative finding previously. Our model in this robustness test did not meet specification criteria[3], so we are hesitant to draw much conclusion

[2] Sargan test = 28.01, p = 0.109; AR(2) test = -1.63, p=0.102.
[3] Sargan test = 53.24, p = 0.001; AR(2) test =-2.96, p=0.003.

for these findings. However, estimates did not provide any contrary indication that our choice of proxies for economic stress was providing spurious results.

Variations in definition of persistence

Our principal measure of persistence with AD medication treatment is ELPT, allowing for a cumulative maximum gap in coverage of 30 days. As sensitivity analyses, we construct two alternate measures of ELPT allowing for a more conservative, 15 days (ELPT-15), and less conservative, 60 days (ELPT-60), maximum allowable gap. We find similar results in the A-B system GMM models using these alternate measures of AD persistence as dependent variables. The estimated effect of economic stress on ELPT-15 is marginally significant at the 10% level (β =-0.339, p=0.069) in a well specified model[4]. The estimated effect of economic stress on ELPT-60 is also marginally significant at the 10% level (β=-0.286, p=0.090). While the Sargan test indicates good specification (Chi^2=10.53, p=0.958), the second-order test of serial correlation calls the specification into question (z=2.59, p=.010).

While not a measure of medication persistence, we also modeled the effect of economic stress on PDC. We do not find any effect of economic stress on PDC (β =-0.009, p=0.329). However, our model is very poorly specified[5]. Results using various definitions of AD persistence (or adherence) as the dependent variable show estimates consistent to those found in section 4.1. While the estimates do not reach statistical significance, the directionality and magnitude of the estimates are all similar for our measures. Specification tests show poor model fit with PDC and questionable model fit with ELPT-60.

[4] Sargan test = 10.26, p = 0.963; AR(2) test = -1.33, p=0.183.
[5] Sargan test = 124.83, p = <0.001; AR(2) test = 4.40, p=<0.001.

Subgroup analyses

We explore whether economic stress differentially affects subgroups of our sample based on our conceptual framework. We identify three factors that may influence how people react to stress or how much economic stress group members likely endure. The first characteristic we consider is gender. Research suggests men are less likely to engage in or prioritize activities to manage their stress (citation from psych group). In addition, men are less likely to report that stress affects their health (citation from psycho group). The predicted direction of a gender effect is unclear. Differential resilience to stress or management techniques for stress may play important roles in how economic stress impacts AD persistence.

The second factor we consider is age. Age is chosen because of its correlation with social and economic changes over the life course (citation from Dave's class). On average, older employees likely have higher work and family responsibilities, as well as, are more likely to have accumulated greater wealth and psychological resources that may help increase resilience during difficult economic times. However, older workers may be more susceptible to economic stress because of higher search costs for new employment or because of proximity to retirement. We define age subgroups as early- (18-39), mid- (40-54), and late-career (55-64) to capture nonlinear effects over the age distribution. The final industry-specific characteristic we consider is level of union coverage. High levels of union coverage within an industry may act as an insulator between unemployment (or other measures of the business cycle) and economic stress.

We test the interaction between a dichotomous or categorical variable of group membership (e.g., female vs. male) and logged unemployment rates to guide whether to proceed with subgroup analyses. Statistical significance levels of 5% or lower are used as a threshold to warrant moving forward with subgroup analyses. We find no empirical evidence of differential

effects of unemployment on AD persistence by gender (p-value = .410) or by level of union coverage (p-value = .694). We do find a significant interaction by age category (p-value = .013). Table 2-8 shows linear effects of economic stress by age group.

While the direction of the estimated effects is consistent across age groups, mid-career employees are the only group showing a statistically significant effect (p=.001). The magnitude of the estimated effect is more than two times larger than the overall effect estimated in section 4.1. Our results show that mid-career employees are most vulnerable to the effects of economic stress on AD persistence, and there appears to be no affect among early- and late-career employees.

To better understand our results, we further examine the effects across age groups by estimating nonlinear effects by age group, presented in Table 2-9. Results are consistent across models of linear and non-linear effects – the effect of economic stress only appears in mid-career employees. No effect, whether linear or not, emerges among early- and late-career employees. Interestingly, while the magnitude of the effect in periods of negative economic shock is slightly larger than the full sample findings (about 15% larger) for mid-career employees, we find evidence in this model of a statistically significant positive effect on AD persistence during periods of decreasing unemployment. During periods of mild to moderate economic growth, as measured by decreasing unemployment, likely resulting in decreasing economic stress, AD persistence increases. We see this result in models utilizing both empirically- and theoretically-constructed linear splines.

Interpretation of effect magnitude

The significant coefficient estimates of the effect of economic stress on AD persistence from Sections 4 and 5 appear small at first pass. A 20% increase in monthly unemployment leads to a 0.10 (0.3%) and 0.22 (0.7%) day reduction in persistence overall and for mid-career employees, respectively. While these percentages may seem trivial, it is important to remember the effects accumulate month to month and that there is significant monthly variation in industry-level unemployment. In our sample of primary subscribers, unemployment increases on average by 7.3% from study entry to exit in our sample, with a standard deviation of 26.3%. The largest decrease in unemployment from entry to exit in our panel is 55.9%, and the largest increase is 177.6%. In addition, we find the effect of unemployment to be much larger in periods of negative economic shock. Among mid-career aged employees, we find a supportive effect on AD persistence during periods of mild to moderate economic growth. The findings from this subgroup analysis roughly translate into a 1.5% reduction in AD persistence in response to a 20% increase in unemployment during a negative economic shock and a 1.1% increase in AD persistence in response to a 20% decrease in unemployment during a period of economic growth. It is also worth noting, as discussed previously, our estimates are the lower bound for the effect of economic stress on AD persistence. Time-varying factors that influence economic stress (e.g., firms reducing benefit packages) are held constant.

Targeting patient behavior around medication compliance is a viable way to improve individuals' and public health, but affecting compliance behavior is complex and difficult. Experts have concluded that effective interventions to improve adherence to treatment for chronic illness, such as depression, could have a broader impact on health outcomes than any specific improvement in medical treatment (Haynes et al., 2005; Haynes et al., 2008). However, general consensus is that efforts to improve adherence, such as patient education, mailed

materials, motivational enhancement, and psychotherapy, can only modestly improve patient adherence (Gilbody et al., 2003; Trivedi et al., 2007).

The magnitude of our findings are not too far from treatment effects found in controlled trials designed to promote patient compliance with pharmacotherapy. For example, automated reminder phone calls resulted in approximately a 2% improvement in medication adherence for patients who were prescribed continuous beta-blocker treatment (Vollmer, 2011) . However, in the case of economic stress, or with programs promoting adherence, even a small effect can result in a significant number of individuals who remain persistent long enough receive a minimum AD therapeutic dose. Relatively small changes on a population basis can have an important public health impact, similar to that which has been shown with blood pressure (Stamler et al., 1993). This paper provides clear evidence that economic stress plays a significant, albeit small, role in AD persistence. Addressed as part of a multi-faceted adherence promotion program, influencing economic stress in at-risk patients could provide important marginal gains in AD persistence.

Conclusion

This paper models the causal effect of economic stress, as proxied by industry-level unemployment, on AD medication persistence using dynamic panel models and patient micro data. We hypothesize the observed effects of unemployment on AD medication persistence manifest through changes in economic stress, resulting from changes in work burden, perceived future income, and economic uncertainly. This study is novel in that it uses rich patient-level data; controls for unobserved heterogeneity; and models industry-specific unemployment rates. Patient data on employment status, demographics, and AD medication persistence come from

EMR records of a large MCO located in the Pacific Northwest, and data on unemployment rates by industry were drawn from BLS.

We find clear empirical evidence of a causal effect of economic stress on AD persistence among employed adults who were medical plan members of the MCO between 2000 and 2009. Results show that persistence decreases as the economy worsens, and that the effect is most pronounced during periods of rapidly increasing unemployment. We show the effect only emerges for mid-career employees in subgroup analyses based on age. In this model, we show stronger negative effects in addition to positive effect on AD persistence during periods of decreasing economic stress. We do not observe significant effects in early- or late-career employees. We do not detect differential effects by gender or the level of union coverage within an industry, nor do we find any evidence of a spillover effect to employees' spouses. Results remain consistent over multiple robustness tests.

Results from this study provide important information for policy makers and to guide future research. Patients who are employed in an industry that is undergoing contraction and begin an incident course of AD treatment appear to be vulnerable to early discontinuation, likely resulting from increasing economic stress. Health plans and providers could identify these patients through membership records or direct assessment and deliver services specific to improving medication persistence. Education about the disruptive effects of economic stress on AD medication persistence during medication consults could help patients better cope with changes in the business cycle, as well as, with other changes in other channels of economic stress.

While this study was not designed to test the effect of economic stress on medication persistence for physical health conditions, as part of our robustness tests we did find some

evidence of a similar effect on persistence to antihypertensives, the largest category of non-mental health related medications in this sample of patients. It is plausible that some of the countercyclical effect of the macroeconomy and physical health is attributable to enduring effects of behavior changes during past phases of the business cycle. For example, worsening health during economic expansions could be partly due to poor medication persistence during the preceding recession for a subset of the population who are prescribed pharmacotherapy for physical health conditions. Realization of detrimental health effects may be delayed for months or even years. Further research on the effects of economic stress on medication persistence across a larger spectrum of mental and physical health conditions could identify beneficial intervention targets to reduce disruptions in optimal pharmacotherapy. In addition, better understanding the effect of age could help improve future services related to economic stress.

Figure 2-1. Unemployment by Calendar Time

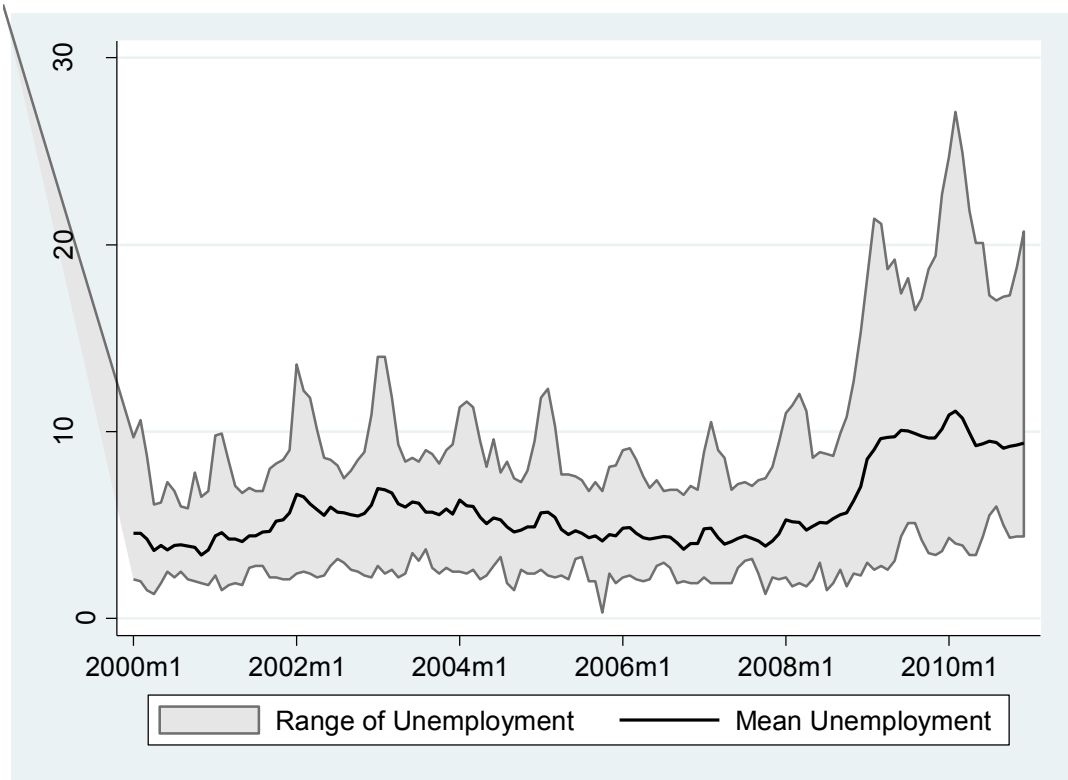


Table 2-1. Characteristics of Sample

	Primary Subscriber (N=21,365)	Spouse (N=10,498)
Age: Mean (SD)	42.88 (11.02)	43.26 (10.55)
Gender: N (%) female	12,868 (60.25)	7,684 (73.19)
Race: N (%) Non-Caucasian Racial Minority	1,453 (6.80%)	625 (5.95%)
Ethnicity: N (%) Hispanic	893 (4.18%)	385 (3.67%)

Table 2-2. Seasonally Adjusted Monthly Unemployment Rates by NAICS Industry Classification between 2000-2010

Industry	Absolute Mean (SD; Median; Range)
Manufacturing	6.33 (2.66; 5.5; 3.1-13.0)
Education and Health Services	3.62 (1.08; 3.3; 1.8-6.7)
Finance	3.81 (1.50; 3.3 2.1-7.7)
Government	2.74 (0.88; 2.5; 1.3-6.0)
Other Services	5.36 (1.55; 4.9; 2.9-10.0)
Trade	5.19 (1.90; 4.6; 2.3-11.3)
Real Estate and Construction	10.28 (5.29; 8.5; 4.4-27.1)
Information Technology	5.81 (2.23; 5.4; 2.4-11.5)
Leisure	8.63 (1.87; 8.2; 5.9-14.2)
Professional Services	7.23 (2.07; 6.5; 4.1-12.4)

Table 2-3. Persistence and Adherence Characteristics

	Estimated Level of Persistence with Therapy % Persistent			Proportion of Days Covered Mean (SD)
	Maximum Allowable Gap (in days)			
	15	30	60	
Primary Subscriber				
Month 1	100%	100%	100%	.982 (.091)
Month 2	97.20%	67.69%	98.02%	.535 (.496)
Month 3	61.60%	67.66%	72.02%	.498 (.498)
Month 4	51.07%	58.68%	64.34%	.434 (.494)
Month 5	43.61%	52.09%	58.50%	.409 (.490)
Month 6	38.08%	47.08%	53.90%	.368 (.481)
Month 7	33.26%	42.70%	49.72%	.343 (.474)
Spouse				
Month 1	100%	100%	100%	.983 (.090)
Month 2	97.35%	97.80%	98.15%	.544 (.496)
Month 3	62.33%	68.67%	73.57%	.506 (.498)
Month 4	52.51%	60.35%	66.18%	.437 (.495)
Month 5	45.14%	53.68%	60.25%	.418 (.492)
Month 6	39.24%	48.37%	55.77%	.373 (.482)
Month 7	34.56%	44.03%	51.77%	.348 (.475)

Table 2-4. Explaining AD Persistence: Primary Subscriber

Covariate	OLS	Fixed Effect	GMM
ELPT (-1)			0.987*** (0.027)
ELPT (-2)			-0.074*** (0.024)
Log(Unemployment)	-0.873*** (0.148)	-0.568** (0.239)	-0.550** (0.235)
Month 2	-1.408*** (0.035)	-1.410*** (0.035)	
Month 3	-9.983*** (0.094)	-9.986*** (0.094)	
Month 4	-12.475*** (0.099)	-12.481*** (0.099)	5.872*** (0.212)
Month 5	-14.451*** (0.101)	-14.460*** (0.101)	5.729*** (0.119)
Month 6	-15.871*** (0.101)	-15.882*** (0.101)	6.080*** (0.115)
Month 7	-17.134*** (0.100)	-17.147*** (0.100)	6.078*** (0.121)
Constant	30.888*** (0.201)	30.479*** (0.329)	-5.284*** (0.360)
Observations	149,492	149,492	106,780
Individuals		21,356	21,356
R-squared (overall)	0.206	0.205	
AR(1) test (*p*-value)			-12.43 (0.000)
AR(2) test (*p*-value)			-1.04 (0.300)
AR(3) test (*p*-value)			1.20 (0.230)
Sargan test (*p*-value)			13.79 (0.841)

* Significant at the 10% level.
** Significant at the 5% level.
*** Significant at the 1% level.
Robust standard errors in parentheses

Table 2-5. Explaining AD Persistence: Primary Subscriber, non-linear effects

Covariate	Empirically constructed linear spines	Theoretically constructed linear spines
ELPT (-1)	0.979*** (0.034)	0.943*** (0.037)
ELPT (-2)	-0.066** (0.030)	-0.036 (0.032)
Lowest unemployment	-0.327 (0.215)	0.064 (0.232)
Moderate unemployment	0.513 (0.644)	1.099 (0.738)
Higher unemployment	0.016 (0.673)	-0.898 (0.835)
Highest unemployment	-0.440 (0.667)	-2.148** (0.848)
Month 2		
Month 3		
Month 4	5.817*** (0.259)	5.662*** (0.273)
Month 5	5.728*** (0.144)	5.844*** (0.164)
Month 6	6.091*** (0.167)	6.314*** (0.209)
Month 7	6.099*** (0.196)	6.432*** (0.260)
Constant	-5.685*** (0.916)	-3.142** (1.213)
Observations	106,780	106,780
Individuals	21,356	21,356
AR(1) test (*p*-value)	-10.09 (0.000)	-8.71 (0.000)
AR(2) test (*p*-value)	-1.10 (0.271)	-1.88 (0.060)
AR(3) test (*p*-value)	0.92 (0.360)	0.33 (0.230)
Sargan test (*p*-value)	39.60 (0.988)	61.55 (0.492)

* Significant at the 10% level.
** Significant at the 5% level.
*** Significant at the 1% level.
Robust standard errors in parentheses; Results from GMM models

Table 2-6. Explaining AD Persistence: Spouse

Covariate	OLS	Fixed Effect	GMM
ELPT (-1)			0.964*** (0.044)
ELPT (-2)			-0.051 (0.039)
Log(Unemployment)	-0.274 (0.206)	-0.374 (0.338)	0.037 (0.322)
Month 2	-1.230*** (0.048)	-1.297*** (0.048)	
Month 3	-9.965*** (0.134)	-9.650*** (0.134)	
Month 4	-12.027*** (0.141)	-12.025*** (0.141)	5.609*** (0.338)
Month 5	-14.008*** (0.144)	-14.004*** (0.144)	5.489*** (0.174)
Month 6	-15.480*** (0.145)	-15.475*** (0.145)	5.804*** (0.172)
Month 7	-16.763*** (0.144)	-16.758*** (0.144)	5.838*** (0.178)
Constant	30.112*** (0.279)	30.248*** (0.466)	-5.852*** (0.488)
Observations	73,486	73,486	52,490
Individuals		10,498	10,498
R-squared (overall)	0.198	0.198	
AR(1) test (*p*-value)			-12.43 (0.000)
AR(2) test (*p*-value)			-1.04 (0.300)
AR(3) test (*p*-value)			1.20 (0.230)
Sargan test (*p*-value)			13.79 (0.841)

* Significant at the 10% level.
** Significant at the 5% level.
*** Significant at the 1% level.
Robust standard errors in parentheses

Table 2-7. Explaining AD Persistence: Spouse, non-linear effects

Covariate	Empirically constructed linear spines	Theoretically constructed linear spines
ELPT (-1)	0.877*** (0.054)	0.955*** (0.057)
ELPT (-2)	0.026 (0.048)	-0.044 (0.051)
Spline 1	0.224 (0.332)	0.233 (0.389)
Spline 2	1.769 (1.012)	-0.028 (0.921)
Spline 3	-1.763* (1.057)	-0.046 (1.165)
Spline 4	-0.461 (0.799)	-0.837 (1.061)
Month 2		
Month 3		
Month 4	5.040*** (0.407)	5.586*** (0.428)
Month 5	5.422*** (0.219)	5.544*** (0.243)
Month 6	5.807*** (0.242)	5.895*** (0.304)
Month 7	5.925*** (0.278)	5.964*** (0.370)
Constant	-5.198*** (1.051)	-4.785*** (1.530)
Observations	52,490	52,490
Individuals	10,498	10,498
AR(1) test (*p*-value)	-5.09 (0.000)	-5.75 (0.000)
AR(2) test (*p*-value)	-0.01 (0.011)	-1.06 (0.288)
AR(3) test (*p*-value)	-0.99 (0.320)	-0.03 (0.977)
Sargan test (*p*-value)	65.81 (0.346)	41.92 (0.976)

* Significant at the 10% level.
** Significant at the 5% level.
*** Significant at the 1% level.
Robust standard errors in parentheses; Results from GMM models

Table 2-8. Explaining AD Persistence: Age Subgroups

Covariate	18-39	40-54	55-64
ELPT (-1)	0.950*** (0.050)	1.020*** (0.044)	0.942*** (0.086)
ELPT (-2)	-0.056 (0.042)	-0.090** (0..039)	-0.020 (0.077)
Log(Unemployment)	0.001 (0.334)	-1.222*** (0.379)	0.379 (0.595)
Month 2			
Month 3			
Month 4	5.651*** (0.390)	5.986*** (0.379)	5.760*** (0.660)
Month 5	5.678*** (0.203)	5.727*** (0.171)	5.808*** (0.300)
Month 6	5.900*** (0.198)	6.186*** (0.162)	6.085*** (0.296)
Month 7	5.917*** (0.206)	6.173*** (0.167)	6.115*** (0.296)
Constant	-5.889*** (1.047)	-4.485*** (0.558)	-4.850** (1.996)
Observations	48,265	71,210	16,360
Individuals	9,653	14,242	3,272
AR(1) test (*p*-value)	-6.97 (0.000)	-7.87 (0.000)	-3.47 (0.001)
AR(2) test (*p*-value)	-0.81 (0.418)	-0.39 (0.693)	-0.90 (0.367)
AR(3) test (*p*-value)	0.41 (0.685)	0.94 (0.346)	-0.17 (0.866)
Sargan test (*p*-value)	9.55 (0.976)	10.46 (0.959)	10.73 (0.953)

* Significant at the 10% level.
** Significant at the 5% level.
*** Significant at the 1% level.
Robust standard errors in parentheses; Results from GMM models

Table 2-9. Explaining AD Persistence: Age Subgroups, Non-linear effects

Covariate	18-39		40-54		55-64	
	Empirical	Theory	Empirical	Theory	Empirical	Theory
ELPT (-1)	0.945*** (0.065)	0.913*** (0.069)	0.939*** (0.051)	0.986*** (0.051)	0.911*** (0.094)	0.928*** (0.083)
ELPT (-2)	-0.051 (0.056)	-0.027 (0.059)	-0.018 (0.046)	-0.060 (0.045)	0.002 (0.084)	-0.013 (0.074)
Spline 1	-0.541 (0.368)	-0.190 (0.385)	-1.222*** (0.379)	0.155 (0.312)	0.328 (0.715)	-0.311 (0.614)
Spline 2	-0.901 (1.007)	-1.037 (1.125)	2.643*** (0.960)	1.798** (1.012)	-0.783 (2.170)	-1.181 (1.699)
Spline 3	1.307 (1.086)	1.199 (1.345)	-1.490 (0.965)	-1.449 (1.006)	0.387 (2.336)	1.702 (1.948)
Spline 4	1.430 (1.124)	-0.582 (1.309)	-1.967** (0.881)	-2.473** (0.983)	-0.330 (1.726)	0.831 (1.800)
Month 2						
Month 3						
Month 4	5.493*** (0.509)	5.320*** (0.529)	5.528*** (0.384)	5.902*** (0.376)	5.525*** (0.759)	5.529*** (0.705)
Month 5	5.456*** (0.256)	5.486*** (0.279)	5.785*** (0.207)	5.963*** (0.224)	5.583*** (0.443)	5.385*** (0.470)
Month 6	5.581*** (0.284)	5.683*** (0.332)	6.364*** (0.236)	6.577*** (0.273)	6.038*** (0.522)	5.726*** (0.566)
Month 7	5.523*** (0.325)	5.561*** (0.402)	6.487*** (0.271)	6.726*** (0.330)	5.988*** (0.607)	5.561*** (0.671)
Constant	-7.921** (1.703)	-4.956*** (2.027)	-4.485*** (0.558)	-3.156** (1.356)	-5.358** (2.416)	-7.501*** (2.511)
Observations						
Individuals						
AR(1) test (*p*-value)	-5.42 (0.000)	-4.78 (0.000)	-5.80 (0.000)	-6.56 (0.000)	-2.98 (0.000)	-3.50 (0.000)
AR(2) test (*p*-value)	-0.69 (0.491)	-1.04 (0.300)	-1.84 (0.066)	-0.99 (0.322)	-1.22 (0.222)	-1.18 (0.239)
AR(3) test (*p*-value)	0.06 (0.955)	-0.09 (0.925)	-0.15 (0.878)	0.43 (0.669)	0.37 (0.713)	0.51 (0.613)
Sargan test (*p*-value)	46.50 (0.929)	44.42 (0.955)	41.80 (0.977)	44.90 (0.950)	44.94 (0.950)	61.48 (0.495)

* Significant at the 10% level.
** Significant at the 5% level.
*** Significant at the 1% level.
Robust standard errors in parentheses; Results from GMM models

References for Chapter 2

Andersen, R. M., 1995. Revisiting the behavioral model and access to medical care: does it matter? Journal of Health and Social Behavior 36, 1–10.

Arellano, M., Bond, S., 1991. Some Tests of Specification for Panel Data: Monte Carlo Evidence and an Application to Employment Equations. The Review of Economic Studies 58, 277-297.

Blundell, R., & Bond, S., 1998. Initial conditions and moment restrictions in dynamic panel data models. Journal of Econometrics 87, 115–143.

Blundell, R., Bond, S., 2000. GMM estimation with persistent panel data, an application to production functions. Econometric Reviews 19, 321–340.

Bone, L. R., et al., 2000. Community health survey in an urban African-American neighborhood: distribution and correlates of elevated blood pressure. Ethnicity & Disease 10, 87-89.

Brand, J., Levy, B., & Gallo, W., 2008. Effects of layoffs and plant closings on subsequent depression among older workers. Journal of Aging Research 30, 701–21.

Cantrell, C. R., et al., 2006. Methods for evaluating patient adherence to antidepressant therapy: a real-world comparison of adherence and economic outcomes. Medical Care 44(4), 300–3

Catalano, R., 1991. The health effects of economic insecurity. American Journal of Public Health 81(9), 1148–52.

Catalano, R., 2009. Health, medical care, and economic crisis. New England Journal of Medicine. 360;8, 749-751.

Catalano, R., Dooley, D., 1983. A Test of Economic Instability: A test of Economic Stress Hypothesis. Journal of Health and Social Behavior 24, 46–60.

Charles, K. K., Decicca, P., 2008. Local labor market fluctuations and health: is there a connection and for whom? Journal of Health Economics 27(6), 1532–50.

Cramer, J. A., et al., 2008. Medication compliance and persistence: terminology and definitions. Value in Health 11(1), 44–47.

Deaton, A.S., 2011. The Financial Crisis and the Well-Being of Americans. National Bureau of Economic Research Working Paper Series, Working Paper 17128.

Fair, R. C. (2012). Predicting presidential elections and other things. Stanford, California: Stanford Economics and Finance, an Imprint of Stanford University Press.

FRED, 2011. Federal Reserve Economic Data, Federal Reserve Bank of St. Louis: Oregon, All Employees; accessed May 31, 2011.".

Gelberg, L., Andersen, R. M., Leake, B. D., 2000. The Behavioral Model for Vulnerable Populations : Application to Medical Care Use and Outcomes for Homeless People. Health Services Research 34(6), 1273–302.

Gilbody, S., Whitty, P., Grimshaw, J., Thomas, R., 2003. Educational and organizational interventions to improve the management of depression in primary care: a systematic review. The Journal of the American Medical Assocation 289, 3145-3151.

Haynes, R. B., Yao, X., Degani, A., Kripalani, S., Garg, A., McDonald, H. P., 2005. Interventions to enhance medication adherence. Cochrane Database of Systematic Reviews, CD000011.

BLS, 2013. United States Department of Labor, Bureau of Labor Statistics: Unemployed persons by industry; accessed October 18, 2013.

Keller, M. B., et al. 2001. Efficacy of paroxetine in the treatment of adolescent major depression: a randomized, controlled trial. Journal of the American Academy of Child and Adolescent Psychiatry 40, 762-772.

Mishra, P., Newhouse, D., 2009. Does health aid matter? Journal of Health Economics 28, 855-872.

Mundt, J. C., Clarke, G. N., Burroughs, D., Brenneman, D. O., Griest, J. H., 2001. Effectiveness of antidepressant pharmacotherapy: the impact of medication compliance and patient education. Depression and Anxiety 13, 1-10.

Lindström, M., Hansen, K., Rosvall, M., 2012. Economic stress in childhood and adulthood, and self-rated health: a population based study concerning risk accumulation, critical period and social mobility. BMC Public Health Sep(11; 12), 761.

Mandal, B., Roe, B., 2008. Job loss, retirement and the mental health of older Americans. Journal of Mental Health Policy Economics 11, 167–76.

Perrewé, P., Halbesleben, J., Rosen, C., 2012. The Role of the Economic Crisis on Occupational Stress and Well Being. Emerald Group Publishing.

Roodman, D., 2009. How to do xtabond2 : An introduction to difference and system GMM in Stata. The Stata Journal 9(1), 86–136.

Ruhm, C. J., 2005. Healthy living in hard times. Journal of Health Economics, 24(2), 341–63.

Saounatsou, M., et al., 2001. The influence of the hypertensive patient's education in compliance with their medication. Public Health Nursing 18(6), 436–442.

Skogstad, A., Matthiesen, S.B., Einarsen, S., 2007. Organizational Changes: A Precursor of Bullying at Work? International Journal of Organization Theory and Behavior 10(1), 58-94.

Staessen J.A., et al., 1997. Randomised double-blind comparison of placebo and active treatment for older patients with isolated systolic hypertension. Lancet. 350, 757-764.

Stock, J., Watson, M., 2001. Vector Autoregressions. The Journal of Economic Perspectives 15(4), 101–115.

Tefft, N., 2011. Insights on unemployment, unemployment insurance, and mental health. Jounral of Health Economics, 30(2), 258–64.

Trivedi, M. H., Lin, E. H., & Katon, W. J., 2007. Consensus recommendations for improving adherence, self-management, and outcomes in patients with depression. CNS Spectrums 12, 1-27.

Vermeire, E., Hearnshaw, H., Van Royen, P., Denekens, J., 2001. Patient adherence to treatment: three decades of research; A comprehensive review. Journal of Clinical Pharmacy and Therapeutics 26, 331–342.

Vollmer W.M., et al., 2011. Use of health information technology to improve medication adherence. American Journal of Managed Care 17(12 Spec No.), SP79-87.

Chapter 3 – Effects of antidepressant adherence and persistence on medical expenditures: Evidence from dynamic panel models

Abstract

Background: Previous observational studies of adherence to antidepressants (AD) and medical expenditures applied methods that may not have eliminated residual unobserved confounding. Moreover, most definitions of adherence do not capture the continuity of possession of AD medications.

Objective: We applied an Arellano-Bond (A-B) dynamic-panel estimator, which can control for both time-varying and non-varying unobserved confounding, to data from a large managed care organization to estimate true effects on medical expenditures of AD adherence and persistence.

***Measurements*:** We selected 18,655 adults with an incident AD dispense between 2006-2008. We measured *adherence* as the proportion of days with possession of an AD medication and *persistence* as the maximum duration of continuous therapy within a 90-day quarter. Categories of quarterly medical expenditures included total, total not including medication (non-medication), and outpatient services. We collected data for up to 3 years following an incident dispense.

Results: Both adherence and persistence were positively associated with all categories of expenditures. After controlling for unobserved time-variant and -invariant confounding though the A-B estimators, persistence alone showed significant negative effects on non-medication and outpatient expenditures; we observed neither effects of persistence on total expenditures nor effects of adherence on total, non-medication, or outpatient expenditures. However, these significant effects disappeared with more lenient definitions of persistence.

Conclusions: Using a conservative definition of persistence, we found that better persistence led to lower non-medication and outpatient expenditures. Although effect sizes were small, medical

organizations could save large amounts of money by increasing persistence because of the large number of patients undergoing AD treatment. Empirical results showing significant effects of measures of persistence but not adherence may suggest that interventions targeting improvement in AD persistence may be more important than those that target overall AD adherence.

Key words: Antidepressant, expenditures, dynamic panel, persistence, adherence.

Introduction

Depression is a debilitating disorder that affects about 1 in 5 people during their lifetimes[1]. Patients with depression suffer from reduced health-related quality of life through changes in both mental- and physical-health domains[2] and are at elevated risk for personal injury, such as occurs from motor-vehicle accidents or suicidal behavior[3]. Unipolar depression is ranked as the 10th leading cause of disability adjusted life years by the World Health Organization[4]. In addition to patient-level disease burden, depression has substantial societal costs through reduced work-place productivity, increased absenteeism, and increased consumption of medical care resources[5]. Estimates of the total societal cost of depression are 0.85% of US gross-domestic product, comparable in total economic burden to the combination of stroke (0.40%) and hypertension (0.40%)[6]. Successful treatment of depression is an extremely important component of health care.

Typical depression treatment options include antidepressant (AD) therapy and/or psychotherapy. About 75% of patients with depression receive AD therapy and 43% receive some form of psychotherapy,[7] although in both cases many patients fail to receive a full curative dose. ADs are widely used because of established but modest efficacy, and because ADs can be prescribed by primary care providers as well as mental health specialists. Despite known benefits, patient adherence to and persistence with AD treatment is low. Guidelines for optimal AD duration[8] for first depressive episodes recommend treating to a satisfactory response (typically +/- 2 months), followed by an addition continuation treatment of 4 to 9 months to consolidate response. Only 60% of patients achieve an adequate level of AD adherence in the acute phase of treatment, and estimates suggest as few as 25% of patients satisfy treatment recommendations over the longer continuation phase of treatment[7].

The level of adherence to almost any medical intervention is a primary factor in treatment-response variation. A patient's adherence to treatment is often (in part) a byproduct of the target condition itself. These are often referred to as 'endogenous' factors. This is particularly true in the study of effects of depression treatment because of the episodic nature of depressive episodes,[9] as well as the low activation and reduced motivation associated with depression. Multiple sources of confounding may bias estimates of the effect of patient adherence to AD treatment on most health outcomes, which may lead to inaccurate interpretations.

The purpose of this study is to control for these confounding factors and accurately estimate the causal effect of AD persistence and adherence on medical expenditures using an Arellano-Bond (AB) dynamic panel estimator[10,11]. We used the most recent version of the Andersen behavioral model[12] to guide the conceptual framework for this study. Our models evaluate the effect of one type of patient behavior (adherence to or persistence with AD treatment) on another health behavior (health-services use as measured through medical expenditures). Findings from this study could be used to provide quantitative data to decisions-makers in health plans, or to public health agencies, to support the use or development of adherence- and persistence-promotion programs for AD treatment.

To the best of our knowledge, no other studies have used instrumentation to quantify the effect of AD adherence and persistence on medical expenditures and thus obtained an unbiased estimate. To date, observational studies of AD adherence and its relationship to overall medical expenditures have been unable to account for the effect of residual unobserved confounding because applied methods only control for observable characteristics[15–17] or used IV analyses to model the selection process of AD class (e.g., choice of SSRI versus TCA) rather than to model

the effect of continuous adherence to AD therapy[18]. Better, unbiased estimates of the relationship between adherence and medical expenditures are policy-relevant because they can inform decisions-makers in health plans and public health agencies about the effects of improving adherence and/or persistence to AD treatment. In addition, better understanding the effect of the continuity of possession of AD medications can help inform future research and policy.

Methods

Setting

Data came from a large integrated MCO located in the Pacific Northwest. Every member of the MCO has a unique, permanent health record number. Every contact an individual makes with the medical care system, and all referrals to outside services, are recorded in a comprehensive EMR under the patient's health record number. Pharmacy dispenses are also recorded, including agent, dose, supply. Other research indicates that 95%+ of MCO members fill their AD prescriptions at MCO pharmacies. This EMR system stores information such as patient demographics, medical history, and visit summaries. All study procedures have been reviewed and approved by the local Institutional Review Board (IRB).

Sample

Patients included in this study met the following criteria: 1) age 18 or older, 2) an "incident" AD dispense (with no AD dispense in the prior 12 months) between 2006 and 2008, 3) a minimum of 12 months of continuous membership prior to and following the incident AD dispense, 4) pharmacy benefits included in the membership package, and 5) EMR evidence of a either a unipolar depression or anxiety diagnosis within one month of the incident AD dispense.

We elected to include anxiety diagnoses in addition to depression diagnoses because of the high likelihood of providers using anxiety and depression codes interchangeably[19] as well as the high comorbidity between these categories. ICD-9 depression and anxiety diagnoses included 296.20-296.25, 296.30-296.35, 296.82, 296.99, 300.00, 300.01, 300.02, 309.0, 309.1, and 311. These criteria yielded our final analytic sample (N=18,655). For 87% of participants we had at least two years of follow up data, and for 77% we had three years of follow-up data.

Measures

For the years 2006 through 2008, we queried electronic medical record (EMR) data from a large integrated managed care organization (MCO) located in the Pacific Northwest to identify adult medical plan members who initiated an incident course of AD therapy for depression. We required participants to be continuously enrolled in the medical plan for at least 12 months prior to and 12 months following their incident AD dispensing. We followed patients for up to 36 months following their incident AD dispense and collected comprehensive EMR data to quantify AD adherence and persistence and medical expenditures. We used proportion-of-days-covered (PDC)[12] as our measure of adherence and estimated-level-of-persistent-therapy (ELPT)[13] as our measure of persistence. Adherence measures a patient's overall possession of a medication over a defined interval, whereas persistence measures the length of time during which a patient had continuous possession of a medication prior to discontinuation[14]. Categorizations of medical expenditures included total, non-medication, and outpatient medical expenditures. All measures were calculated by 90 day quarter, and the unit of analysis was person-quarters.

We modeled the effects of both adherence and persistence on medical expenditures because these two measures provide different but related information. Adherence measures how well a patient complies with treatment over a fixed interval, whereas persistence captures the

accumulation of continuous treatment until discontinuation[14]. Persistence is particularly relevant for AD treatment because of the duration of continuous treatment needed to reach a minimum therapeutic effect[8]. We used proportion-of-days- covered (PDC) as our measure of adherence because it allows for switching between different types of ADs as well as for augmentation of one medication with an additional medication[20]. We calculated PDC as total days' supply of AD divided by days in the follow-up interval, multiplied by 100. Persistence was defined using ELPT with a conservative 15 day maximum allowable gap in coverage[13]. Our calculations included adjustments for under and over supply of medication, switching from one AD to another, and augmentation of one AD with another. We also analyzed ELPT with more liberal maximums of 30 and 60 day gaps as sensitivity analyses.

We calculated medical expenditures using comprehensive profiles of HMO services from the EMR and other electronic administrative data. These data, used in previous studies, accurately represent services paid for by the HMO[21]. Expenditures included outpatient, inpatient, and pharmacy categories, and we adjusted all values to 2008 US dollars using the consumer price index multiplier from the medical-services category[22]. Expenditures were categorized into total expenditures, inclusive of all medical services; non-medication expenditures, which included total expenditures less medications; and outpatient expenditures, which included only ambulatory outpatient visits. All measures were calculated by 90 day quarter.

Analysis

We modeled associations between AD adherence and persistence and categories of medical expenditures using ordinary-least-squares, referred to as our "naïve" regressions. We

regressed medical expenditures on each of our definitions of persistence or adherence in separate models. We then applied fixed-effects models to remove patient-specific confounding. Estimates from our fixed-effects models were still likely confounded by time-varying factors, so we turned to the A-B framework to attempt to control for these time-variant biases[10,11]. In addition, the A-B framework allowed for a dynamic process in the dependent variable by including a one-period lag of the dependent variable as an independent variable in the model, likely an important consideration for medical expenditures.

We applied A-B estimators to estimate a series of regression equations using Generalized Method of Moments (GMM). First-differences were taken to remove time-invariant confounding, comparable to our fixed-effects models. The estimation procedure then utilized lagged values of the independent variables as instruments and to establish an initial set of moment conditions. We chose lags to be sufficiently far enough back in time to ensure they were uncorrelated with the error term in our regression equations. We estimated the A-B estimator as a fully augmented system GMM, which derives potential instruments from both from the first-difference equation and the levels-equation (non-differenced)[11]. The system GMM specification has been shown to provide substantially more accurate estimates when the outcome is persistent.[11]

We evaluated our A-B models using a variety of metrics, including testing over-identifying restrictions and testing for autocorrelation. We used Hansen J-tests to test over-identifying restrictions, a necessary condition of the models. In addition, we used the A-B test for autocorrelation to test for the presence of autocorrelation, which would call into question the ability to use lags as instruments. Detection of autocorrelation in the first-order process was

expected because of the mathematical construction of the model. Only tests of autocorrelation beyond the first-order process were considered relevant.[23]

We chose to apply the A-B estimator because it provided the potential to control multiple sources of confounding and the identification assumptions underlying the system GMM are strong[24]. In addition, our data were well suited for the underlying asymptotic properties to hold. We had a large number of patients and a relatively low number of time measurements relative to each patient. We considered applying alternate methods of IV analysis to control confounding but were unable to identify theoretically valid instruments. Given the lack of convincing external instruments, the choice of using system GMM estimators likely produced the most accurate estimates with available data[24]. In all models, we calculated robust standard errors and selected a two-sided significance level of α=.05 for all statistical tests. All models were estimated using Stata version 13.1, and A-B models were estimated with the xtabond2 prodedure.[23]

Results

Table 3-1 presents sample characteristics as well as AD persistence and AD adherence cumulatively over the first 12 months of the study. A majority of the sample was female (64.8%), and AD treatment typically started with an SSRI (71.7%). Nearly a third of the sample (32.9%) had an anxiety diagnosis associated with their incident AD dispense, either in combination with depression or alone. Average ELPT ranged from 130.0 to 169.5 total days of persistence during the initial 12 months following initiation of AD treatment, depending on the length of allowable gaps we used in our calculations. Using the most conservative definition of ELPT, allowing for a maximum of 15 day gaps, about half the sample (49.0%) discontinued

prior to reaching 90 days of persistence, and about three quarters (72.8%) discontinued prior to reaching 180 days of persistent AD therapy. Average PDC over the first 12 months following initiation of AD therapy was 50.4 (SD=33.0). Total, non-medication, and outpatient annual medical expenditures were $5,576 (SD=12,964), $4,014 (SD=11,429), and $3,897 (SD=10,051) in the first year of the study, respectively.

Specification and fit statistics from our A-B dynamic panel models showed consistently favorable model performance, as Table 2-2 indicates. In all models, our instrument sets predicted persistence or adherence in the first stage strongly enough to warrant inclusion as instruments. In addition, we did not detect autocorrelation beyond the first-order process, and Hansen *J*-statistics failed to reject over-identifying restrictions, a necessary condition of the models.

Total Medical Expenditures. Table 2-3 summarizes results from the four separate persistence/adherence models, where total medical expenditures was regressed on different measures of persistence and adherence. Higher levels of ELPT were significantly associated with higher total medical expenditures, allowing for maximum gaps in coverage of 15 ($p<.001$), 30 ($p<.001$), and 60 ($p<.001$) days. Larger values of PDC were also associated with higher total medical expenditures ($p<.001$). Fixed-effects models, which control patient-level time-invariant confounding, also showed significant positive associations between ELPT with 15 ($p<.001$), 30 ($p<.05$), and 60 ($p<.001$) day maximum gaps as well as PDC ($p<.001$). Application of the A-B estimator showed no significant effect of AD persistence or adherence on total medical expenditures. The estimate of the dynamic process in total medical expenditures was positive and significant in models with ELPT, with 15 ($p<.01$), 30 ($p<.05$), and 60 ($p<.05$) day gaps, as well as PDC ($p<.05$), which demonstrated that current realizations of expenditures are function

of previous use. Using ELPT with a 15-day gap, a $100 increase in the current period results in approximately a $30 increase in the subsequent quarter.

Non-Medication Expenditures. Associations between adherence and persistence and non-medication medical expenditures are similar, as shown in Table 3-4. Higher levels of ELPT were significantly associated with higher levels of non-medication expenditures, allowing for maximum gaps in coverage of 15 ($p<.001$), 30 ($p<.001$), and 60 ($p<.001$) days. Increased PDC was also associated with higher non-medication expenditures ($p<.001$). Fixed effects models also showed significant, positive associations between ELPT with 15 ($p<.001$), 30 ($p<.05$), and 60 ($p<.001$) day maximum gaps and non-medication expenditures, as well as PDC ($p<.001$). Estimates from the A-B models revealed a significant, negative effect of ELPT with 15 days maximum gap on non-medication medical expenditures ($p<.05$), with a 1 day increase in ELPT resulting in a $1.62 decrease in expenditures No other estimates of persistence or adherence were significant. In addition, the parameter estimates of the dynamic process were not significant in models of non-medication medical expenditures.

Outpatient Medical Expenditures. Table 3-5 presents results for outpatient medical expenditures. Associations between adherence and persistence and outpatient expenditures are similar to one another and to preceding results. Higher levels of ELPT were significantly associated with higher outpatient medical expenditures, allowing for maximum gaps in coverage of 15 ($p<.001$), 30 ($p<.001$), and 60 ($p<.001$) days. Higher levels of PDC were also associated with higher outpatient medical expenditures ($p<.001$). Fixed effects models also showed significant positive associations between ELPT with 15 ($p<.001$), 30 ($p<.05$), and 60 ($p<.001$) day maximum gaps as well as significant associations between PDC ($p<.001$) and outpatient medical expenditures. Estimates from the A-B models revealed a significant, negative effect of

ELPT with 15 days maximum gap on outpatient medical expenditures ($p<.05$), with a 1 day increase in ELPT resulting in a $1.21 decrease in expenditures. No other estimates of persistence or adherence were significant. In addition, the parameter estimates of the dynamic process were no longer significant in models of outpatient medical expenditures.

Discussion

Participants in the study sample persisted, on average, with AD treatment in a similar manner as has been reported in previous studies[7,25], with about half of the sample meeting at least an acute-phase treatment duration, and about a quarter of the sample meeting the longer continuation-phase treatment duration, using our most conservative definition of persistence (ELPT with a maximum allowable gap of 15 days). Associations between all measures of persistence and adherence and all categories of medical expenditures were significant, with higher levels of adherence and persistence associating with higher levels of medical expenditures based on naïve regressions. The statistical significance and directionality of results persisted when employing models that controlled for patient-specific fixed effects. However, the magnitude of the estimates almost always decreased markedly, highlighting the presence of substantial patient-specific bias.

Models using instrumentation, and accounting for the potential dynamic process of medical expenditures, showed counter results and illustrated the effects of time-variant confounding. Increased persistence with AD therapy, using our most conservative definition of ELPT, resulted in lower non-medication and outpatient expenditures. For the average person, an increase of 90 days in ELPT would result in a $145.63 decrease in non-medication expenditures and a $108.44 decrease in outpatient expenditures per quarter. Using model estimates, these

changes translate into effect sizes of Cohen's *d*=.146 for non-medication expenditures and Cohen's *d*=.084 for outpatient expenditures. Although these effect sizes are below the threshold that is typically considered small by effect-size standards[26], the benefit of improved AD persistence could be substantial because it would be applied over large populations.

The effects of adherence and our other measures of persistence, ELPT with 30 and 60 day allowable gaps, on medical expenditures were not significant. While not statistically significant, it is worth noting that the signs of the parameter estimates for both measures of ELPT were negative. As recommended for observational research and analysis of patient persistence with treatment[20], we used multiple definitions of persistence as sensitivity analyses to evaluate the robustness of study results. Model estimates suggest that the definition of maximum amount of allowable time a patient can be without medication and still considered to be persistent with AD therapy is important; reducing the gap during which a patient is not persistent may achieve better treatment outcomes.

The effect of persistence on non-medication and outpatient expenditures attenuates as the allowable 'gap' window is increased from 15 days to 30 or 60 days. As the allowable window increases, patients who have longer gaps in consistent possession of medication are categorized as persistent. The change in estimated effects with longer gaps could be attributable to interference with the biological mechanism of ADs via inconsistent dosing. Or, more sporadic refilling of prescribed AD medications could be a proxy for other, related human behavior that reduces AD benefit; e.g., more likely to miss or vary doses. Regardless, better understanding of the influence of maximum allowable breaks in persistence may identify intervention targets to improve patient outcomes. Certainly, these results suggest that minimizing gaps in AD coverage

may improve the clinical benefit of treatment and be more likely to reduce some categories of medical expenditures.

To the best of our knowledge, there are no other studies that use instrumentation to isolate the causal effect of AD adherence and persistence on medical expenditures. Our application of A-B estimators provides useful information on the true effect of AD adherence and persistence on medical expenditures, providing several contributions to the literature. First, results of this study show significant benefit of increased persistence to AD therapy in terms of non-medication and outpatient medical expenditures. Second, findings demonstrate the magnitude and direction of biases in these types of analyses, which result from multiple sources of confounding. Third, it highlights the importance of the maximum time a patient can be temporarily non-persistent and still be considered persistent overall with AD treatment. Results from this study show attenuation of any benefit to non-medication or outpatient expenditures in maximum allowable gaps of more than 15 days. Future research could increase understanding of the mechanisms related to sub-optimal persistence that may be interfering with therapeutic benefit.

Findings from our study may be limited by our analytic methods. While model performance metrics suggest good model fit and specification, instrument performance may not be optimal. The A-B estimator is pragmatic in its selection of potential instruments in that it assumes researchers do not have better choices of instruments available[24], which we do not have available. Another limitation of this approach is the use of linear models to model medical expenditures. However, within the A-B framework, the regression is about changes in expenditure between two consecutive periods. As such, the outcome values lie over the entire real scale. Model evaluations suggested linear models provided good fit to the data.

An addition limitation is that our definitions of adherence and persistence assume patients consume the full dose of each dispensed medication, which may not be an accurate representation of patients' patterns of medication use. Our findings are generalizable to MCO patients who began a new AD regime, and will likely be generalizable to the Pacific Northwest, given that the MCO is similar to the general population in the region. However, due to regional and national differences, we cannot confidently say these results can be generalized to the US population – suggesting the need for replication with geographically and demographically diverse populations.

In summary, we found better persistence with AD therapy to lower non-medication and outpatient medical expenditures using our most precisely defined measure of persistence. In all cases, our applied methods removed substantial biases from multiple sources. The amount of time patients can be without continuous AD coverage and still be considered persistent appears to play an important role that warrants further research. In addition, findings suggest that interventions that target improvement in AD persistence may be more important than those that target overall AD adherence in patients undergoing AD pharmacotherapy.

Table 3-1. Sample Characteristics Over First Year of Study

Patient Demographics	
Gender: % female	64.8%
Age: mean (SD)	47.0 (17.2)
AD Characteristics	
AD class at index dispense	
SSRI	71.7%
SSNRI	2.9%
Tricyclic	4.2%
Other	21.2%
Diagnosis associated with Index AD dispense	
Depression	67.1%
Anxiety	19.1%
Both	13.8%
AD Persistence	
ELPT-15 day gap: Mean (SD)	130.0 (114.0)
ELPT-30 day gap: Mean (SD)	153.7 (122.5)
ELPT-60 day gap: Mean (SD)	169.5 (123.6)
AD Adherence	
PDC: Mean (SD)	50.4 (33.0)
Medical Care Expenditures	
Total: Mean (SD; Median)	5,576 (12,964; 2,392)
Non-Drug: Mean (SD; Median)	4,015 (11,429; 1,568)
Outpatient: Mean (SD; Median)	3,897 (10,051; 1,567)

Table 3-2. Fit Statistics from Arellano-Bond Models

Statistical Test	Total Medical Expenditures	Non-Drug Medical Expenditures	Outpatient Medical Expenditures
ELPT-15 day gap			
AR tests			
AR(1)	.000	.000	.000
AR(2)	.068	.852	.488
AR(3)	.797	.820	.841
Hanson-J test	.105	.156	.133
ELPT-30 day gap			
AR tests			
AR(1)	.000	.000	.000
AR(2)	.190	.869	.570
AR(3)	.540	.800	.879
Hanson-J test	.116	.101	.121
ELPT-60 day gap			
AR tests			
AR(1)	.000	.000	.000
AR(2)	.117	.888	.656
AR(3)	.830	.903	.715
Hanson-J test	.165	.243	.352
PDC			
AR tests			
AR(1)	.000	.000	.000
AR(2)	.108	.966	.601
AR(3)	.813	.874	.808
Hanson-J test	.174	.305	.263

p-values reported
ELPT, estimated level of persistent therapy; AR, auto-regressive; PDC, proportion of days covered

Table 3-3. Model Results: Total Medical-Care Expenditures

Model No.	Independent Variables	Naïve Regression	Patient-Level Fixed-Effects Regression	Arellano-Bond Regression
1	ELPT-15 day gap	3.186***	1.930***	-0.105
		(0.319)	(0.364)	(0.659)
	Lag(1) Expenditures	-	-	0.312**
				(0.110)
	Constant	1280.824***	1302.901***	1058.145***
		(12.224)	(11.552)	(169.468)
2	ELPT-30 day gap	3.957***	1.102*	0.224
		(0.300)	(0.431)	(3.146)
	Lag(1) Expenditures	-	-	0.243*
				(0.104)
	Constant	1244.175***	1298.620***	1532.178***
		(12.426)	(12.712)	(224.826)
3	ELPT-60 day gap	4.584***	1.769***	0.536
		(0.266)	(0.364)	(0.937)
	Lag(1) Expenditures	-	-	0.284*
				(0.113)
	Constant	1203.605***	1285.423***	744.012***
		(13.325)	(14.302)	(180.024)
4	PDC	6.762***	3.618***	0.291
		(0.252)	(0.327)	(2.233)
	Lag(1) Expenditures	-	-	0.295*
				(0.117)
	Constant	1075.918***	1197.212***	711.684***
		(14.553)	(15.879)	(153.868)
N (Observations)		202952	202952	184297
N (Groups)		18655	18655	18655

Standard errors in parentheses
Quarter-specific dummies excluded for parsimony
* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Table 3-4. Model Results: Non-Medication Medical Expenditures

Model No.	Independent Variables	Naïve Regression	Patient-Level Fixed-Effects Regression	Arellano-Bond Regression
5	ELPT-15 day gap	1.876***	1.974***	-1.618*
		(0.297)	(0.353)	(0.739)
	Lag(1) Expenditures			0.109
				(0.114)
	Constant	883.586***	881.865***	804.501***
		(11.367)	(11.229)	(152.065)
6	ELPT-30 day gap	1.838***	0.937*	-0.218
		(0.277)	(0.418)	(3.180)
	Lag(1) Expenditures			0.059
				(0.083)
	Constant	860.651***	877.818***	677.940***
		(11.496)	(12.337)	(200.405)
7	ELPT-60 day gap	2.406***	1.404***	-1.138
		(0.247)	(0.354)	(0.962)
	Lag(1) Expenditures			0.071
				(0.093)
	Constant	846.633***	875.759***	1035.005***
		(12.395)	(13.903)	(166.580)
8	PDC	3.660***	2.280***	0.180
		(0.234)	(0.318)	(2.045)
	Lag(1) Expenditures			0.080
				(0.130)
	Constant	775.331***	828.599***	959.659***
		(13.547)	(15.438)	(145.439)
N (Observations)		202952	202952	184297
N (Groups)		18655	18655	18655

Standard errors in parentheses
Quarter-specific dummies excluded for parsimony
* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Table 3-5. Model Results: Outpatient Medical Expenditures

Model No.	Independent Variables	Naïve Regression	Patient-Level Fixed-Effects Regression	Arellano-Bond Regression
9	ELPT-15 day gap	1.938***	2.142***	-1.205*
		(0.257)	(0.303)	(0.613)
	Lag(1) Expenditures			0.165
				(0.121)
	Constant	854.867***	851.270***	801.547***
		(9.856)	(9.622)	(114.793)
10	ELPT-30 day gap	1.890***	1.181**	-0.288
		(0.245)	(0.366)	(2.872)
	Lag(1) Expenditures			0.129
				(0.088)
	Constant	833.320***	846.852***	1116.254***
		(10.151)	(10.798)	(217.702)
11	ELPT-60 day gap	2.430***	1.585***	-0.811
		(0.215)	(0.303)	(0.877)
	Lag(1) Expenditures			0.122
				(0.094)
	Constant	818.296***	842.875***	972.347***
		(10.747)	(11.913)	(160.469)
12	PDC	3.642***	2.398***	0.092
		(0.203)	(0.273)	(1.980)
	Lag(1) Expenditures			0.146
				(0.129)
	Constant	748.410***	796.405***	894.705***
		(11.745)	(13.228)	(132.127)
N (Observations)		202952	202952	184297
N (Groups)		18655	18655	18655

Standard errors in parentheses
Quarter-specific dummies excluded for parsimony
* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

References for Chapter 3

1. Kessler, R. C. et al. The epidemiology of major depressive disorder: results from the National Comorbidity Survey Replication. JAMA 289, 3095–3105 (2003).

2. Fleming, J. E., Offord, D. R. & Boyle, M. H. Prevalence of childhood and adolescent depression in the community. Ontario Child Health Study. Br. J. Psychiatry 155, 647–54 (1989).

3. Murray, C. J. & Lopez, A. D. Alternative projections of mortality and disability by cause 1990-2020: Global Burden of Disease Study. Lancet 349, 1498–504 (1997).

4. World Health Organization, Health statistics and health information systems.

5. Simon, G. E. Social and economic burden of mood disorders. Biol. Psychiatry 54, 208–15 (2003).

6. Devol, R. & Bedroussian, A. An Unhealthy America: The Economic Burden of Chronic Disease. (2007).

7. Simon, G. E., Peterson, D. & Hubbard, R. Is Treatment Adherence Consistent Across Time, Across Different Treatments, and Across Diagnoses? Gen Hosp Psychiatry 35, 195–201 (2012).

8. Qaseem, A., Snow, V., Denberg, T. D., Forciea, M. A. & Owens, D. K. Using second-generation antidepressants to treat depressive disorders: a clinical practice guideline from the American College of Physicians. Ann. Intern. Med. 149, 725–33 (2008).

9. Talbott, J. A. & Sharfstein, S. S. A Proposal For Future Funding of Chronic and Episodic Mental Illness. Psychiatr. Serv. 55, 1126–1130 (2004).

10. Arellano, M. & Bond, S. Some Tests of Specification for Panel Data: Monte Carlo Evidence and an Application to Employment Equations. Rev. Econ. Stud. 58, 277 (1991).

11. Blundell, R. & Bond, S. Initial conditions and moment restrictions in dynamic panel data models. J. Econom. 87, 115–143 (1998).

12. Cantrell, C. R., Eaddy, M. T., Shah, M. B., Regan, T. S. & Sokol, M. C. Methods for evaluating patient adherence to antidepressant therapy: a real-world comparison of adherence and economic outcomes. Med. Care 44, 300–3 (2006).

13. Cramer, J. A. et al. Medication compliance and persistence: terminology and definitions. Value Health 11, 44–7

14. Cramer, J., Rosenheck, R., Kirk, G., Krol, W. & Krystal, J. Medication Compliance Feedback and Monitoring in a Clinical Trial: Predictors and Outcomes. Value Heal. 6, 566–573 (2003).

15. Katon, W., Cantrell, C. R., Sokol, M. C., Chiao, E. & Gdovin, J. M. Impact of antidepressant drug adherence on comorbid medication use and resource utilization. Arch. Intern. Med. 165, 2497–503 (2005).

16. Cantrell, C., Eaddy, M. & Shah, M. Methods for evaluating patient adherence to antidepressant therapy: a real-world comparison of adherence and economic outcomes. Med. Care 44, 300–303 (2006).

17. Von Knorring, L., Akerblad, a-C., Bengtsson, F., Carlsson, a & Ekselius, L. Cost of depression: effect of adherence and treatment response. Eur. Psychiatry 21, 349–54 (2006).

18. Kaplan, C. & Zhang, Y. Assessing the Comparative-Effectiveness of Antidepressants Commonly Prescribed for Depression in the US Medicare Population. J Ment Heal. Policy Econ. 15, 171–178 (2013).

19. Sheehan, D. V., Keene, M. S., Eaddy, M., Krulewicz, S., Kraus, J. E., & Carpenter, D. J. (2008). Differences in medication adherence and healthcare resource utilization patterns: older versus newer antidepressant agents in patients with depression and/or anxiety disorders. CNS Drugs, 22, 963-973.

20. Hess, L. M., Raebel, M. A., Conner, D. A. & Malone, D. C. Measurement of adherence in pharmacy administrative databases: a proposal for standard definitions and preferred measures. Ann. Pharmacother. 40, 1280–88

21. Hornbrook, M. C. & Goodman, M. J. Chronic disease, functional health status, and demographics: a multi-dimensional approach to risk adjustment. Health Serv. Res. 31, 283–307 (1996).

22. Bureau of Labor Statistics, Consumer Price Index. http://www.bls.gov/home.htm.

23. Roodman, D. How to do xtabond2 : An introduction to difference and system GMM in Stata. The Stata Journal. 9(1) 86–136 (2009).

24. Mishra, P., Newhouse, D. Does health aid matter? Journal of Health Economics 28, 855-872 (2009).

25. Trivedi, M. H., Lin, E. H. B. & Katon, W. J. Consensus recommendations for improving adherence, self-management, and outcomes in patients with depression. CNS Spectr. 12, 1–27 (2007).

26. Cohen, J. Statistical Power Analysis for the Behavioral Sciences (second ed.). (Lawrence Erlbaum Associates, 1988).

Chapter 4 – Longer-term cost-effectiveness of a cognitive-behavioral program for preventing depression in at-risk adolescents and the effect of intervention dose

Abstract

Objective:

We evaluated the longer-term cost-effectiveness of the "Prevention of depression in at-risk adolescents" (POD) study from a limited-societal perspective and examined causal effects of intervention dose on economic outcomes using instrumental variable methodology to control multiple source of bias.

Methods:

The POD trial was a randomized control trial designed to test the clinical- and cost-effectiveness of a cognitive behavioral prevention (CBP) program created to prevent depression in high-risk adolescents. Study participants were recruited from four US sites and were required to have a history of depression and/or current subsyndromal depressive symptoms in addition to being offspring of a parent with a current or prior depressive episode. A total of 316 youth aged 13-17 were randomized to CBP or usual care and were assessed at baseline and 3, 9, 21, and 33 months post baseline. Depression-free-days (DFD), the primary clinical outcome in the cost effectiveness analysis, were calculated from the Children's Depression Rating Scale-Revised and were used to estimate quality-adjusted-life-years (DFD-QALY) based on published decrement weights of depression. Cost data were collected concurrently using the Child and Adolescent Services Assessment, financial records, and interviews with study staff. Adjusted incremental cost-effectiveness ratios (ICER) and cost-acceptability acceptance curves were calculated to assess cost-effectiveness and uncertainty around estimates. We used weather patterns, travel

time, and randomization status to instrument the effects of intervention dose on incremental clinical and cost outcomes. We used these estimates to construct ICERs representative of specified intervention doses.

Results:

Neither total nor outpatient costs were significantly different between groups (p=.437) in the full sample, and intervention adolescents had 35.8 additional DFDs (*p*=.049) greater in the intervention arm than usual care, translating into 0.04 additional DFD-QALY. Using total costs in the numerator of the ICER, we calculated the cost per DFD gain as $61 (95% CI: -20 – 1,043) and the cost per DFD-QALY as $54,888 (95% CI: -18,631 – 938,679) in the full sample. Sensitivity analyses which removed an identified high cost outlier resulted in 77% reductions in estimated ICERS. A full intervention dose in the full sample reduced ICERs by 13% when defined as 75% or better attendance of acute-phase intervention sessions. A full intervention dose defined as 100% attendance decreases ICERs by 56%.

Conclusions:

We demonstrated the cost-effectiveness of the POD prevention program endured through the longer-term. Our estimates of cost per DFD and cost per DFD-QALY were comparable to an earlier economic evaluation showing the program to be cost-effective in the short-term. Removing the influence of a high cost outlier in our estimates or focusing on outpatient costs suggest the cost per DFD and DFD-QALY may be lower in the longer-term than the shorter-term. We also demonstrated the benefit of higher intervention dose on economic outcomes. A full intervention dose, measured in multiple ways, results in gains in clinical outcomes that

outpace additional costs. Increased clinic-effectiveness that does not increase the cost per clinical outcome demonstrates potential added benefit of adherence promotion. In addition, reductions in estimated ICERs at higher levels of intervention dose signal decision-makers of resource availability for adherence promotion that may make them equally or better off than without additional adherence promotion.

Introduction

The National Institute of Mental Health estimates that 11 percent of adolescents have a depressive disorder by age 18[1]. Risk of developing a depressive disorder increases with age, and is almost twice as high among female compared to males. The strongest risk factor, however, is a parental history of depression[2]. Adolescents with one or more parents who are actively depressed or have a history of depression are 2 to 3 times more likely to develop depression than offspring of parents with no history of depression[2].

Decrements to mental- and physical-health are similar between adolescents and adults, and the World Health Organization names major depressive disorder as the leading cause of disability among Americans age 15 to 44[1]. Youth who are depressed are more likely to engage in risky behaviors, such as substance abuse, and are at elevated risk for adverse events including accidents and suicide attempts[3]. Depression also interferes with educational attainment and interpersonal relationships and influences adolescents' long-term trajectories as they enter into adulthood[4].

Depression can have enduring, negative effects over the life-course, highlighting the importance of early intervention[4]. Despite multiple treatment options, including psychotherapy and pharmacotherapy, only 25 percent of depressed youth receive treatment[5]. In addition to the low levels youth who receive treatment, adherence to treatment is likely suboptimal. Multiple barriers limit treatment options and interfere with adherence to recommended treatment guidelines. A more efficient care delivery model to reduce the burden depression would be to prevent depressive episodes in the first place.

Effective prevention programs have been developed[6] but are not widely accessible and are often not available to the youth who need them the most. The Prevention of Depression

(POD) study addressed these care gaps by testing a cognitive behavior prevention (CBP) program designed to prevent depression in at-risk adolescents who were offspring of a parent with current or prior depressive disorders[7]. The POD study demonstrated that a CBP program was clinically effective at reducing depressive episodes over the acute and continuation phases of the study[7] as well as over a longer-term 33 month follow-up period[8]. The CBP program was also shown to be cost-effective over the combined acute/continuation phase[9].

Participation by adolescents and their parents in the POD intervention varied. Any estimates of clinical-effects or cost-effectiveness will be anchored to the rate of participation that naturally occurred in the study. This is an important consideration because adherence to intervention protocol is a primary factor in treatment-response heterogeneity[10]. Variation in dose, or participation patterns, has often been addressed in clinical trials through per-protocol or similar types of analyses. However, results from such methods likely contain substantial, unclear biases because patients' behavior around adherence patterns is not random.

Factors related to both the outcome under study, such as depression, and adherence will confound attempts to model the influence of adherence on outcomes. For example, people who respond better to an investigational treatment or who began a study with better prognosis than their peers may attend intervention sessions differentially than others participants. Our interest in this study is to understand the causal effect of intervention adherence, total acute-phase CBP intervention dose, on economic outcomes. Better understanding the dose-response relationship would provide important information about program implementation and the value of CBP. The effect of intervention dose on cost-effectiveness estimates may demonstrate potential benefit gains though intervention adherence promotion.

The current study provides an economic evaluation from a limited-societal perspective[11] of the POD intervention over the longer-term follow-up period. Understanding the relative costs and benefits of a prevention program over nearly three years provides important information to decision makers considering implementing prevention services. In addition, this study assesses the effect of intervention dose on the economic outcomes. We apply instrumental variables (IV) methodology, which controls multiple sources of confounding[12], to attempt to establish causal effects of intervention dose on clinical and cost outcomes.

Methods

Participants

Study eligibility required adolescents to have a parent with a current or prior depressive disorder in addition to having elevated but subdiagnostic depressive symptoms and/or a prior depressive episode[7]. A total of 316 youth aged 13-17 were enrolled across 4 US sites, including Vanderbilt University, Nashville, TN; University of Pittsburgh, Pittsburgh, PA; Kaiser Permanente Northwest, Center for Health Research in Portland, OR; and Judge Baker Children's Center/Children's Hospital in Boston, MA. Institutional review boards at each site approved the study, and all parents and adolescents provided written informed consent and assent, respectively, prior to being enrolled and randomized into the study.

About half the sample received UC only, and the other half received intervention services in addition to UC. The intervention included 8 weekly group sessions followed by 6 monthly continuation session. Parents were also invited to participate in 2 parent break-out sessions as part of the intervention. Further details about the methods, sample, intervention, and clinical outcomes are described elsewhere[7].

Clinical Outcomes

Both youth and parent were assessed on multiple clinical outcomes at study entry (baseline) and at 3, 9, 21, and 33 months post randomization. Following other cost-effectiveness analyses of depression treatment trials[13–16], we used these clinical data to create several summary measures for the economic analyses. We constructed summary measures of adolescents' depression symptoms and severity using the17-item Children's Depression Rating Scale - Revised (CDRS-R)[17]. To compare the cost-effectiveness of this intervention with others, we created a measure of depression-free days (DFD)[13–16] using CDRS-R scores from all follow-up points[14,15] to categorize (a) depression-free days, (b) days with some depression but not meeting full criteria[13], and (c) days in a depressive episode. To calculate depressive symptoms for each day over the follow-up, we used linear weighting to interpolate between the non-depressed and fully depressed thresholds and assign an estimated depression value to each day in the follow-up interval. Number of DFDs was the total number of days in the interval minus days with significant depressive symptoms. As used in previous work[13], this approach captures the effects of the intervention, including both elevated-symptom days and days in a full depressive episode.

We transformed DFDs into quality-adjusted life-years (QALYs) with preference weights assigned to depression reflecting the value of different health or disease states derived from empirical studies. For example, DFDs are typically assigned a utility weight of 1.0 (full health), whereas days in a depressive episode are estimated to have a lower weight, such as 0.6. Empirical studies indicate that depression is associated with a decrease in health-related quality of life of 0.2-0.6[18]. Based on these previous reports, we used 0.4 as the decrease in preference weight for the base-case analysis[16,19].

Cost Outcomes: Intervention Service Costs

Accounting records provided costs for payroll, facilities and overhead, and goods and services. Group leaders estimated their time to complete the intervention tasks and use of capital equipment, space, and supplies. We included costs of CBP sessions, time CBP group leaders spent with individual youth by phone or in person, supervision, training, and materials. We excluded research-specific costs such as randomization and research assessments.

Cost Outcomes: Non-protocol Costs

The Child and Adolescent Services Assessment (CASA)[20] provided data on youths' mental health services utilization outside of the study protocol. To estimate health care costs, we applied unit costs developed for this study from the Truven Health Marketscan Commercial Claims and Analytics Database for medical services and social services unit costs developed for other studies[13,14]. At baseline, both adolescents and their parents separately reported on any services the youth had received in the previous three months; at 3-, 9-, 20-, and 33-month follow-ups, we again assessed youths' service use since the previous evaluation.

Family Costs

Following recommended guidelines[21] we estimated costs for the time parents spent taking youth to related services. We created profiles of parent time spent for the intervention, non-protocol services, travel to services and waiting based on published research[14,16,19], and wages to value parent time.

Intervention dose

We calculated measures of acute-phase intervention dose using detailed attendance records. Group leaders recorded whether an adolescent attended scheduled CBP sessions and their level of participation within the group. We defined two measures of full dose. The first definition required at least 75% attendance to CBP sessions (7 or 8 sessions total), and the

second required 100% attendance of all CBP sessions (8 sessions). We chose multiple definitions because it was not clear *a priori* if missing one session would be meaningful in terms of outcomes.

Instruments

Viable instruments must be highly predictive of acute-phase CBP attendance but uncorrelated with factors related to depressive symptoms. Extensive details on the selection process and performance of our instrument sets are reported elsewhere[22]. In summary, we chose potential instruments based availability and on theoretical independence from depressive symptomology, we then empirically tested their predictive power. Instruments included in these analyses were randomization status, travel time to the CBP facility, and daily weather patterns on the day of CBP sessions, specifically maximum recorded wind gust and average temperature.

Randomization status acts as the perfect instrument assuming there no systematic error in the process because it randomly allocates unobservable factors related to depression. Measures of distance from a medical facility have been used previously as instruments[23], as has weather[24]. One could argue that there is some evidence weather patterns are related to depression[25,26], and therefore violate a key assumption of IV analyses. We believe our measures of weather are unrelated to depression symptomology because they are constructed using single-day measurements rather averages over long periods, and it is unlikely weather on any one day influences depression over the long term.

Statistical Analyses

Analyses were conducted using a limited-societal perspective[11] and were intention-to-treat unless otherwise specified as part of sensitivity or subgroup analyses. We used

nonparametric bootstrapping with 1,000 replications to calculate point estimates and measures of uncertainty of incremental costs, effects, and cost-effectiveness ratios (ICER). Our aggregate measures of costs included total cost and outpatient costs over the 33 month follow-up period; and our measures of clinical outcomes were DFD and DFD-QALY calculated cumulatively between study entry and the 33 month follow-up. Point estimates of incremental costs and effects from each bootstrap replication were used to construct graphs of the cost-effectiveness plane, which are scatter plots of the cost-effect pairs, and to calculate ICERS. ICERs represent the cost per outcome and are calculated as the incremental cost divided by the incremental effect. All analyses were adjusted for baseline depression, baseline costs, race, age, sex, and socioeconomic status (SES).

We addressed uncertainty in our analyses by constructing bootstrapped 95% confidence intervals around our estimated ICER, using a bias-corrected and accelerated method to adjust for both bias and skewness in the bootstrap distribution[27]. We also applied the net benefit framework to construct cost-effectiveness acceptability curves (CEAC)[28] to evaluate the probability of cost-effectiveness across a range of values a hypothetical decision-maker may be willing to pay per unit gain in an outcome. In this study, we calculated probabilities of cost-effectiveness by willingness to pay per DFD-QALY gain.

We identified one high-cost outlier (+15.5 SD above the mean), who we removed as part of sensitivity analyses. We also analyzed outpatient costs only, but for all participants. Many cost-effectiveness studies of depression interventions have limited their analyses to outpatient costs because of small samples, and utilization of higher levels of care (e.g., inpatient) are rare and likely would not be affected by a short-term intervention (e.g., CBP). We also conducted subgroup analyses based on baseline parental depression, which was shown previously to be an

important moderator[7,8]. We conducted subgroup analyses with and without the high cost outlier included.

We used IV methodology to estimate the effect of intervention dose on incremental outcomes and costs, and then used these estimates to construct ICERs. We estimated three equations using three-stage residual inclusion[29] in IV analyses. The first equation predicted whether or not an adolescent receives any CBP (i.e., one or more sessions). The second equation predicted full dose among those youth who received some CBP dose. Finally, the third equation modeled the effect of dose on outcome (DFD or DFD-QALY) informed by estimates from the first two equations. All models controlled for the same covariates used in earlier models, and we used similar nonparametric methodology to construct bootstrapped 95% confidence intervals around our ICERs. We did not report analyses with first-stage *F*-tests below 10[30] because of concern of bias related to weak instruments.

Approximately 85% the sample completed the 33-month assessment, and 69.3% percent of adolescents had complete data at all waves. Missing data were imputed using multiple imputation with chained equations[31,32] We included baseline demographics and all non-missing values of costs or outcomes at all time points in the models that generated imputed estimates. We created five imputation datasets and combined estimates so that standard errors reflected the variability introduced by the imputation process[32]. Analyses of the effects of intervention dose were limited to participants who had were assessed at the final month 33 assessment (N=268; 85%=268/316).

Results

Balance on baseline characteristics has been shown in previous studies to be comparable between CBP and UC[7]. Table 1 presents the baseline characteristics by randomization condition.

Non-protocol Service Use and Cost

Table 4.2 shows details on health services use costs by randomization condition during the 33 month follow-up period. Unadjusted total costs were $1,920 higher on average in the CBP group compared to UC, but the difference was not statistically different (p=.216). While we did not test for statistical differences between groups at the micro-level, one participant who was hospitalized for most of the follow-up period was identified as a high cost outlier, with total costs 15.5 standard deviations higher than average.

Adjusted incremental costs, effects, and cost-effectiveness ratios

Table 4.3 provides adjusted estimates of incremental costs and effects along with cost-effectiveness ratios from analytic samples, including our full sample, removal of an identified high cost outlier, and subgroups based on parental depression at study entry. Figure 1 displays complimentary information with the incremental cost-effectiveness planes from each analysis group. Each point in Figure 4-1 represents a bootstrapped replicate of the adjusted difference in clinical effect and costs over 33 months between CBP and UC.

Full sample

Results for the base-case analysis indicated that compared to youth in UC, those in the CBP condition had an average of 35.8 more DFDs (p=.049) and 0.04 more DFD-QALYs (p=.049) through follow-up. Total costs and outpatient costs were higher among CBP participants but were not significantly different. At 33 months using total costs in the numerator,

the estimated cost per DFD was $61 (95% CI: -20 –1,043) and the estimated cost per DFD-QALY was $54,888 (95% CI: -18,631 – 938,679). Removing the effects of inpatient services, as measured by outpatient costs, resulted in an estimated cost per DFD of $29 (95% CI: -1,470 – 170) and an estimated cost per DFD-QALY of $26,313 (95% CI: -332,055 –384,681). Figure 1 shows observations from the full sample lie mostly in the northeast quadrant of the cost-effectiveness plane, where CBP is more effective and more expensive than UC.

Removal of identified outlier

Removal of the high cost outlier from analyses did not meaningfully alter the pattern of findings with incremental clinical effects; CBP participants had 40.2 additional DFDs (p=.031) and 0.40 additional DFD-QALYs (p=.031) over follow-up. Estimates of incremental total cost, however, were markedly different. While average cost was not different between study groups, it was about one forth that of the full sample. Outpatient costs were similar on average to those from the full sample were not different between study conditions. At 33 months using total costs in the numerator, the estimated cost per DFD was $14 (95% CI: -44 – 138) and the estimated cost per DFD-QALY was $12,263 (95% CI: -39,667 – 124,335). The estimated cost per DFD was $23 (95% CI: -11 – 819) and the estimated cost per DFD-QALY of $20,827 (95% CI: -3,957 – 158,371) using outpatient costs in the numerator of the cost-effectiveness calculation. Figure 4-1 shows the influence of the outlier in ICER calculations as the north-south spread displayed in the upper panels was reduced substantially by removal of the outlier.

Subgroup analyses

Parent actively depressed at baseline

Subgroup analyses of adolescents whose parents were actively depressed at baseline showed no statistically significant intervention effects on DFD or DFD-QALYs. Total costs and outpatient costs were higher among CBP participants but were not significantly different. We did not calculate ICERs within this subgroup because there was no evidence the intervention was effective, regardless of cost.

Parent depression in remission at baseline

Results among adolescents whose parents' depression was in remission at study entry indicated that compared to youth in UC, those in the CBP condition had an average of 77.9 more DFDs (p=.002) and 0.09 more DFD-QALYs (p=.002) through follow-up. Total costs and outpatient costs were higher on average among CBP participants but were not significantly different. At 33 months using total costs in the numerator, the estimated cost per DFD was $64 (95% CI: -1,014 – 1,141) and the estimated cost per DFD-QALY was $57,331 (95% CI: -912,362 – 1,027,024). Using outpatient costs in the numerator resulted in a cost per DFD of $13 (95% CI: -7,554 – 67) and an estimated cost per DFD-QALY of $11,353 (95% CI: -3,193 – 57,865). Figure 1 shows most of the bootstrap replicates fall within the northeast quadrant. Compared to the full sample, the clinical effect is shown be stronger, as seen by the eastward movement along the vertical axis, and the incremental total cost is shown to have more variability, as seen by the less concentrated distribution along the cost axis.

Probability of cost-effectiveness across willingness to pay for DFD-QALY

Figure 4-2 presents the cost-effectiveness acceptability curve (CEAC) for DFD-QALY at 33 months for each analysis group. Red vertical bars in Figure 2 represent common thresholds

used in evaluation of new medical interventions, at $50,000, $100,000, and $150,000 per QALY gain. Using estimates of total cost from our full sample, the probability of CBP being cost effective at $50,000, $100,000, and $150,000 was 46.7%, 70.8%, and 80.8%, respectively. Removal of the high cost outlier increased the probability of cost-effectiveness at each threshold. The probability CBP was cost-effective was 86.9% at $50,000 per DFD-QALY, 93.7% at $100,000 per DFD-QALY, and 95.2% at $150,000 per DFD-QALY. Figure 2 emphasizes the lack of clinical effect of CBP among adolescents whose parents are actively depressed at baseline; the probability of cost-effectiveness never exceeds 54.6% regardless of the value of wiliness to pay. Finally, the probability of cost-effectiveness among youth whose parents' depression was in remission at baseline was 43.8%, 76.1%, and 89.2% for willingness to pay values of $50,000, $100,000, and $150,000 per DFD-QALY, respectively.

Instrumented effects of acute-phase intervention dose on incremental costs, outcomes, and cost-effectiveness ratios

Observed attendance patterns showed 66.4% of youth randomized to CBP attended 7 or more acute CBP sessions and 35.0% attended all 8 sessions. Prior to proceeding with dose analyses, we tested the predictive power of our potential instruments. Using data from the full sample, the *F*-test for receipt of any CBT was $F(1,259)=912.7$, for full dose at 75% of acute sessions was $F(1,118)=18.9$, and for full dose at 100% of acute sessions was $F(1,117)=18.0$. Among analyses excluding an identified cost outlier, the *F*-test for receipt of any CBT was $F(1,258)=905.0$, for full dose at 75% of acute sessions was $F(1,116)=17.9$, and for full dose at 100% of acute sessions was $F(1,116)=17.9$. In subgroup analyses of youth whose parents' depression was in remission at baseline, the *F*-test for receipt of any CBT was $F(1,131)=1,063.6$,

for full dose at 75% of acute sessions was $F(1,61)=11.7$, and for full dose at 100% of acute sessions was $F(1,61)=20.6$. We were unable to establish sufficient predictive power among the subgroup of youth whose parents were actively depressed at baseline.

Table 4-4 shows the incremental costs, outcomes, and ICERs after instrumentation. An intervention dose of at least 75% of acute CBP sessions among the full sample resulted in 61.4 more DFDs (p=.041) than the UC group, 0.07 more DFD-QALYs (p=.041), and no statistical difference in costs, which translate into a cost per DFD of $53 (95% CI: -27 – 777) and a cost per DFD-QALY of $47,760 (95% CI: -25,041 – 699,376). After removing the influence of the high cost outlier, the same CBP dose resulted in 68.4 more DFDs (p=.023), 0.08 more DFD-QALYs (p=.023), and no statistical difference in costs, which translate into a cost per DFD of $4 (95% CI: -45 – 82) and a cost per DFD-QALY of $3,608 (95% CI: -40,507 – 73,608).

Among the sub group of participants whose parents' depression was in remission at baseline, a 75% intervention dose led to 121.0 more DFDs (p=.002), 0.13 more DFD-QALYs (p=.002), and no statistical difference in costs, which translate into a cost per DFD of $64 (95% CI: -9 – 610) and a cost per DFD-QALY of $57,757 (95% CI: -89,460 – 548,594). Removal of the high cost outlier among the sub group of participants whose parents' depression was in remission at baseline, a 75% intervention dose led to 135.8 more DFDs (p=.004), 0.15 more DFD-QALYs (p=.004), and no statistical difference in costs, which translate into a cost per DFD of $8 (95% CI: -21 – 39) and a cost per DFD-QALY of $7,392 (95% CI: -18,456 – 34,924).

A 100% intervention dose of acute CBP sessions among the full sample resulted in 138.0 more DFDs (p=.013), 0.15 more DFD-QALYs (p=.013), and no statistical difference in costs, translating into a cost per DFD of $27 (95% CI: -26 – 271) and a cost per DFD-QALY of $24,427 (95% CI: -23,541 – 243,864). After removing the influence of the high cost outlier, the

same CBP dose resulted in 147.4 more DFDs (p=.008), 0.16 more DFD-QALYs (p=.008), and no statistical difference in costs, translating into a cost per DFD of $-1 (95% CI: -50 – 39) and a cost per DFD-QALY of -$1,169 (95% CI: -44,899 – 34,662).

Among the sub group of participants whose parents' depression was in remission at baseline, a 100% CBP dose led to 216.1 more DFDs (p=.004), 0.24 more DFD-QALYs (p=.004), and no statistical difference in costs, which translate into a cost per DFD of $40 (95% CI: -11 – 274) and a cost per DFD-QALY of $36,322 (95% CI: -9,871 – 246,858). Removal of the high cost outlier among the sub group of participants whose parents' depression was in remission at baseline, a 100% CBP dose led to 233.0 more DFDs (p=.004), 0.26 more DFD-QALYs (p=.004), and no statistical difference in costs, which translate into a cost per DFD of $8 (95% CI: -26 – 45) and a cost per DFD-QALY of $6,891 (95% CI: -23,141 – 40,851).

Discussion

Preventing depressive episodes in adolescents is important to youth and their family. Adverting depressive episodes lowers mental- and physical-health related morbidity as well as influences trajectories of educational achievement, employment outcome, and social development. The POD study has demonstrated clinical-effectiveness at preventing depressive episodes in high-risk adolescents over acute and continuation phases of the study (through 9 months)[7] as well as through longer-term follow-up (through 33 months)[8]. In addition, the POD CBP program has been shown to be cost-effective through 9 months[9]. Prior studies show compelling evidence of the effectiveness and value of the POD CBP program. However, the longer-term cost-effectiveness of CBP, an important consideration to decision-makers considering implementation of the program, has been unknown.

This study provides two import contributions to prevention research. First, our results demonstrate enduring cost-effectiveness of the POD CBP program through 33 months. While the estimated ICER from the full sample does not fall below the informal threshold of $50,000 per QALY as it does in the earlier cost-effectiveness analysis, sensitivity analyses show results are highly skewed by a high cost outlier. Analyses without the influence of the outlier and show ICERs well below $50,000 per QALY. In addition, it is unclear about the appropriateness of the continued use of the $50,000, which has been widely criticized for being out of date and not particularly useful[33].

Despite our results being highly influenced by a single high cost outlier, our findings are consistent with the earlier cost-effectiveness evaluation[9]. Results from sensitivity analyses suggest the cost per DFD and per DFD-QALY may decline over time; removal of the identified outlier reduces the ICERs in our study by 77%. And focusing on outpatient costs rather than total costs shows the longer-term evaluation to have ICERs approximately 40% lower than estimates through 9 months.

The second contribution this study makes is the novel evaluation of the effect of dose on economic outcomes. To be best of knowledge, no other researchers have used instrumentation to isolate causal effects of non-random factors in an economic evaluation of a randomized controlled trial. We show clear evidence that higher intervention dose leads to better clinical outcomes that outweigh higher costs. Receiving a full dose of CBP as measured by 75% or more attendance of acute-phase sessions results in a 13% ICER reduction, and receiving a full CBP dose as measured by 100% adherence of acute-phase sessions leads to a 56% ICER reduction. By showing that better adherence leads to better economic outcomes, we demonstrate there is potential additional benefit gains available through better adherence to an existing program. At a

static value of willingness to pay per QALY, ICER reductions increase available resources to promote better adherence.

This study includes several limitations. We did not include productivity losses related to depression in our cost estimates, which are commonly excluded in studies with adolescents because of their disengagement with the labor market. However, depression is associated with educational attainment, which may alter long-term employment outcomes[4,34] In addition, we did not include a preference-based measure of health-related quality of life that directly measured the impact of the intervention on youth QALYs. Rather, we relied on indirect established methods for translating DFDs into QALYs[13–16] that use preference weights reported in the literature for depressed adults. However, adult weights may not accurately represent the impact of depression on adolescents' quality of life, but no empirical weights yet exist for youth[35]. The preference weights used here measured the decrease in health-related quality of life associated with only depression and not those linked to other psychopathology or impairment, although presumably these were distributed randomly across conditions. Finally, for non-protocol services we used nationally representative unit costs, which may not represent the actual unit costs at individual study sites.

In summary, we demonstrate long-term cost-effectiveness of the POD CBP program. Despite distributional challenges associated with evaluation of cost data, we show similar cost-effectiveness estimates to prior short-term evaluations. Sensitivity analyses and focus on outpatient costs signal the cost per DFD and DFD-QALY may decrease over the longer-term. In addition, we show clear evidence of the value of intervention adherence. The POD CBP intervention is a cost-effective program in the short- and long-run, and implementation of additional adherence promotion efforts likely improve overall cost-effectiveness of the program.

Table 4-1. Baseline Characteristics

	CBP	***UC***	
Adolescents (N=316)	n=159	n=157	
Demographics	**M (SD)**	**M (SD)**	***p***
Age	14.8 (1.5)	14.8 (1.3)	.66
Female	93 (58.5%)	92 (58.6%)	.98
Caucasian	129 (82.7%)	125 (80.6%)	.64
Latino/Hispanic	10 (6.3%)	11 (7.1%)	.78
Socioeconomic status	46.3 (12.1)	45.2 (11.9)	.39
Adolescent Depression			
Center for Epidemiological Studies - Depression Scale	18.5 (9.1)	18.8 (9.6)	.83
Children's Depression Rating Scale - Revised	28.6 (8.0)	29.1 (8.5)	.52

Table 4-2. Unadjusted service use and cost (2009 USD) by randomization condition through 33 months

	% with use		*Mean (SD) visits*	
	CBP	*UC*	*CBP (N=159)*	*UC (N=157)*
Section 1a: Non-Protocol Services				
Inpatient Mental Health Days	4.1%	3.4%	37.8 (76.6)	15.2 (15.0)
Inpatient Alcohol or Drug Days	1.4%	0%	34.5 (13.4)	
Counseling or Medication Management Visits	47.6%	43.8%	17.1 (24.5)	15.2 (22.0)
Day Hospital Days	1.4%	2.1%	69.0 (53.7)[1]	11.7 (9.5)
Alcohol or Drug Treatment Visits	4.1%	2.1%	8.0 (5.1)	31.0 (26.1)
Crisis Services	2.7%	2.7%	24.3 (34.3)	4.3 (4.0)
Medical doctor visits	15.6%	15.8%	2.6 (1.9)	2.8 (4.8)
Emergency Room Visits	3.4%	2.1%	1.0 (--)	2.0 (1.7)
Days of Antidepressant Medication	15.7%	12.7%	145.0 (194.5)	168.8 (214.4)
Days of Stimulant Medication	8.8%	6.4%	202.1 (257.0)	535.9 (806.6)
Days of Other Psychotropic Medication	1.3%	1.9%	380.5 (367.0)	223.7 (236.1)
ANY School Services	32.7%	34.2%	33.5 (91.9)	38.6 (99.2)
Juvenile correction contact	4.1%	11.6%	6.2 (4.5)	7.6 (9.3)
Section 1b: Non-Protocol Costs of Services				
% with Any Cost, Mean Cost	65.7%	70.2%	4,075 (19,798)	2,690 (6,642)
Non-Protocol Family Costs	55.0%	59.0%	391 (1,038)	276 (676)
Total Non-Protocol Costs[a]			4,183 (19,832)	2,670 (6,642)
Section 2: Intervention Costs				
CBP Program Costs			277 (108)	
Intervention Family costs			314 (200)	
Total Intervention Costs			591 (286)	
Section 3: Total Costs				
TOTAL COST[b,c]			4,590 (19,403)	2,670 (6,642)

[a]not statistically significant; [b]statistically significant $p < .05$; [c]total costs imputed using multiple imputations with chained equations, if missing. (--) = only one case (no variance)

[1]The average length of stay was highly influenced by the identified high cost outlier

Table 4-3. Adjusted incremental costs, outcomes, and cost-effectiveness ratios thru 33 months

	Incremental Cost Estimates		Incremental Outcomes		ICERs			
	Total	Outpatient	DFD	QALY	Total Cost/DFD	Total Cost/QALY	Outpatient Cost/DFD	Outpatient Cost/QALY
	Mean (SE)	*Mean (SE)*	*Mean (SE)*	*Mean (SE)*	*Mean (95% CI)*	*Mean (95% CI)*	*Mean (95% CI)*	*Mean (95% CI)*
Full Sample (N=316)	2,184 (1,809)	1,047 (1,825)	35.8 (18.2)*	0.04 (0.02)*	61 (-20 – 1,043)	54,888 (-18,631 – 938,679)	29 (-1,470 – 170)	26,313 (-332,055 – 384,681)
High cost outlier removed	547 (861)	930 (826)	40.2 (18.5)*	0.04 (0.02)*	14 (-44 – 138)	12,263 (-39,667 – 124,335)	23 (-11 – 819)	20,827 (-3,957 – 158,371)
Parent actively depressed at baseline	-140 (1,343)	1,039 (1,259)	2.4 (26.3)	0.00 (0.03)	NA	NA	NA	NA
Parent's depression in remission at baseline	4,959 (3,375)	982 (4,107)	77.9 (26.8)**	0.09 (0.03)**	64 (-1,014 – 1,141)	57,331 (-912,362 – 1,027,024)	13 (-7,554 – 67)	11,353 (-3,193 – 57,865)
… and high cost outlier removed	1,106 (1,066)	698 (1,131)	88.4 (24.4)***	0.10 (0.03)***	13 (-12 – 51)	11,259 (-10,769 – 45,468)	8 (-22 – 31)	7,101 (-5,737 – 25,796)
Column	2A	2B	2C	2D	2E	2F	2G	2H

*p<.05, **p<.01, ***p<.001; NA, not applicable because CBP is dominated by UC

Figure 4-1. Cost-effectiveness planes of adjusted incremental total costs and depression-free-days (DFD) thru 33 months

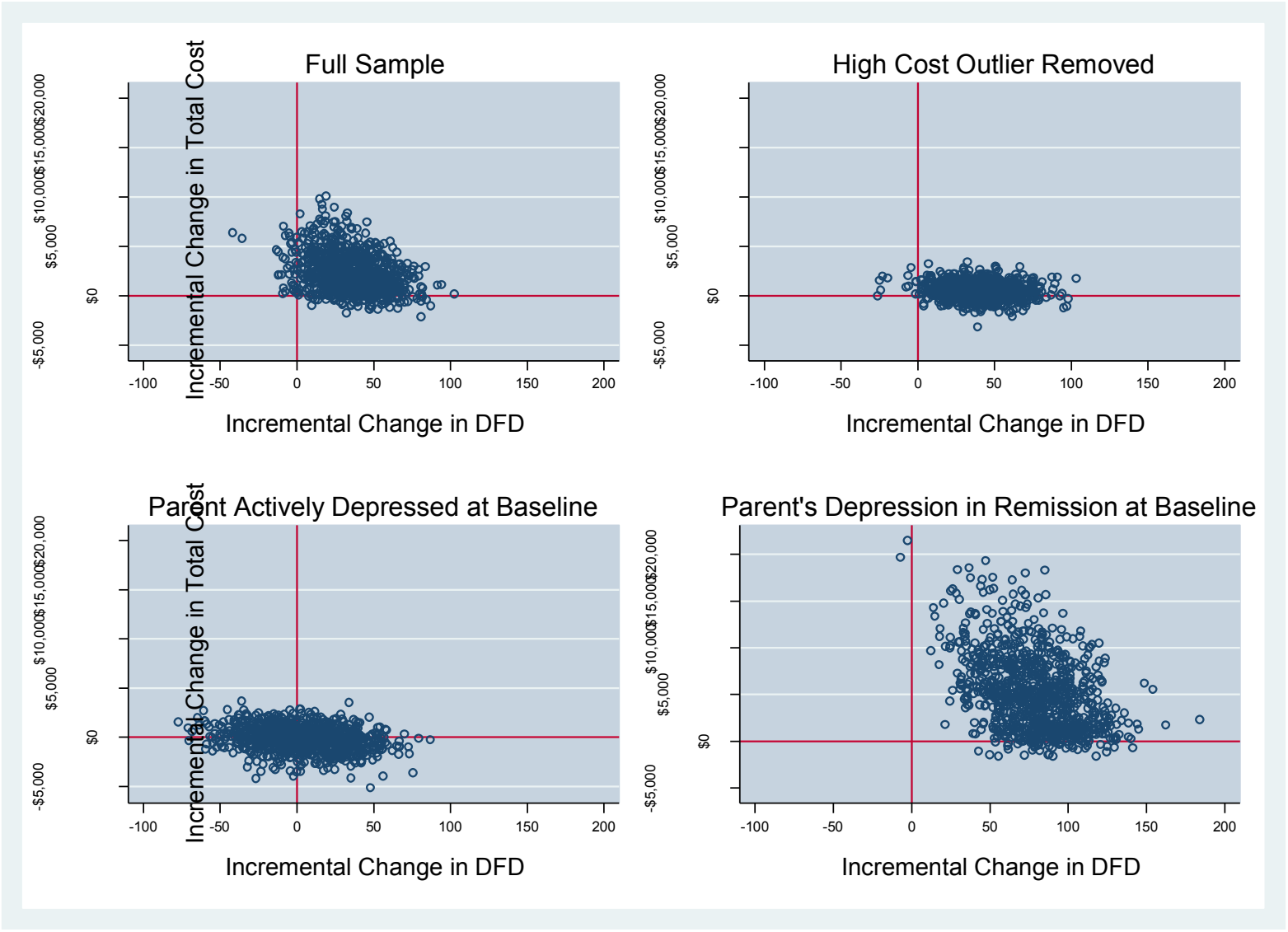


Figure 4-2. Cost effectiveness acceptability curves

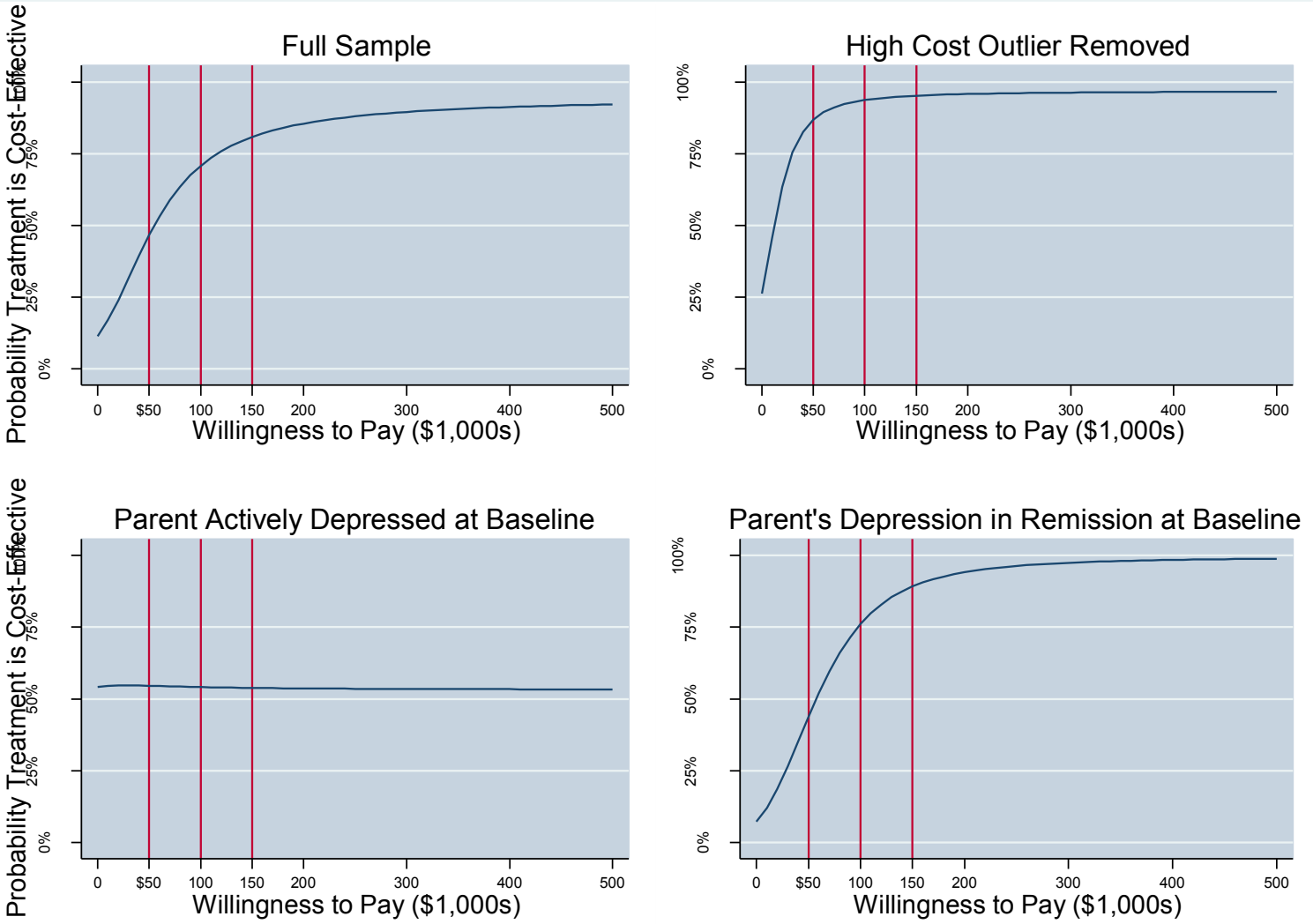


Table 4-4. Instrumented effects of acute-phase intervention dose on adjusted incremental costs, outcomes, and ICERs thru 33 months

	Cost Estimates		Outcomes		ICERs			
	Total	Outpatient	DFD	QALY	Total Cost/DFD	Total Cost/QALY	Outpatient Cost/DFD	Outpatient Cost/QALY
	Mean (SE)	*Mean (SE)*	*Mean (SE)*	*Mean (SE)*	*Mean (95% CI)*	*Mean (95% CI)*	*Mean (95% CI)*	*Mean (95% CI)*
Acute-Phase Intervention Dose								
75% Intervention Dose								
Full Sample (N=268)[1]	3,261 (3,109)	1,401 (845)	61.4 (30.0)*	0.07 (0.03)*	53 (-27 – 777)	47,760 (-25,041 – 699,376)	23 (-7 – 225)	20,515 (-6,427 – 202,332)
High cost outlier removed	274 (1,183)	1,176 (795)	68.4 (30.0)*	0.08 (0.03)*	4 (-45 – 82)	3,608 (-40,507 – 73,602)	17 (-6 – 124)	15,461 (-3,541 – 111,860)
Parent's depression in remission at baseline	7,765 (6,801)	2,093 (1,285)	121.0 (39.7)**	0.13 (0.05) **	64 (-9 – 610)	57,757 (-89,460 –548,594)	17 (-2 – 76)	15,569 (-1,969 – 69,794)
… and high cost outlier removed	1,115 (1680)	1,556 (1167)	135.8 (39.7)**	0.15 (0.04)**	8 (-21 – 39)	7,392 (-18,456 – 34,924)	11 (-4 – 40)	10, 315 (-3,242 – 34,688)
100% Intervention Dose								
Full Sample (N=268)[1]	3,747 (4,534)	2,290 (1,705)	138.0 (55.4)*	0.15 (0.06)*	27 (-26 – 271)	24,427 (-23,541 – 243,864)	17 (-6 – 99)	14,928 (-5,462 – 88,673)
High cost outlier removed	-191 (2,306)	1,998 (1,594)	147.4 (55.5)**	0.16 (0.06)**	-1 (-50 – 39)	-1169 (-44,899 – 34,662)	14 (-6 – 68)	12,197 (-5,692 – 61,361)
Parent's depression in remission at baseline	8,722 (8,111)	3,810 (2,638)	216.1 (81.8)**	0.24 (0.09)**	40 (-11 – 274)	36,322 (-9,871 – 246,858)	18 (-3 – 75)	15,866 (-2,794 – 67,668)
… and high cost outlier removed	1,782 (3,308)	3,255 (2,642)	233.0 (75.2)**	0.26 (0.08)**	8 (-26 – 45)	6,891 (-23,141 – 40,851)	14 (-5 – 53)	12,584 (-4,506 – 47,275)
Column	3A	3B	3C	3D	3E	3F	3G	3H

*p<.05, **p<.01, ***p<.001; IS, not applicable because of insufficient predictive power of instrument(s) in first-stage equation; NA, not applicable because of non-significant intervention effects on depression outcomes.

[1]Limited to youth who completed 33-month follow-up assessment

References for Chapter 4

1. Jellinek MS, Snyder JB. Depression and suicide in children and adolescents. Pediatr Rev. 1998;19:255–64..

2. Beardslee W, Versage E, Gladstone T. Children of affectively ill parents: a review of the past 10 years. J Am Acad Child Adolesc Psychiatry 1998;37(11):1134-1141.

3. Brent D, Weersing V. Rutter's Child and Adolescent Psychiatry. In: Rutter M, Bishop D, Pine D, et al., eds. Oxford, England: Blackwell Publishing Ltd; 2008:587-613.

4. Smith JP, Smith GC. Long-term economic costs of psychological problems during childhood. Soc. Sci. Med. 2010;71(1):110-5. doi:10.1016/j.socscimed.2010.02.046.

5. Hirschfeld R, MB K, Panico S, Al E. The National Depressive and Manic-Depressive Association consensus statement on the undertreatment of depression. JAMA 1997;277(4):333-340.

6. Merry SN, Hetrick SE, Cox GR, Brudevold-Iversen T, Bir JJ, McDowell H. Psychological and educational interventions for preventing depression in children and adolescents. Evidence-Based Child Heal. A Cochrane Rev. J. 2012;7(5):1409-1685.

7. Garber J, Clarke GN, Weersing VR, et al. Prevention of depression in at-risk adolescents: a randomized controlled trial. JAMA 2009;301(21):2215-24. doi:10.1001/jama.2009.788.

8. Beardslee WR, Brent DA, Weersing VR, et al. Prevention of depression in at-risk adolescents: longer-term effects. JAMA psychiatry 2013;70(11):1161-70. doi:10.1001/jamapsychiatry.2013.295.

9. Lynch F, Dickerson J, Clarke G, et al. Incremental Cost-Effectiveness of Preventing Depression in At-Risk Adolescents. Under Rev. 2014.

10. Simpson SH, Eurich DT, Majumdar SR, et al. A meta-analysis of the association between adherence to drug therapy and mortality. BMJ 2006;333(7557):15. doi:10.1136/bmj.38875.675486.55.

11. Garrison LP, Mansley EC, Abbott TA, Bresnahan BW, Hay JW, Smeeding J. Good research practices for measuring drug costs in cost-effectiveness analyses: a societal perspective: the ISPOR Drug Cost Task Force report--Part II. Value Health 13(1):8-13. doi:10.1111/j.1524-4733.2009.00660.x.

12. Angrist J, Imbens G, Rubin D. Identification of causal effects using instrumental variables. J. Am. … 1996;91(434):444-455. Available at:

http://www.tandfonline.com/doi/abs/10.1080/01621459.1996.10476902. Accessed November 10, 2013.

13. Lynch FL, Hornbrook M, Clarke GN, et al. Cost-effectiveness of an intervention to prevent depression in at-risk teens. Arch. Gen. Psychiatry 2005;62(11):1241-8. doi:10.1001/archpsyc.62.11.1241.

14. Lynch FL, Dickerson JF, Clarke G, et al. Incremental cost-effectiveness of combined therapy vs medication only for youth with selective serotonin reuptake inhibitor-resistant depression: treatment of SSRI-resistant depression in adolescents trial findings. Arch. Gen. Psychiatry 2011;68(3):253-62. doi:10.1001/archgenpsychiatry.2011.9.

15. Domino ME, Burns BJ, Silva SG, et al. Cost-effectiveness of treatments for adolescent depression: results from TADS. Am. J. Psychiatry 2008;165(5):588-96. doi:10.1176/appi.ajp.2008.07101610.

16. Lave JR, Frank RG, Schulberg HC, Kamlet MS. Cost-effectiveness of treatments for major depression in primary care practice. Arch. Gen. Psychiatry 1998;55(7):645-51. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9672056. Accessed February 13, 2013.

17. Poznanski EO, Grossman JA, Buchsbaum Y, Banegas M, Freeman L, Gibbons R. Preliminary studies of the reliability and validity of the children's depression rating scale. J. Am. Acad. Child Psychiatry 1984;23(2):191-7. Available at: http://www.ncbi.nlm.nih.gov/pubmed/6715741. Accessed February 13, 2013.

18. Pyne JM, Fortney JC, Tripathi S, Feeny D, Ubel P, Brazier J. How bad is depression? Preference score estimates from depressed patients and the general population. Health Serv. Res. 2009;44(4):1406-23. doi:10.1111/j.1475-6773.2009.00974.x.

19. Schoenbaum M, Unützer J, Sherbourne C, et al. Cost-effectiveness of practice-initiated quality improvement for depression: results of a randomized controlled trial. JAMA 2001;286(11):1325-30. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11560537. Accessed November 24, 2014.

20. Ascher BH, Z. Farmer EM, Burns BJ, Angold A. The Child and Adolescent Services Assessment (CASA): Description and Psychometrics. J. Emot. Behav. Disord. 1996;4(1):12-20. doi:10.1177/106342669600400102.

21. Gold M, Siegel J, Russell L, Weinstein M. Cost-Effectiveness in Health and Medicine. New York: Oxford Univeristy Press; 1996.

22. Process I. Attendance and Therapy Process Factors in the Prevention of Depression in At-Risk Adolescents (POD) Study.

23. McClellan M. Does More Intensive Treatment of Acute Myocardial Infarction in the Elderly Reduce Mortality? JAMA 1994;272(11):859. doi:10.1001/jama.1994.03520110039026.

24. Miguel E, Satyanath S, Sergenti E. Economic Shocks and Civil Conflict: An Instrumental Variable Approach. J. Polit. Econ. 2004;112(3):725–753.

25. McWilliams S, Kinsella A, O'Callaghan E. Daily weather variables and affective disorder admissions to psychiatric hospitals. Int. J. Biometeorol. 2014;58(10):2045-57. doi:10.1007/s00484-014-0805-9.

26. Tomita T, Yasui-Furukori N, Nakagami T, Kaneda A, Kaneko S. The association between sunshine duration and paroxetine response time in patients with major depressive disorder. J. Affect. Disord. 2012;136(3):1067-71. doi:10.1016/j.jad.2011.11.012.

27. Thompson SG, Barber JA. How should cost data in pragmatic randomised trials be analysed? BMJ 2000;320(7243):1197-200. Available at: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=1127588&tool=pmcentrez&rendertype=abstract. Accessed November 24, 2014.

28. Hoch JS, Rockx MA, Krahn AD. Using the net benefit regression framework to construct cost-effectiveness acceptability curves: an example using data from a trial of external loop recorders versus Holter monitoring for ambulatory monitoring of "community acquired" syncope. BMC Health Serv. Res. 2006;6:68. doi:10.1186/1472-6963-6-68.

29. Terza J V, Basu A, Rathouz PJ. Two-stage residual inclusion estimation: addressing endogeneity in health econometric modeling. J. Health Econ. 2008;27(3):531-43. doi:10.1016/j.jhealeco.2007.09.009.

30. Murray M. Avoiding Invalid Instruments and Coping with Weak Instruments. J. Econ. Perspect. 2006;20(4):111-132.

31. Royston P. Multiple imputation of missing values. Stata J. 4(3):227-241.

32. Potthoff RF, Tudor GE, Pieper KS, Hasselblad V. Can one assess whether missing data are missing at random in medical studies? Stat. Methods Med. Res. 2006;15(3):213-34. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16768297. Accessed November 24, 2014.

33. Updating Cost-Effectiveness — The Curious Resilience of the $50,000-per-QALY Threshold — NEJM. Available at: http://www.nejm.org/doi/full/10.1056/NEJMp1405158. Accessed November 24, 2014.

34. Marcotte DE, Wilcox-Gök V. Estimating earnings losses due to mental illness: a quantile regression approach. J. Ment. Health Policy Econ. 2003;6(3):123-34. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14646005. Accessed November 24, 2014.

35. De Civita M, Regier D, Alamgir AH, Anis AH, Fitzgerald MJ, Marra CA. Evaluating health-related quality-of-life studies in paediatric populations: some conceptual, methodological and developmental considerations and recent applications. Pharmacoeconomics 2005;23(7):659-85. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15987225. Accessed November 24, 2014.

Chapter 5 – Conclusion

Patients' behavior related to treatment adherence is not a simple mechanism. People face many different barriers to receiving and adhering to treatment, such as financial burden, time constraints, negative side effects, and social stigmas[1]. Analysis of the effect of patient adherence on outcomes is difficult too because patient adherence is often correlated with the outcomes the treatment is targeting, resulting in biased estimates of the effect of adherence. This dissertation project addresses these complexities and provides policy-relevant evidence to inform decision-makers about the allocation of medical care resources.

In our first aim, we find clear evidence that persistence to antidepressant treatment is negatively affected by worsening economic conditions among employed individuals, and is most pronounced during periods of economic shocks and among mid-career employees. Areas of future research that may have important public health benefits include designing and evaluating programs such as employer-sponsored programs to promote medication adherence during economic contractions or provided education programs to more thoroughly assess economic stressors that may be interfering with optimal medication adherence[2].

Results from our second aim demonstrate potential economic benefit of adherence promotion for antidepressant therapy to organizations that bear part or the entire financial burden of health care delivery. We demonstrate that increased patient persistence with antidepressant therapy reduces non-medication total medical expenditures and outpatient medical expenditures. Given the large number of people on antidepressant therapy, there is potential for large savings to health plans or other organizations. Patients could benefit by adherence promotion programs through reduced depression symptomology, higher work productivity, and higher health-related quality of life.

The third aim of this dissertation shows long-term clinical benefit and cost-effectiveness for an intervention program designed to prevent depressive episodes in high risk youth. Little was known about long-term cost-effectiveness of prevention programs in mental health when this project began. Findings provide valuable information to policy makers about the long-term benefit and costs of the program. In addition, we show improved adherence to intervention study protocol increases clinical benefit at small additional cost. The intervention is shown to be cost-effective as adherence improves. Our research advocates for further research about the ability to add value to existing medical technologies through adherence improvement. In addition, further research to develop a theoretical framework to evaluate potential benefit gains of improved adherence to existing medical technologies would be valuable.

Each aim in this dissertation provides novel policy-relevant research about barriers to patient adherence or about the effects of adherence on important patient outcomes. We apply rigorous quantitative methods to establish causality in our analyses, and apply these methods rich datasets from multiple sources[3], [4]. Our research projects provide meaningful contributions to the research literature in comparative effectiveness research, health economics, patient adherence, and mental health that is relevant for other researchers and policy makers. I intend to continue to build on the work presented in this dissertation through potential future collaborations with my committee members and coauthors involved in this project as well development of new research projects examining the complexities of patient adherence and design of interventions designed to impact patient behavior specific to adherence.

References for Chapter 5

[1] R. M. Andersen, "Revisiting the behavioral model and access to medical care: does it matter?," *J. Health Soc. Behav.*, vol. 36, no. 1, pp. 1–10, Mar. 1995.

[2] R. Catalano, D. Dooley, and D. Charles, "A Test of Economic Instability : of Economic Health Effects Stress Hypothesis," vol. 24, no. 1, pp. 46–60, 1983.

[3] E. Mileva, "Using Arellano – Bond Dynamic Panel GMM Estimators in Stata Tutorial with Examples using Stata 9.0 (xtabond and xtabond2)," *Econ. Dep. Fordham Univ.*, vol. 0, no. 1, pp. 1–10, 2007.

[4] J. Angrist, G. Imbens, and D. Rubin, "Identification of causal effects using instrumental variables," *J. Am. ...*, vol. 91, no. 434, pp. 444–455, 1996.

Acknowledgements

First I would like to thank my wonderful wife, Shannon, and my loving children, Vincent and Isla, who encouraged and supported me through my PhD education. Without their support, this journey would not have been possible. I would also like to thank my family and friends who helped me remain focused during my studies.

My dissertation committee was delight to work with and a major contributor to my success. I extend enthusiastic thanks to Anirban, Gary, Fen, and Beth for their excellent guidance, critical reviews, and continued support. The mentorship and collaborative input I received from my committee helped me grow intellectually and establish a strong commitment to pursuing creative, meaningful research.

I would also like to acknowledge the overall excellent experience I had studying in the UW department of Health Services. Faculty members and staff are incredibly generous with their time and clearly committed to helping students succeed. Thank you to all who helped me navigate my way through the program requirements and put together my research project.

Finally, I would like to thank the investigators I primarily work with at the Kaiser Permanente Center for Health Research: Frances Lynch, Greg Clarke, and Lynn DeBar. I very much appreciate their continued flexibility and mentorship during my PhD program.

Funding support

The research presented in the this dissertation was supported by both the AHRQ/NRSA T32 Training Grant (T32HS013853; PI: Grembowski) and the University of Washington Dissertation Fellowship in Comparative Effectiveness Research, Pharmaceutical Outcomes Research & Policy Program, School of Pharmacy. The findings and conclusions in this paper are those of the authors and do not necessarily represent the views of their supporting agencies.