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Person-Centered Treatment to Optimize Psychiatric Medication Adherence

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by

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CHAPTER 1

Background

"Health is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity."[1]

As an increasing number of people are living with chronic conditions in the United States, advances in medical care are progressively focusing on quality of life for individuals with these conditions.[2] For example, a diagnosis of human immunodeficiency virus (HIV) is no longer a death sentence, but can be managed as a chronic disease with current treatments.[3] However, a number of chronic illnesses have complex treatment regimens, and the effectiveness of these regimens is dependent on individuals strictly following instructions from their care providers (i.e., adhere). For example, HIV pharmacological treatment involves complex regimens of medications that need to be taken at specific times during the day, with exacting regularity or the infection will adapt to those treatments.[3, 4] Diabetes is another chronic illness requiring complex routines including checking blood regularly, taking medication throughout the day, monitoring insulin administration, and dietary restrictions.[5]

As treatment for these once acute illnesses has moved from an acute to chronic care model, there has been increasing attention to the potential for adverse effects associated with these medications. For example, early HIV treatments began to redistribute body fat (e.g. lipodystrophy) towards the abdomen leading to chronic cardiometabolic conditions and facial fat loss (e.g. lipoatrophy).[6, 7] Adverse effects such as these were not only severe, but led to lower quality of life and poor adherence. To counter these effects, researchers developed new efficacious treatments with fewer of these adverse effects.[8, 9] However, these newer treatments

have increased the cost of care for chronic conditions not only due to the expense of the new treatments, but also extending the lifespan of individuals receiving these treatments.[10, 11]

Included in this list of conditions that have moved from an acute care to chronic care model are psychiatric illnesses.[12, 13] Bipolar disorders (BD) are among the more costly of these conditions to treat, due to inpatient care, the wide variety and complexity of psychotropic medication treatment, and disability.[14] BD often onsets in the early 20s and is a life-long condition.[15] Treatment for BD is generally divided into phases of acute symptom management and maintenance of symptom remission.[16] Maintenance (i.e., chronic) treatment for BD focuses on maintaining symptom remission, often with the same treatments that were found to be effective during the acute stage. Although adverse effects of these medications are an acknowledged concern, the primary focus has been on treating these effects as they emerge, rather than to change medication regimens to avoid such adverse effects due to valid concerns that frequently changing medications can lead to instability of psychiatric symptoms.[16]

Person-centered approaches to identify quality of life experienced by individuals treated for BD has seen increased importance to date as therapies have become more effective over longer periods of time.[17] BD involves a wide range of symptoms, including depression, psychosis and manic symptoms.[18, 19] This results in treatment with a broad range of medications including antidepressants, mood stabilizers, antipsychotics, and sedatives/hypnotics in addition to psychotherapy. This complexity makes it an ideal choice to study the quality of life and benefit of long-term medication treatment for serious mental illness more generally.

Diagnostic Criteria for Bipolar Disorder

According to the American Psychiatric Association Diagnostic and Statistical Manual of Mental Disorders (DSM-5),[20] BD is characterized by signature episodes of mania or hypomania and episodes of depression often intermingled with euthymia (i.e., a stable mental state or mood that is neither manic nor depressive). Briefly, manic episodes involve at least one week of abnormally and persistently elevated, expansive or irritable mood with increased activity or energy most of the day, nearly every day. This episode must also be severe enough to cause marked impairment in social or occupational functioning, up to and including hospitalization, and may involve psychosis. A hypo-manic episode is similar to a manic episode, but lasts a shorter period of time and does not lead to marked impairment in social or occupational functioning, and does not include psychosis. Depressive episodes involve two weeks of depressed mood or loss of interest or pleasure, causing clinically significant distress to the individual and may impair functioning. Diagnosis of a manic episode is necessary for a diagnosis of bipolar I disorder, and a hypo-manic episode for bipolar II disorder, but a diagnosis of depression is not needed for a diagnosis of bipolar I disorder (DSM-5 diagnostic criteria in Appendix).

Individuals with BD experience high levels of disability and healthcare costs.[12] Onset of BD often presents as depression,[15] often first detected in the emergency room, sometimes after a person harms themselves.[21, 22] It is not uncommon for individuals in a manic episode with irritability to initially be detected by law enforcement, often by being arrested for belligerent behavior.[23] Left untreated, individuals with BD have difficulty acquiring and maintaining employment,[24] leading to poverty and use of Medicaid.[25] As with other psychiatric illness, comorbidity with other psychiatric illnesses is extremely common. Individuals with BD most

commonly have comorbid anxiety disorders [26] or substance use disorders.[27] Persons with BD have excess premature mortality.[16, 28, 29]

Treatment options for BD

Treatment for BD is life-long and centers on psychotropic medications. Treatment is generally divided into two main phases: acute symptom management and maintenance of symptom remission. The acute phase entails treatment at the first onset of symptoms. The Canadian Network for Mood and Anxiety Treatments (CANMAT) guidelines recommend initial treatment for mania with the mood stabilizer lithium, which has consistently been found to be the most effective mood stabilizer.[30] However, lithium has serious adverse effects that emerge during long-term use, including weight gain, polyuria (i.e., excessive urination), and hypothyroidism.[31] If lithium adverse effects are intolerable, divalproex (an antiepileptic or mood stabilizer) is among the other first-line treatments during the acute phase.[16] Due to the episodic nature of BD, achieving remission may take years, which has resulted in many individuals taking two or more psychotropic medications concurrently (i.e., polypharmacy), and even up to five or more different medications (i.e., complex polypharmacy) has been commonly identified.[32] As symptoms subside and euthymia is maintained, the maintenance phase begins. Clinical guidelines recommend continuing whatever treatments were found to be effective from the acute phase while in maintenance. Other medications with known efficacy during the maintenance phase are lamotrigine (an antiepileptic or mood stabilizer),[33, 34] and quetiapine (an antipsychotic)[35] among others. If symptoms recur or new symptoms arise, adjunct medications can be added to treat those symptoms.[16] Multiple adjunct medications are often needed to reach stability and eventual remission.[32]

Non-Adherence to Psychotropic Medication Treatment

For all medical conditions, individuals who do not consistently adhere to their medication regimens often experience worse clinical outcomes, whether due to suboptimal management of the underlying condition or adverse effects from the medications themselves, BD is no exception. Unfortunately, adherence to medication is low in this population, ranging from 20-70%.[36, 37] Moreover, as individuals move into the maintenance phase of treatment they often experience increasingly severe symptoms that are more difficult to treat when they do not adhere to their medications.[38]

Numerous studies have attempted to understand the factors contributing to non-adherence for individuals with BD from the perspective of the provider and the client. Health care providers suggest non-adherence is due to symptoms of the illness itself such as "lack of insight" about the condition [39, 40] or denial of the severity of the disorder.[41] The complexity of medication regimens themselves (i.e., it is more difficult to take multiple medications concurrently) has been associated with non-adherence.[42] However, as noted above, clinical guidelines indicate adding adjunct medications to treat new symptoms experienced while in the maintenance phase, which has the effect of increasing medication burden over time. Providers have also indicated that adverse effects of the medications (i.e., weight gain, somnolence, sexual dysfunction) may lead to non-adherence.[43, 44] Studies that examine the determinants of non-adherence by surveying individuals treated for BD suggest that concern about medications (i.e., "I sometimes worry about long-term effects of this medicine") versus perceived necessity of taking those medications (i.e., "Without this medication I would be very ill") is also associated with non-adherence.[43] Individuals who perceived their illness as severe and that medication was beneficial were more

likely to maintain adherence.[40] Despite these studies, adherence remains suboptimal for persons with BD.

Measuring Adherence

Undermining common limitations to these studies of medication treatment for BD are the challenges stemming from (mis)measuring adherence. It is commonly understood that few individuals are perfectly adherent to their medication regimens, regardless of the condition under study.[41] However, there is not a consistent definition of adherence or agreed upon gold standard of how to measure it.[45, 46] For example, non-adherence could be defined as individuals' inconsistently taking their medications (e.g., "drug holidays"), missing doses as a result of schedule changes (e.g., when traveling away from home), or taking too much of their medications purposefully (i.e., abuse). Non-adherence may be a general behavior, or be tied to specific medications. For example, individuals may be non-adherent to one type of medication, but fully-adherent to others (i.e., antipsychotics versus antidepressants).[46] In addition, although self-report of medication adherence is one of the most common ways to measure this behavior, and is encouraged due to the rapport building it instills between the practitioner and the individual they treat,[47] it is subject to the same limitations of all self-report measures. The only way to ensure an individual is adherent is to visually confirm medication usage (e.g., component 2 of the tuberculosis monitoring programs).[48] Pill bottle counts, and even blood serum level measurements involve some error. Individuals may take a pill out of their bottle every day, but not consume the pill. Serum levels can indicate that a pill is being taken and that it has reached a therapeutic level, but for many longer-lasting medications it may not confirm if the medication is being taken at the frequency of time of day as prescribed.[49]

Modeling person-centered care for BD

Person-centered care, as described by Davidson et al. (2015), is a patient-centered model of care in the medical domain recognizing the person and his/her active role beyond the "patient" status.[50] Person-centered care is becoming more prominent in clinical settings as a means to identify and account for individual differences in responses to treatment for a multitude of illnesses, including BD.[51] All medical interventions, even those benign as aspirin, have some risk of adverse effects. When prescribing medications, providers routinely weight the benefit versus risks of those treatments to arrive at a care plan that is net beneficial. Clinical guidelines indicate that three core aspects, or dimensions, should be considered when balancing these aspects for treating BD: psychiatric symptoms, adverse effects, and overall functioning.[16] These dimensions are not independent of each other and work synergistically to influence clinical outcomes. Identifying how groups of individuals differentially experience these three dimensions, and whether this heterogeneity relates to adherence, can give further insight into improving treatment regimens for this population.

To conceptualize this intersection we have created a three-dimensional model of Clinical Net Benefit (CNB). Each dimension of CNB is an axis: (1) psychiatric symptoms; (2) adverse effects; and (3) overall functioning. The intent of this construct is to model individual heterogeneity in the experience of treatment for BD along each of these dimensions, grouping individuals at different coordinates as depicted in Figure 1.2. The relationship between adherence and CNB is also bi-directional: poor adherence may be a consequence of inability to tolerate medication adverse effects, for example. Alternatively, when individuals with BD are in maintenance and feel their condition is well-controlled (e.g., low psychiatric symptoms) they

may not take their medications as prescribed.[39] Therefore the specific coordinates of individuals will differ, and those coordinates will change over time.

To address the complexity between CNB and medication adherence for BD, this research will address three core research questions:

1. Can the conceptual model of CNB be identified in a population of individuals with BD? In addition, is this model externally valid in this population and does it enhance our understanding of the experiences these individuals have with their medical treatment?
2. Does the association between CNB and adherence remain stable or change over time while individuals are being closely monitored by treating psychiatrists? In addition, do the medication regimens differentially affect adherence?
3. Will the results from question 2 hold in a more naturalistic setting where individuals are not as closely monitored by their treating psychiatrist? That is, will the association between CNB, medication regimens, and adherence, remain stable or change over time when individuals do not meet as regularly with their psychiatrists?

These questions are addressed using the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD), a large, stepped-care randomized clinical trial (RCT) for persons with BD.

Methods

Sample

Sachs, et al. (2003) and the ClinicalTrials.gov Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) website detail STEP-BD study design.[52, 53] STEP-BD was a large (N=4,360) five-year longitudinal RCT designed to test the utility of different treatment modalities (i.e., psychotropic medications and psychotherapy) for individuals diagnosed with bipolar spectrum disorders (BD; i.e., meeting DSM-IV criteria for Bipolar I Disorder, Bipolar II Disorder, Bipolar Disorder Not Otherwise Specified [NOS], Cyclothymic Disorder, or Schizoaffective Disorder, Bipolar Subtype). The first two years involved active study participation where participants had regularly scheduled follow up appointments with their treating psychiatrist, and the last three years of participation involved a naturalistic follow-up with little oversight beyond usual care. Recruitment began in 1998 and the study ended in 2005. The goal of the study was to evaluate the efficacy and risk/benefit ratio of different study psychotropic medications (e.g., the mood stabilizers lithium, valproate and lamotrigine; the atypical antipsychotic risperidone; the oral supplement inositol [possible antidepressant [54]]); and the antidepressants paroxetine, tranylcypromine and bupropion) and regimens (i.e., taking two or more different medications concurrently, or polypharmacy) as participants aimed to achieve successful psychiatric symptom management.

STEP-BD was chosen for this analysis due to its wealth of information regarding psychotropic medication use, psychological assessments, large sample size, broad age range, diverse study population and length of follow up. The decision to use a RCT rather than a nationally-representative observational study was due in part to the fact that observational studies do not include all of these factors in one study. Nationally-representative samples such as the

National Health and Nutrition Examination Survey (NHANES) and the Medical Expenditure Panel Survey (MEPS) generally have detailed information on medications, large sample sizes and a broad range of ages.[55, 56] However, like many population-based surveys, MEPS does not differentiate between major depressive disorder and BD,[57] and these surveys only include psychological assessments measuring general distress (12-item short-form health survey (SF-12); Kessler-6 (K6); Center for Epidemiological Studies Depression Scale (CES-D)) [16, 58-60] or that are not BD specific. Also, longitudinal data is necessary to examine the bi-directional relationship between CNB and adherence. Moreover, there are numerous strengths to using a RCT as opposed to an observational study for these research questions. Finally, the STEP-BD trial had a public-health focused design to simulate the real-world experiences of individuals being treated for BD, unique for an RCT.[52]

Inclusion Criteria

In keeping with the "real world" perspective of STEP-BD, multiple locations and types of outpatient practices were selected as treatment centers for participation in the study across the United States. These treatment centers had to be actively treating at least 100 individuals with BD. They included university hospitals and medical centers (Stanford University School of Medicine; University of Colorado, Colorado Psychiatric Health Clinical Investigation Center; University of Massachusetts Medical Center; University of Oklahoma Health Sciences Center; University of Pennsylvania Medical Center; Baylor College of Medicine; University of Texas Health Science Center at San Antonio), a general hospital (Massachusetts General Hospital), a Veteran's Affairs hospital (Portland Veteran's Administration Medical Center), and two universities (Case Western Reserve University; University of Pittsburgh).

In addition, in order for treating psychiatrists or other clinical interviewers to participate in the study, they underwent an accredited continuing medical education program to learn Model Practice Procedures for routine care of individuals with BD. The main evaluation tools utilized in this training were the Affective Disorders Evaluation (ADE)[61] and the Clinical Monitoring Form (CMF).[62] Once psychiatrists or other clinical interviewers could demonstrate proficiency using these tools, they were deemed STEP-BD certified.

Individuals were eligible to participate in the study if they were 15 years of age or older, could meet with their clinical specialist as scheduled and could complete all study registration forms within three months of registration. Written assent was given by those aged 15 to 17 years, with informed consent given by their legal guardians. Those aged 18 years and older gave their informed consent to participate. Individuals had to meet the criteria for BD to participate in the study, and all diagnostically eligible individuals were offered STEP-BD enrollment. These diagnoses were determined after administration of the ADE given by a STEP-BD certified psychiatrist and the Mini-International Neuropsychiatric Interview administered by a second certified clinical interviewer (i.e., psychiatrist, psychologist, social worker or psychiatric nurse). Once consensus was achieved between these two interviewers, the final diagnosis would be determined. Exclusion criteria for this study included an unwillingness or inability to adhere to basic study requirements (i.e., completing rating forms or attending scheduled evaluations), and lacking competence to give informed consent in the opinion of the study investigator. No healthy volunteers were included in the study.

STEP-BD Study Design: Standard Care Pathway and Randomized Care Pathways

STEP-BD had two overall treatment pathways: the Standard Care Pathway (SCP) and the Randomized Care Pathways (RCPs). Upon entrance to the study, individuals were assigned to the SCP with individuals aged between 15 and 17 years limited to participation in the SCP, but those aged 18 and over could participate in either pathway. In the SCP individuals could retain their existing psychiatrists, if they were STEP-BD certified, and could remain on their existing medications and regimens, in essence treatment as usual. If a certain medication was not found to be efficacious, the participant's treating psychiatrist would make the determination as to whether and what medication changes to make. While individuals participated in STEP-BD, they were also given a battery of clinician- and self-administered psychological assessments to identify symptoms of depression and mania, detect comorbid diagnoses, adverse effects experienced by participates while taking their medications, quality of life, and social and occupational functioning at multiple time points during study participation (Table 1.1.). Clinicians also determined participants' adherence at multiple time points.

There were three RCPs in which some medications and regimen combinations were randomized and placebo controlled. A participant could enter a RCP if they met criteria for that pathway, and were blinded to the treatments if that was the protocol for that pathway.

Acute Depression Pathway: This pathway could be entered by individuals who met criteria for current major depressive episode, who were currently taking or agreed to begin taking a mood stabilizer, and agreed to taper off non-study antidepressants. This pathway was double-blinded for up to 24 weeks and included two random assignments: (1) a mood stabilizer plus a placebo versus a mood stabilizer plus paroxetine and (2) a mood stabilizer plus a placebo versus a mood stabilizer plus bupropion.

Refractory Depression Pathway: This treatment resistant pathway, was open (non-blinded) for up to 24 weeks. Individuals could enter this pathway if they failed to respond to treatment in the first two weeks while in the Acute Depression Pathway. Alternatively, they could enter this pathway if they failed to respond to two trials of antidepressants during their current depressive episode. They also needed to meet criteria for a major depressive episode for eight weeks before they entered the STEP-BD study. To begin this RCP, they needed to be currently taking or agree to begin a mood stabilizer. The three assignments were: (1) inositol versus risperidone; (2) risperidone versus lamotrigine; and (3) lamotrigine versus inositol.

Relapse Prevention Pathway: This pathway was double-blinded for up to two years. An individual could enter this RCP if they had a manic, mixed or hypomanic episode while taking lithium or valproate. They also had to have normal levels of thyroid stimulating hormone and creatinine. The assignment for this pathway was one mood stabilizer plus a placebo versus divalproex plus lithium.

As a stepped-treatment trial, treating psychiatrists' could discontinue participants' ineffective treatments and either advance to the next level of randomized treatments until they achieved effective symptom management, or could prescribe a different medication in the SCP. Additionally, participants could elect to return to the SCP at any time during their participation in the RCPs.

Strengths and limitations of STEP-BD

The strengths of STEP-BD include the large number of psychological assessments administered at multiple time points, explicit details of psychotropic medication use identifying up to 12 distinct medications an individual could be taking, their dosages and missed doses, the

large sample size for a clinical trial, and length of follow up that included both an active participation phase and a naturalistic follow-up. The rigorous design of an RCT is the gold standard of study design, and the fact that a treatment as usual arm was also included added the complexity we see in an observational setting.[52]

Limitations of STEP-BD included missing data on many psychological measures (Chapter 1, Table 1.1.), which limited the number of measures used in the subsequent analyses. In addition, participants' perceptions of their care or medications, including believes about the necessity of taking medications to maintain remission (i.e., scales like the Beliefs about Medicines Questionnaire), were not measured.[63] This limited our analysis to inference on CNB to clinical experience, without the added knowledge of participants' opinions and perceptions of benefit. Medication usage was determined via clinical interviews with the treating psychiatrist, which is the best-practice for large and complex trials,[47] but was not confirmed by pill counts or blood serum levels. Finally, although STEP-BD was designed to have a diverse population of individuals with bipolar spectrum disorders from multiple locations across the United States, the sample was not nationally representative of persons with BD.

Statement Regarding Human Subjects Research

This dissertation used data from the previously collected, de-identified, limited access clinical trial STEP-BD. No original data was collected as part of this research. This data was included in the National Institute of Mental Health Data Repositories, which were accessed after completion of a Data Use Agreement. On June 30, 2015, the VCU Office of Research found that the proposed study qualified for HHS Exemption 45 CFR 46.101(b)(4) (*Research involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic*

specimens, if these sources are publicly available or if the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects) for Human Subjects Research.

Measures: The Clinical Monitoring Form

The CMF is a clinician administered assessment used at each study visit. It was designed as a substitute for traditional narrative clinical follow-up notes and consisted of nine sections including current mood modules, functional assessments and an overall clinical status.

Psychiatric Symptoms

Beck Hopelessness Scale: The self-report 20-item BHS assesses an individual's negative expectancies of the future. Each item is scored as true or false, with scores ranging from 0=none to 20=severe; higher scores indicating higher levels of hopelessness. Internal consistency of total BHS scores was found to be 0.93 by Beck, et al., (1974) with an inpatient sample of individuals who made recent suicide attempts.[64] Later studies found the reliability to be 0.86 and 0.83 in psychiatric samples,[65] and 0.92 in clinical populations.[66, 67] Validity of the scale was based on a comparison between clinician ratings of hopelessness and the scale scores in both a general practice outpatient sample, validity of 0.74, and a psychiatric inpatient sample hospitalized for a recent suicide attempt, validity of 0.62.[64]

Young Mania Rating Scale: The clinician-administered 11-item YMRS assesses the severity of mania an individual is experiencing. Items 1, 2, 3, 4, 7, 10, and 11 are on a Likert scale from 0=absent to 4=severe. Items 5, 6, 8, and 9 are given extra weight as they are more difficult to gauge in severely impaired individuals, with a Likert scale of 0=absent to 8=severe.

Scores range from 0=absent to 60=severe, with higher scores indicating greater severity of mania symptoms. When examining an inpatient sample of manic individuals, the interrater reliability of the scale was 0.93 when compared between two physicians administering the scale independently. The concurrent validity when comparing the YMRS to other mania rating scales (Petterson Scale and Beigel Scale)[68, 69]was between 0.71 and 0.89.[70]

Montgomery-Asberg Depression Rating Scale: The clinician administered 10-item MADRS assesses the severity of depression with particular sensitivity to psychotropic medication treatment response. It is scored on a Likert scale from 0=no symptoms to 6=severe symptoms, and scores range from 0=absent to 50=severe, with higher scores indicating greater severity of the illness. Testing of the reliability and validity of the scale was conducted with a sample including both Swedish and English individuals with a primary depressive illness. Reliability between the raters ranged from 0.89 to 0.97. Validity of the scale was compared with a clinician's global judgement of an individual's response to treatment and other scales that also measure depression severity. MADRS had the highest correlation with the clinician's judgement at 0.70.[71]

Psychiatric Comorbidities

Diagnoses of comorbid psychiatric and substance use conditions were obtained from the CMF. These included current alcohol abuse (yes or no), current substance abuse or dependence (yes or no), current panic disorder (yes or no), and current binge purge (yes or no) disorders in addition to the licit substance use current caffeine cups per day (continuous) and current nicotine packs per day (continuous).[62]

Measures: Adverse effects

Adverse effects from medications were obtained from the CMF. Nine adverse effects were assessed, each rated on a 4-point Likert Scale ranging from 0=none to 4=severe. The adverse effects collected on the CMF were: tremor, dry mouth, sedation, constipation, diarrhea, headache, poor memory, sexual dysfunction, and increase appetite.

Measures: Overall Functioning

Quality of Life Enjoyment and Satisfaction Questionnaire (QLESQ): The 16-item QLESQ is completed by the participant and assesses the degree of enjoyment and satisfaction experienced in various areas of daily functioning. Example items include: "Taking everything into consideration, during the past week how satisfied have you been with your physical health?" Items are scored on a Likert scale from 1=very poor to 5=very good, with the first 14 items summed for a raw score and items 15 and 16 as stand-alone scores. Scores range from 14 to 70 with higher scores indicating higher satisfaction. In populations with psychiatric illnesses, test-retest reliability ranges from 0.63 to 0.89. Internal consistency ranged from 0.90 to 0.96.[72]

LIFE Range of Impaired Functioning Tool (LRIFT): The LRIFT is a tool that was originally administered during the Longitudinal Interval Follow-up Evaluation (LIFE) study.[73] The LIFE assessed the longitudinal course of psychiatric disorders determining time to recovery, length of wellness intervals and time to relapse.[73] Examples of items from the LRIFT include: "Which of the following categories best characterizes the degree to which the patient's current (past week) work activities have been impaired as a result of psychopathology?" Item responses are on a Likert scale ranging from 1=no impairment to 5=severe impairment. In addition, four summary scores (work, interpersonal relations, satisfaction, and recreation) are determined: (1)

Work score is the sum of items 1 – 3; (2) Interpersonal relations score is the sum of items 4 – 6; (3) Satisfaction is the score from item 7; and Recreation is the score from item 8. These four scores are summed for a total score ranging from 4-20 with higher scores indicating increased impairment.[74] The validity of the LRIFT was determined in a sample of individuals with mood disorders. Concurrent validity of the LRIFT compared to the Clinical Global Measures Scale, another measure of functioning (GAS)[75] was 0.56. Reliability across the two-year study period ranged from 0.81 at six months to 0.83 at 24 months.[74]

Work Impact Form: The WIF uses a portion of the World Health Organization Disability Assessment Schedule, or WHODAS-2.[76] The portion utilized in STEP-BD included three questions regarding levels of ability to work or carry out participants' normal activities over the past 30 days. For each question, there was a subset of three questions asking participants whether they were due to mental health or substance use. Scores for the three main questions were counts of the how many days in the past 30 days they experienced difficulties, and were categorized as 0=0 days, 1=1 day, and 2=greater than 1 day. The three sub-questions were binary scores of yes or no. Garin, et al., (2010) tested the validity of the full WHODAS-2 (36 items) with a sample of individuals with different chronic illnesses including individuals with BD.[77] When compared with scores on the YMRS and the Hamilton Depression Rating Scale,[78] the Cronbach's alpha=0.88 and the Intra-class Correlation Coefficient=0.612 for individuals with BD.

Global Assessment of Functioning (GAF): The GAF score came from the CMF. The GAF is an overall assessment of psychiatric disturbance and evaluates the psychological, social and occupational functioning of an individual. It ranges from 1 to 100, with higher scores indicating higher functioning.[79] In a sample of individuals with three consecutive admissions to a psychiatric hospital and with diagnoses of schizophrenia, schizophreniform or schizoaffective

disorders, the reliability of the GAF ranged from 0.89 to 0.95 over 3 time points when administered by two independent raters. The validity of the score when compared with the Scale for the Assessment of Negative Symptoms (SANS),[80] Scale for the Assessment of Positive Symptoms (SAPS)[81] and Social Behavior Schedule (SBS) [82] ranged from 0.37 to 0.77 over three time points.[79]

Primary outcome: Medication Adherence assessed using the CMF

In the CMF the treating psychiatrist indicated both the names of the medications and prescribed dosages, and dosages missed in the past seven days, as well as an indication of significant noncompliance (yes vs. no) with a space for a description of the noncompliance if yes. If an individual missed less than 25% of their medication dosage according to the CMF, they were identified as *adherent*. This adherence is consistent with prior analyses using STEP-BD as well as other analyses of adherence.[83]

Overview of Analysis

Chapter 2

Can the conceptual model of CNB be identified in a population of individuals with BD? In addition, is this model externally valid in this population and does it enhance our understanding of the experiences these individuals have with their medical treatment?

The purpose of the first paper was to create the CNB construct and determine its external validity using data from the baseline assessment of STEP-BD. This involved two latent variable methods: Exploratory Factor Analysis (EFA), and Latent Class Analysis (LCA). Latent variable

techniques are commonly used when identifying concepts that cannot be directly measured, or can only be measured with error (i.e., situations in which there is no gold standard for assessment).[84-86] For example, there is no gold standard way to measure depression, a complex symptom cluster of low mood and disturbances in appetite, sleep, cognition, and physical functioning. Instead various self-report assessments are used to identify different symptoms of depression and the scores on these scales are summed to determine a probable case of depression. Another advantage of the latent variable framework is that it does not employ artificial cut-points of symptom counts to determine "caseness" (e.g., DSM-5 diagnosis of major depression requires endorsement of 5 of 9 symptom groups, one of which is low mood or anhedonia). Instead, latent variable techniques like EFA and LCA use the correlations between variables (e.g., symptoms) to empirically identify distinct subgroups in the data (e.g., high vs. low depressive symptoms) rather than artificial cutpoints. Unlike regression techniques that aim to remove collinearity, latent variable techniques identify latent constructs by the strength of the very correlations between items that are indicating a common construct.[87]

Determining the indicators of CNB using Exploratory Factor Analysis

The goal of EFA is to reduce the number of measures (e.g., psychometric measures, adverse effect measures, and functioning measures) to those that are most reliable, common and with the highest shared variance with the three dimensions of CNB. It is a data reduction technique used to understand the correlation between a set of observed variables that are believed to describe a common (unobserved) factor. EFA is often used in the creation or modification of scales to measure psychological constructs. This method was used to determine the indicators that best describe the three dimensions of the novel construct of CNB.

In EFA, multiple techniques can be used to determine the number of factors and measured indicators that comprise a latent construct. EFA empirically identifies the number of indicators and factors of a latent construct that provide the best fit to the data, without any pre-specifications as is done in Confirmatory Factor Analysis.[88] We conducted three EFAs, one for each of the dimensions of CNB using the measures listed previously to define each latent construct. Measures for the psychiatric symptoms dimension included not only scales of symptoms such as the YMRS, but also comorbidities that may be used as self-medication or behaviors to mitigate psychiatric symptoms such as caffeine cups per day and binge purge disorders.

EFA uses statistical methods to identify and reduce the number of measured indicators to only those necessary for each factor of a latent construct. It does this without *a priori* assumptions of the number of factors. The resulting latent factor should explain most of the shared variance seen in the associations between the original measured variables, (i.e., the correlation among the variables).[86] For example, when creating a depression scale, one wants to be able to use the fewest number of questions (i.e., measured variables) necessary to accurately capture the latent construct of "depression". EFA has four main assumptions: (1) measurement error has a constant variance that is on average approximately 0; (2) there is no association between the factor and measurement error; (3) there are no associations between error terms; and (4) given the factor, observed indicators are independent of one another (i.e., there is no relationship between the measured indicator except through their relationship with the factor).[89, 90] EFA can incorporate dichotomous, ordinal and continuous measures in the same analysis, thereby decreasing error due to transformation of variables into the same format (i.e., transforming all measures into dichotomous variables).[88] However, EFA is sensitive to missing

data and outliers, therefore we could only use the measures from STEP-BD with less than 10% missing data, and missing data was estimated using Full Information Maximum Likelihood Estimation (FIML).[91, 92]

To determine the final number of measures and factors from an EFA, the type of rotation must first be determined to use in the analysis. Rotations are the ways in which to account for the level of correlation between the measures as identified via the correlation matrix. If the measures are highly correlated an oblique rotation is used, if correlation is low an orthogonal rotation is used. Verimax rotation identifies preliminary factor loadings, but to group factor loadings closest to the two extremes (1 or 0), an additional promax rotation is needed.[93] This will identify simple structure, factor loadings exceeding absolute value of 0.50 with cross loadings of at least 0.15 less than item's highest factor loading among the factors.[94, 95] With factor loadings closest to the extremes one can be more confident that each factor is distinct from the others, with very low correlation between the factors.[88] Results from an EFA indicate the eigenvalues for the number of factors up to the highest number of measures used in the analysis (if 15 measures were initially included, there will be 15 eigenvalues). An eigenvalue of one indicates the number of factors to include in the final EFA, which can also be visualized with a scree plot.[96]

Identifying distinct subgroups based on CNB using Latent Class Analysis

LCA is a method used to identify distinct unobserved (latent) subgroups (called classes) within a given population based on the correlations between a set of observed variables. LCA has three elements: measurement, characteristics, and grouping. First, as a measurement approach it evaluates whether an unobserved latent binary variable exists (i.e., do the measured indicators represent a common construct). Then LCA is used to determine the number of classes (i.e.,

subgroups) of the latent variable that exist in the sample. Finally, LCA is used to assign participants to a particular class of the latent variable from their posterior probabilities of symptom endorsement.[97] For example, with LCA one can assess whether a latent binary variable of depression exists, and then can identify different classes within that latent variable, such as low, medium and high levels of depression. Participants can then be assigned as belonging to the different classes of depression (i.e., low, medium and high). LCA has two main assumptions: (1) exhaustiveness is the assumption that every set of responses to measured indicators is associated with membership in that particular class, thus participants are provisionally assigned to a particular class based on their responses to the measured indicators; and (2) local independence assumes that members of a particular class will have independent responses from those of other members of the same class.[98] Typically, the latent class is a binary measure, therefore ordinal, continuous and categorical variables must be transformed into binary variables.[99]

LCA was chosen for this analysis, rather than other methods of clustering individuals into groups, due to the empirical nature of the analysis. LCA uses a statistical model to derive the groups of individuals based on their responses to measured indicators [84] rather than a more arbitrary method of class identification based on apparent groupings such as is used in Cluster Analysis.[93] The measures identified in the EFA that defined each dimension of CNB were then included as measures of the CNB in the LCA. The scores on each measure of each dimension defined each class. For example, individuals would be identified by their degree of psychiatric symptoms (high or moderate), adverse effects (low or high) and overall functioning (moderate or low). Using these degrees, the classes would be identified by their overall degree of the three (i.e., individuals with low psychiatric symptoms, low adverse effects, and high overall functioning would be identified as the High CNB Class).

To determine the number of classes that best fits the sample, the following measures are used: Akaike Information Criterion (AIC), Bayesian Information Criterion (BIC), Sample-Size Adjusted BIC (BIC_N), Bootstrapped Likelihood Ratio Test (BLRT) and Entropy.[100] For each of these indices smaller values, and Entropy values closest to 1, indicate better relative fit.[99] With large sample sizes large numbers of classes may be indicated, therefore measures of model fit, prevalence of class membership and model interpretability are all used to determine the final number of classes.[101]

Chapter 3

Does the association between CNB and adherence remain stable or change over time while individuals are being closely monitored by treating psychiatrists? In addition, do the medication regimens differentially affect adherence?

After determining the classes of CNB in STEP-BD, we wanted to test whether these classes changed over time and whether individuals moved between classes. In addition we wanted to know whether these changes affected adherence. We conducted this analysis using data from the active participation phase of STEP-BD, approximately two years. Two main methods can be used to analyze change over time of latent classes. The Repeated Measures Latent Class Analysis identifies the arch of change in all time points simultaneously, but does not give the detail regarding incidence of change between time points. We not only wanted to determine class membership at each time point, but also the probability of participants changing class membership (i.e., transitioning) at each consecutive time point. Therefore we chose to conduct a Latent Transition Analysis.[99, 102]

Examining the short-term relationship between CNB and Adherence using Latent Transition Analysis

LTA is able to determine the probability of an individual in a specific latent class at one time point transitioning to the same or different class at a subsequent time point. These probabilities are determined by a multinomial regression of the classes at the subsequent time point on the classes at the previous time point (i.e., classes at time 3 regressed onto classes at time 2). This entails two models, a measurement model to identify the latent classes at each time point, (i.e., an LCA), and a structural model showing how the latent classes related to each other.[102] The first step in conducting the LTA is to determine the best fitting number of latent classes at each time point using AIC, BIC, BIC_N, BLRT and Entropy as is done in LCA. However, when running the LTA, probabilities of movement between classes is also adjusted for, which cannot be accounted for with an LCA at each time point. This may lead to slightly different numbers of classes and class memberships. Thus, after determining the best fitting number of classes from the individual LCAs, an initial LTA should be analyzed to determine the number of best fitting classes when all time points are in the model.[102] Fit indices for the LTA using AIC, BIC, and BIC_N can confirm if the number of LCA classes are the best fit for the LTA classes. For example, if the analysis using LTA will include five time points, an LCA for each time point should be conducted to determine the number of classes that best fit the data. If four and five classes fit the data for each time point, then in the LTA the fit of four classes and five classes should be tested to determine the number of classes that best fit the data using LTA.

Once the best fitting classes are determined for the LTA, the actual LTA can be conducted. We wanted to determine if the classes themselves changed over time (i.e., values for

the MADRS in time two differed from time one) as well as whether participants changed classes at each subsequent time point. Therefore we did not hold the classes invariant across time.[99, 102] In addition, a large number of random starts is preferred to ensure the validity of the LTA results. However, because we were comparing multiple latent variables, we reduced the number of random starts as is indicated in the literature.[102]

Chapter 4

Will the results from question 2 hold in a more naturalistic setting where individuals are not as closely monitored by their treating psychiatrist? That is, will the association between CNB, medication regimens, and adherence, remain stable or change over time when individuals do not meet as regularly with their psychiatrists?

After completing the short term analysis of change in classes and CNB over the approximately two years of active study participation, we wanted to determine whether these CNB classes, changes in classes over time, and adherence held during the naturalistic follow-up in STEP-BD. The final three years of STEP-BD were designed to approximate the treatment environment in the general population, where individuals have fewer appointments with their treating psychiatrist leading to much less monitoring.[52] The results from the LTA in Paper 2 may not be fully capturing adherence and CNB in a real world setting. We wanted to determine if less monitoring would differentially affect both CNB class membership, changes in benefit and subsequent adherence.

Examining the long-term relationship between CNB and Adherence using Latent Transition Analysis

We conducted this analysis from the last time point in paper 2, time 5, until time 8, which was approximately the end of the three-year naturalistic follow-up. Few individuals completed the full five years of STEP-BD. Only approximately 200 individuals completed exit interviews, which is at the extreme low end of sample size with enough power to adequately complete latent variable modeling. Therefore, we conduct analyses using data through time 8, which gave us a sample size of approximately 500, considered a "very good" level of power.[103]

Our analysis used the same methods as in Paper 2. We first conducted LCAs for each time point to determine the number of classes that best fit the data for those time points using AIC, BIC, BIC_N, BLRT and Entropy. We kept the number of classes the same across time points to more easily identify changes in values of the measures making up the classes of CNB and to identifying how class membership changed over time. Once the number of classes that best fit the data were determined, we conducted an LTA to confirm the fit of the number of classes using AIC, BIC and BIC_N. Finally, we conducted the LTA for time 5 – 8 to determine transition between classes from the previous to each subsequent time point.

The characteristics of members of each class, including medication regimens they took, adherence to their regimens, and membership in SCP or RCPs were determined and compared to individuals who did not complete the study.

Table 1.1. Psychological assessments either clinician- or self-administered to all participants in STEP-BD. Includes the number of participants that completed these assessments.

Clinician-Administered[a]	**Final Sample Size**
Affective Disorders Evaluation	4107
Clinical Monitoring Form	3730
Care Utilization Form	3908
Demographic Form	3867
Family Contacts	3098
Montgomery-Asberg Depression Rating Scale	3931
Hospitalization Form	3073
Range of Impaired Functioning Tool	3904
Mini International Neuropsychiatric Interview	3790
UCLA Social Attainment Scale	381
Work Impact Form	3899
Young Mania Rating Scale	3927
Participant Self-Administered	
Beck Depression Inventory Version II	300
Edinbergh Handedness Inventory	2977
Family History	2860
Medication History	2963
NEO Five Factor Inventory	2338
Attributional Style Scale	265
Beck Hopelessness Scale	3179
Care Satisfaction Questionnaire	3377
Dysfunctional Attitudes Scale	285
Helping Alliance Questionnaire	2595
Interpersonal Support Evaluation List	283
Life Experience Survey	3118
Perceived Criticism Scale	1225
Personality Diagnostic Questionnaire – Version 4	2897
Quality of Life Enjoyment and Satisfaction (Short Form)	3371
Religiosity	2574
SF-36 Health Survey	2920
Social Rhythm Metric "Short Form"	31
a. Includes treating psychiatrist, clinical specialist, or other certified rater	

Figure 1.1. Participant flow chart for STEP-BD.

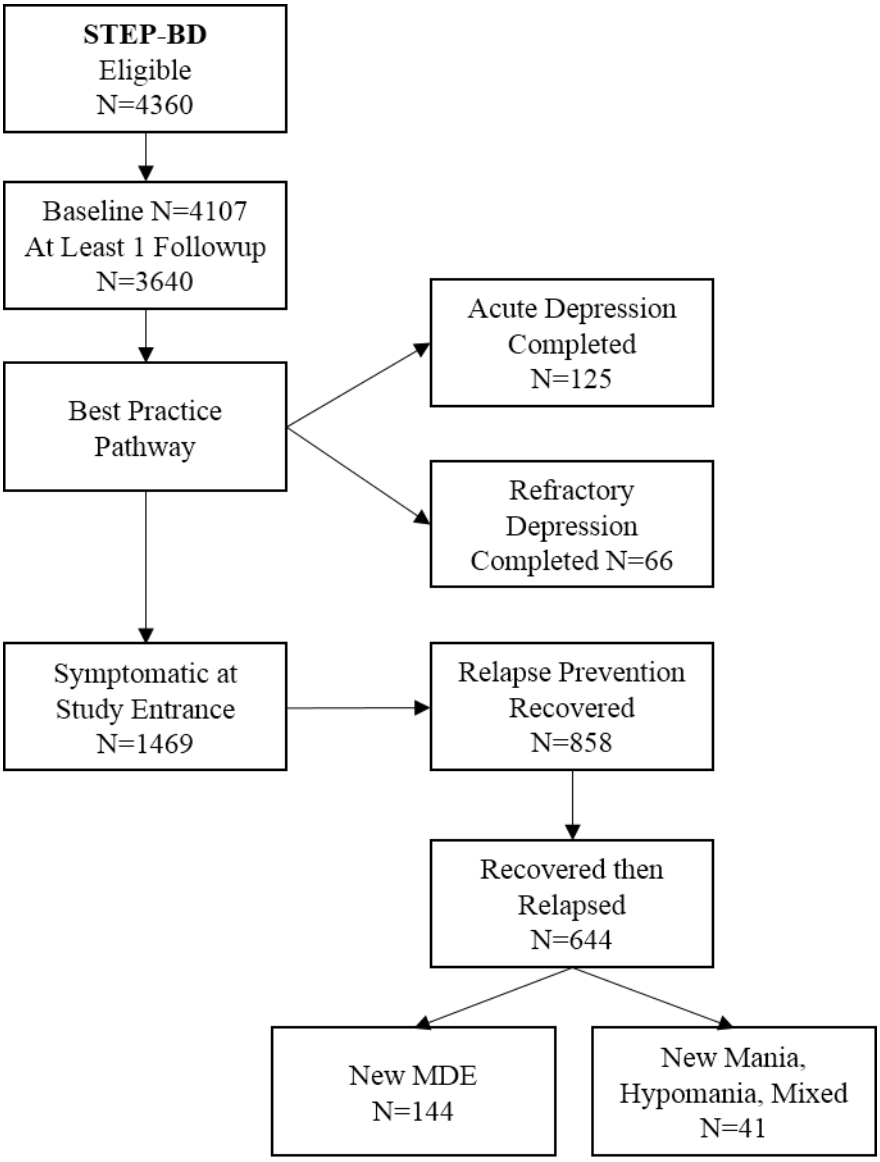
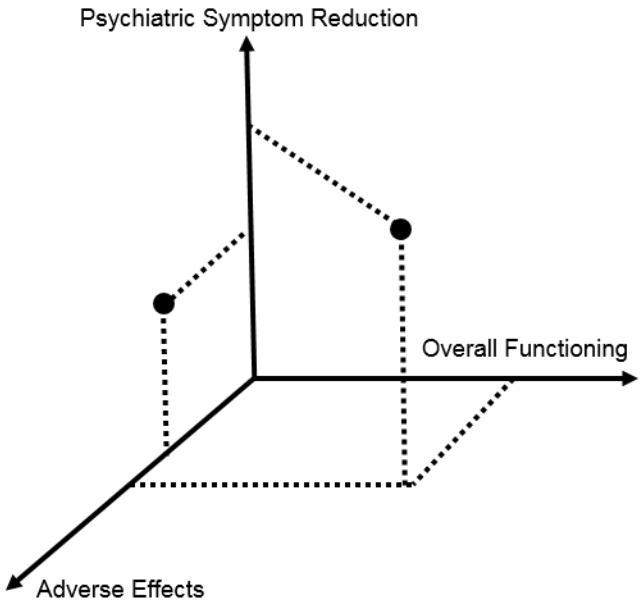


Figure 1.2. Conceptual diagram of Clinical Net Benefit latent construct.



Caption: Dots represent different hypothetical CNB groups and their relative coordinates of psychiatric symptoms, adverse medication effects, and overall functioning.

CHAPTER 2

Identifying Clinical Net Benefit of Psychotropic Medication Use with Latent Variable Techniques: Evidence from Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD)

ABSTRACT

Objectives: Adherence to psychotropic medication is poor among individuals with bipolar disorder (BD). Multiple factors influence the clinical net benefit (CNB) experienced from treatment, however existing models may fail to capture the complex intersection of psychiatric symptoms, adverse effects, and functioning. This study empirically quantified a novel construct of CNB and characterized its relationship with polypharmacy and medication adherence.

Methods: Data come from baseline assessments of individuals aged 18+ from the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD). Latent class analysis identified distinct groups based on the intersection of the three factors of CNB: psychiatric symptoms (i.e., decrease in episodes), adverse effects (e.g., sedation), and functioning (i.e., employment, quality of life). Adherence was defined as taking 75% or more of medications as prescribed. Polypharmacy was categorized as number of medications taken concurrently. Associations between CNB and adherence were tested using multiple logistic regression adjusting for sociodemographic characteristics.

Results: Five classes of CNB were identified: High (24%), Moderately high (26%), Moderate (12%), Moderately low (27%) and Low (12%). Adherence did not differ between classes (71% to 74%, χ^2=1.34, p=0.854). Medication regimens differed by class: 57% of the High CNB were taking two or fewer medications; 49% of the Low CNB were taking four or more medications.

Conclusions: CNB is substantially heterogeneous in individuals treated for BD. Despite this variation, and differences in polypharmacy regimens, adherence is similar across classes of CNB. Understanding why individuals adhere to their regimens, despite suboptimal CNB, may provide novel insights into important aspects influencing adherence.

Keywords: Adverse Effects, Medication Adherence, Polypharmacy, Bipolar Disorder

INTRODUCTION

Bipolar disorder (BD) is among the leading causes of disability-adjusted life-years lost worldwide.[13] Effective treatment with psychotropic medication, often in combination with psychotherapy, can help individuals with BD manage their illness.[16, 104]

Despite advances in pharmacotherapy, adherence to medication among individuals with BD has not markedly improved since the 1950's when medications with serious adverse effects were the primary treatment modalities.[43] Approximately 20-60% of individuals with BD will be non-adherent to their medication at some point in their treatment;[105] medication non-adherence contributes to elevated relapse, suicidal behavior and greater healthcare costs.[106, 107] Poor adherence is thought to stem from multiple sources, including effects of the illness itself (e.g., "lack of insight" about the condition),[39, 40] adverse effects of medications (e.g., heart disease, somnolence),[43, 44, 108] and complexity of medication regimens (e.g., multiple pills taken multiple times per day).[39, 42]

When considering prescribing medications, practitioners routinely weigh the clinical net benefit (CNB) of each treatment, seeking a positive balance between expected benefits and risk of adverse effects.[16] However, existing notions of CNB are limited in two important ways. First, although long-term treatment guidelines identify the importance of preventing relapse and promoting quality of life and functioning,[104] most approaches are unidimensional (i.e., reducing the benefit-risk ratio to a single quantity like Number Needed to Treat).[109] This does not appropriately capture the complexity of what CNB means for the patient; from the patient's perspective, CNB of medications can be conceptualized as the complex intersection between psychiatric symptom reduction, medication adverse effects, and overall functioning.

Second, there has been only limited discussion of how CNB relates to medication adherence for individuals with BD, with focus instead on psychoeducation promoting adherence [42] and the individual's perception of their providers' confidence in the medication regimen.[110] A handful of studies explored how perspectives of individuals with BD relate to medication adherence. Using the Beliefs about Medication Questionnaire [63] Clatworthy, et al. (2009) found that perceptions of higher concern and lower necessity regarding medication were associated with lower adherence.[43] Using components of the Rating of Medication Influences Scale (ROMI),[111] Adams and Scott (2000) found that participants' perceived benefits-to-risks for medications differentiated those who were highly adherent and partially adherent.[112] Other descriptive studies of individuals with BD have identified treatment of depression, improved functioning, and management of adverse effects as factors most important to CNB, but these studies did not examine the relationships between these factors and medication adherence.[16, 113] These reports were also limited in scope (i.e., small samples, limited to one type of medication) and relied on self-administered mail-in questionnaires with lower validity relative to clinical assessments.[113-115]

The Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) overcame many limitations of these prior studies. It was a large (N=4360), 5-year longitudinal randomized controlled trial (RCT) designed to test the utility of different treatment modalities (medications and psychotherapy) for individuals with BD. It included stepped-treatment where participants were allowed to discontinue ineffective treatments and advance to the next level of randomized treatments until they achieved effective symptom management. Participants were also given a battery of clinician- and self-administered psychological assessments as well as clinician determined medication adherence at multiple time points.[52]

The objective of this study was to use the baseline assessments of STEP-BD participants to identify and characterize subgroups of CNB. Due to the complex, multi-dimensional nature of CNB this project employed two latent variable approaches, exploratory factor analysis (EFA) and latent class analysis (LCA), to quantify CNB in the context of medical treatment.[116] Latent variable modeling is ideal for quantifying a complex construct such as CNB,[117, 118] and can effectively classify people into discrete subgroups. Classes of CNB were characterized according to indicators of symptom management, adverse effects, and overall functioning. Further, the association between these CNB classes with characteristics of medication treatment (i.e., type of medication, polypharmacy) and medication adherence was assessed. We hypothesized that LCA will identify unique classes of individuals who systematically differ in characteristics of CNB. We also hypothesized that these distinct classes will be differentially associated with medication adherence.

METHODS

Sample

All eligible participants aged 18 years and older from the STEP-BD trial were included in the current study, as medications prescribed in STEP-BD were only approved for this population when the study began.[119, 120] The details of the original study design were described elsewhere.[52] Briefly, STEP-BD was a 5-year RCT of individuals treated for bipolar spectrum disorders. It was designed to simulate the "real world" experiences in treatment of individuals with BD. STEP-BD was not solely a RCT, as eligible participants could choose to enter either the Randomized Care Pathways (RCPs) or Standardized Care Pathway (SCP). In the RCPs, participants were randomly assigned to specific medications (i.e., mood stabilizers, antipsychotics, antidepressants or placebos) to minimize self-selection bias. In the SCP, participants maintained current treatment. If initial regimens were ineffective, participants moved on to subsequent medications until an effective regimen was reached. Participants routinely underwent a battery of clinician- and self-administered psychological assessments, including medication adherence.

Although 4,360 participants enrolled in the original study, this study further excluded 321 participants with incomplete data on the psychological assessments and physical measures with less than 10% missing data used in this analysis, and 301 individuals who were less than aged 18 years. Missing data <10% was imputed using Full Information Likelihood Estimation.[92] The final analytic sample size was 3,738 (Supplemental Figure 2.1.).

Outcomes

Clinical Net Benefit

CNB incorporates three main effects of treatment on the individual: (1) symptom reduction; (2) adverse effects; and (3) overall functioning. CNB can be conceptualized as a 3-dimensional construct lying at the intersection of these axes. Individuals differentially experience these components of treatment, depicted as points in Figure 2.1. These different experiences, or coordinates, may in turn uniquely relate to medication adherence. To conceptually define and quantitatively measure these three dimensions of CNB, we used the baseline scores of the following variables. Three EFAs empirically reduced measures to only those necessary for the three dimensions of CNB. LCA then grouped participants into distinct subgroups of CNB.

Psychiatric Symptoms

Nine symptom scales and psychiatric diagnoses were explored as potential indicators of this component of CNB at baseline.[16] All symptom indicators were reverse coded such that higher scores indicated lower symptomology. The treating psychiatrist-administered Clinical Monitoring Form (CMF),[62] indicated binary (yes/no) comorbid DSM-IV diagnoses of alcohol abuse, substance abuse/dependence, binge/purge, and panic disorder; the number of caffeine cups per day (mean: 1.83, SD: 2.35) and number of cigarettes per day (mean: 6.04, SD: 10.96) were transformed into binary variables above and below the sample mean. Mania and depression were measured using the participant self-reported 20-item Beck Hopelessness Scale (BHS) (range: 0=none to 20=severe; mean: 11.49, SD: 5.75); the clinician-rated 11-item Young Mania Rating Scale (YMRS) (range: 0=absent to 60=severe; mean: 32.00, SD: 6.53); and the clinician-rated 10-item Montgomery-Asberg Depression Rating Scale (MADRS) (0=absent to 50=severe; mean: 33.19, SD: 10.90). Externalizing symptoms (i.e., alcohol abuse, substance

abuse/dependence, binge/purge, caffeine cups per day, cigarettes per day)[117] were combined into an externalizing count variable.

Adverse Effects

Ten adverse effects from the CMF were explored as potential indicators of CNB at baseline. Each was scored on a 4-point scale ranging from 0=none to 4=severe. All of these indicators were reverse coded so that higher scores indicated fewer effects. These included tremor (mean: 3.77, SD: 0.60); dry mouth (mean: 3.75, SD: 0.63); sedation (mean: 3.70, SD: 0.69); constipation (mean: 3.90, SD: 0.43); diarrhea (mean: 3.88, SD: 0.45); headache (mean: 3.78, SD: 0.60); poor memory (mean: 3.74, SD: 0.64); sexual dysfunction (mean: 3.80, SD: 0.63); increased appetite (mean: 3.80, SD: 0.60); and extrapyramidal symptoms (mean: 3.99, SD: 0.17).

Overall Functioning

Four scales were explored as potential indicators of CNB at baseline. All items were reverse-coded so higher scores indicated better functioning: (1) participant self-reported 16-item Quality of Life Enjoyment and Satisfaction Questionnaire (QLESQ) (mean: 42.53, SD: 10.87); (2) clinician-rated LIFE Range of Impaired Functioning Tool (LRIFT),[74] (mean: 39.88, SD: 6.45); (3) three indicators from the clinician-rated Work Impact Form (WIF), were combined creating a weighted work impairment score (totally unable to work/carry out normal activities score X 2; able to work/carry out normal activities but had to cut down score X 1.5; extreme effort to perform up to usual level of work/normal daily activities score X 1) (ranging from 0=no impact to 9=high impact; mean: 4.18, SD: 3.11); (4) the CMF Global Assessment of Functioning (GAF) for the past week (mean: 62.40, SD: 11.07).

Adherence

The CMF recorded milligrams missed for each medication in the past seven days at baseline. Adherence was defined as missing 25% or less of participants' medication regimens in the past week; participants who missed more than 25% were considered non-adherent. This is consistent with the definitions used in STEP-BD studies.[83]

Demographic Characteristics

Demographic characteristics at baseline included age; gender; race (White, Black, and Other); educational attainment (≤high school, high school diploma or GED, some college, Bachelor's degree, and Graduate or professional degree); current marital status (married or living as though married, divorced or separated, never married, or widowed); whether participants lived alone; primary residence (private home, group home or something else); income (greater or less than $50,000); whether participants received disability insurance or welfare; and employment status (employed, unemployed, disabled or something else). In addition, whether individuals entered the SCPs or RCPs were noted.

Medication

Medications taken at baseline were listed by name (either generic or brand) on the CMF. All medications were identified and grouped into six families: (1) antidepressants, (2) mood stabilizers, (3) antipsychotics, (4) sedatives/hypnotics, (5) stimulants, and (6) other.[121] A regimen count variable was created indicating whether a participant was taking one (monotherapy), two, three, four or five or more medications (polypharmacy).

Analytic Approach

Analyses took place in two steps. First, EFAs reduced the number of measures to only those necessary to comprise each of the three dimensions of CNB (symptoms, adverse effects, and functioning). Second, LCA grouped the participants into distinct classes (subgroups) of CNB. We characterized and examined the correlates of those subgroups in terms of demographic characteristics, medication regimens and medication adherence.

Exploratory Factor Analysis

We conducted three EFAs, (psychiatric symptoms, adverse effects and overall functioning) using the previously described indicators. Using Equamax rotation,[122] eigenvalues > one indicated the number of factors to retain. We only retained indicators meeting the definition of simple structure (factor loadings exceeding 0.50 and a cross loading of at least 0.15 less than the items' highest factor loading).[87, 88, 94-96]

Latent Class Analysis

To improve interpretability of the classes, we dichotomized all continuous and ordinal indicators retained from the EFAs based on the participants' mean scores,[123, 124] with 1=above the mean (better outcomes). The number of distinct latent classes of CNB were determined by comparing model fit using the Akaike Information Criterion (AIC), Bayesian Information Criterion (BIC), Sample-Size Adjusted BIC (BIC_N), Bootstrapped Likelihood Ratio Test (BLRT) and Entropy; for each of these indices smaller values, and Entropy values closest to 1, indicate better relative fit. Measures of model fit, prevalence of class membership and model interpretability were all used to determine the final number of classes.[97, 125] Most likely class membership for each participant was determined from their posterior probabilities.

Characterizing the latent classes of CNB

The demographic characteristics, adherence to medication regimens, types of medication regimens (i.e., monotherapy versus polypharmacy) and makeup of these medication regimens (i.e., percent antidepressants versus mood stabilizers) of the latent classes of CNB were compared using ANOVA for continuous measures and Chi-square analyses for categorical measures.

Descriptive statistics were calculated using SAS version 9.4 (SAS Institute Inc.). EFA and LCA were conducted using Mplus version 7.[91]

RESULTS

Table 2.1. describes the baseline characteristics of the sample. Mean age was 40 years, a little over half (58%) were female and 91% were non-Hispanic white. Only 1% lived in group homes, and most lived with at least one other person (73%). Over 15% received Social Security Disability Insurance. Two medications were the most common regimen, and 72% of participants were adherent to their medication regimen. Only 5% of the sample entered a RCP.

Exploratory Factor Analysis

Table 2.2. provides factor loadings for the three EFAs. Eigenvalues for the *psychiatric symptoms* EFA indicated one factor (first factor: 1.981, and second factor: 0.950). Although the factor loading for YMRS was less than 0.50 (0.312), BHS and MADRS only measure depressive states, therefore YMRS was retained to account for mania. The final *psychiatric symptoms* EFA retained one factor with three indicators: MADRS, BHS and YMRS. The *overall functioning* EFA eigenvalues indicated a one factor model (first factor: 2.090 and second factor: 0.704), therefore the final *overall functioning* EFA retained one factor with four indicators: QLESQ, LRIFT, GAF and Work Impairment. Although the eigenvalues for the *adverse effects* EFA indicated a two factor model (first factor: 4.179 and second factor: 1.123), the second factor had only one measure. Therefore, the one factor model was retained, and the final *adverse effects* EFA included: memory difficulties, dry mouth, sexual dysfunction, headache, constipation, sedation, diarrhea, and tremor.

Latent Class Analysis

Model fit statistics indicated that both the five and six class models had comparable fit (Supplementary Table 2.1.). However, the smallest class in the five class model consisted of

N=432 (12%) of the participants, whereas the smallest class in the six class model consisted of only N=259 (7%) of the participants. Thus, the five class model was chosen due to the best balance of interpretability and model fit.

Results for the five class model of CNB defined by their responses on the three dimensions of CNB (psychiatric symptoms, overall functioning, and adverse effects) are in Figure 2.2. and Supplementary Table 2.2. The five classes were: (1) *high benefit* (low symptoms, low adverse effects and high functioning; class prevalence: 24%); (2) *moderately high benefit* (moderate symptoms, low adverse effects and moderate functioning; class prevalence 26%); (3) *moderate benefit* (moderate symptoms, moderate adverse effects and moderate functioning; class prevalence 12%); (4) *moderately low benefit* (high symptoms, low adverse effects and low functioning; class prevalence 27%); and (5) *low benefit* (high symptoms, moderate adverse effects, and low functioning; class prevalence 12%).

Characterizing the classes

The results of both the ANOVA and Chi-square tests between the classes are indicated as P-values in Table 2.1. Classes differed in all characteristics except in terms of age (F=2.01; p=0.09), race (χ^2=5.51, p=0.70) and primary residence (χ^2=8.33, p=0.40). The *high benefit* class had the highest proportion with graduate education (N=189, 24%), employment (N=467, 57%) and the lowest percentage entering the RCP (N=5, 0.61%), while the *low benefit* class had the highest proportion unemployed (N=117, 28%), receiving social security disability insurance (N=87, 21%) and entering the RCP (N=42, 10%).

Medication adherence did not differ across the classes (χ^2=1.34, p=0.854), ranging between 71% and 74%. This held true after adjusting for all significantly different between class demographic characteristics including medication regimens (i.e., monotherapy versus taking five

or more medications; see bottom of Table 2.1.). However, medication regimens did differ between classes (χ^2=167.39, p<0.001; see Figure 2.3.). In the *high benefit* class over 50% were taking two or fewer medications. In contrast, in the *low benefit* class almost 50% were taking four or more medications. Only the monotherapy regimens (i.e., proportions of antidepressants, mood stabilizers, etc.) differed between the classes (Supplementary Table 2.3. and Supplementary Figure 2.2.; χ^2=39.8, p<0.001). As the number of medications increased (i.e., two medications to three medications) the percent mood stabilizers decreased and other medications taken increased in all classes (i.e., 84% to 28% and 2% to 34% respectively in the *high benefit* class).

DISCUSSION

The primary finding from this study is that the notion of CNB from medical intervention can be expanded beyond traditional metrics using latent variable techniques. We empirically identified subgroups of individuals with distinctly intersecting clinical characteristics of psychiatric symptoms, adverse effects and overall functioning using a novel three dimensional model. Supporting our hypothesis and the external validity of these classes of CNB, the five subgroups of *high*, *moderately high*, *moderate*, *moderately low* and *low benefit* also differed in terms of sociodemographic characteristics such as education, employment, disability status, and entry into the Randomized versus Standard Care Pathways in STEP-BD.

Importantly, contrary to our hypothesis, although classes differed in the three CNB dimensions, they did not differ in medication adherence. Approximately 70% were adherent, which is typical for BD populations.[42] These results suggest that factors associated with adherence identified by prior work (e.g., effects of the illness itself, adverse effects from medications, and complex regimens) are only part of the complex interplay of experiences individuals have of their illness and its treatment. Future work should examine whether the relationship between CNB and adherence changes over time.

Strengths and Limitations

Strengths of this study include use of a large RCT with rigorous and extensive assessments. STEP-BD was a more heterogeneous sample than most RCTs in that it enrolled individuals with comorbidities, already taking medications, at different stages of illness, from a wide age range, and from the full spectrum of BD; this increases generalizability of the results. By using latent variable techniques we empirically identified the indicators of CNB rather than relying solely on theoretical conceptualizations. Finally, detailed information on medications

allowed us to examine components of complex medication regimens commonly used to treat individuals with BD and their relationship with adherence.

Limitations included the lack of measures of participants' perceptions of their illness or of medications used to treat it, or of their individual preferences. Medication usage was not confirmed by pill counts or blood serum levels; however, the clinical interview used here is best-practice for large, complex trials like STEP-BD. Missing data limited the number of measures used to describe the CNB construct.

Conclusions

Our findings support the importance of collaborative, person-centered, shared decision-making approaches to treatment to identify targets for supporting medication adherence. Our results are broadly consistent with previous studies of the experience of individuals with BD that highlight the importance of perceived necessity of medication versus concerns about adverse effects; if perceptions of necessity outweigh concerns, individuals may continue taking their medications even if symptom management and functioning is suboptimal. This may contribute to the unexpected finding of high adherence across these groups that differed substantially in CNB.

Table 2.1. Demographic Characteristics of the Full Sample, and by LCA Class. Includes logistic regression results testing association of classes with adherence*.

	Full Sample	**Class 1**	**Class 2**	**Class 3**	**Class 4**	**Class 5**	**P-values**
		High Benefit	*Moderately High Benefit*	*Moderate Benefit*	*Moderately Low Benefit*	*Low Benefit*	
N (%)	3738	889 (23.78)	961 (25.71)	432 (11.56)	1010 (27.02)	446 (11.93)	
Age (Mean, SD)	40.45 (12.78) N=3568	41.13 (14.33) N=837	39.54 (12.93) N=930	41.04 (13.18) N=417	40.50 (11.39) N=958	40.46 (11.65) N=426	0.091
Female – no./total no. (%)	2054/3563 (57.65)	445/837 (53.17)	530/929 (57.05)	266/417 (63.79)	553/955 (57.91)	260/425 (61.18)	**0.004**
Race – no./total no. (%)							0.702
White	2531/2789 (90.75)	565/621 (90.98)	656/724 (90.61)	281/305 (92.13)	722/798 (90.48)	307/341 (90.03)	
Black	162/2789 (5.81)	33/621 (5.31)	45/724 (6.22)	12/305 (3.93)	53/798 (6.64)	19/341 (5.57)	
Other	96/2789 (3.44)	23/621 (3.70)	23/724 (3.18)	12/305 (3.93)	23/798 (2.88)	15/341 (4.40)	
Education – no./total no. (%)							**<0.001**
Less than high school diploma	105/3448 (3.05)	16/800 (2.00)	29/907 (3.20)	6/401 (1.50)	44/926 (4.75)	10/414 (2.42)	
High school diploma or GED	521/3448 (15.11)	100/800 (12.50)	127/907 (14.00)	42/401 (10.47)	168/926 (18.14)	84/414 (20.29)	
Some college	1296/3448 (37.59)	256/800 (32.00)	335/907 (36.93)	143/401 (35.66)	390/926 (42.12)	172/414 (41.55)	
College diploma (Bachelor's degree)	911/3448 (26.42)	239/800 (29.88)	265/907 (29.22)	118/401 (29.43)	197/926 (21.27)	92/414 (22.22)	
Graduate or professional degree	615/3448 (17.84)	189/800 (23.63)	151/907 (16.65)	92/401 (22.94)	127/926 (13.71)	56/414 (13.53)	
Marital Status – no./total no. (%)							**<0.001**
Married/Living as married	1300/3531 (36.82)	305/829 (36.79)	336/923 (36.40)	174/414 (42.03)	313/942 (33.23)	172/423 (40.66)	
Divorced/Separated	888/3531 (25.15)	171/829 (20.63)	214/923 (23.19)	98/414 (23.67)	298/942 (31.63)	107/423 (25.30)	
Never married	1285/3531 (36.39)	341/829 (41.13)	357/923 (38.68)	137/414 (33.09)	317/942 (33.65)	133/423 (31.44)	
Widowed	58/3531 (1.64)	12/829 (1.45)	16/923 (1.73)	5/414 (1.21)	14/942 (1.49)	11/423 (2.60)	
Lives alone – no./total no. (%)	956/3526 (27.11)	232/828 (28.02)	226/922 (24.51)	113/414 (27.29)	287/940 (30.53)	98/422 (23.22)	**0.015**
Primary residence – no./total no. (%)							0.402
Private home	3310/3459 (95.69)	767/801 (95.76)	869/910 (95.49)	375/400 (93.75)	898/932 (96.35)	401/416 (96.39)	
Group home/assisted living facility	37/3459 (1.07)	8/801 (1.00)	9/910 (0.99)	4/400 (1.00)	11/932 (1.18)	5/416 (1.20)	
Other	112/3459 (3.24)	26/801 (3.25)	32/910 (3.52)	21/400 (5.25)	23/932 (2.47)	10/416 (2.40)	
Income – no./total no. (%)							**<0.001**
$50,000 or less	1968/3261 (60.35)	413/760 (54.34)	505/851 (59.34)	201/382 (52.62)	603/873 (69.07)	246/395 (62.28)	
More than $50,000	1293/3261 (39.65)	347/760 (45.66)	346/851 (40.66)	181/382 (47.38)	270/873 (30.93)	149/395 (37.72)	
Other sources of income							
SSDI – no./total no. (%)	523/3405 (15.36)	78/786 (9.92)	119/894 (13.31)	55/395 (13.92)	184/921 (19.98)	87/409 (21.27)	**<0.001**
Welfare – no./total no. (%)	65/3405 (1.91)	5/786 (0.64)	7/894 (0.78)	8/395 (2.03)	30/921 (3.26)	15/409 (3.67)	**<0.001**
Employment – no./total no. (%)							**<0.001**
Employed	1623/3504 (46.32)	467/818 (57.09)	432/917 (47.11)	202/414 (48.79)	372/934 (39.83)	150/421 (35.63)	
Unemployed	816/3504 (23.29)	157/818 (19.19)	229/917 (24.97)	87/414 (21.01)	226/934 (24.20)	117/421 (27.79)	
Disabled	629/3504 (17.95)	74/818 (9.05)	138/917 (15.05)	62/414 (14.98)	250/934 (26.77)	105/421 (24.94)	

Other	436/3504 (12.44)	120/818 (14.67)	118/917 (12.87)	63/414 (15.22)	86/934 (9.21)	49/421 (11.64)	
Medication Regimens – no./total no. (%)							**<0.001**
Monotherapy	620/3393 (18.27)	202/785 (25.73)	150/869 (17.26)	57/429 (13.29)	158/875 (18.06)	53/435 (12.18)	
Two Medications	863/3393 (25.43)	244/785 (31.08)	249/869 (28.65)	85/429 (19.81)	208/875 (23.77)	77/435 (17.70)	
Three Medications	738/3393 (21.75)	145/785 (18.47)	203/869 (23.36)	87/429 (20.28)	210/875 (24.00)	93/435 (21.38)	
Four Medications	504/3393 (14.85)	85/785 (10.83)	130/869 (14.96)	69/429 (16.08)	145/875 (16.57)	75/435 (17.24)	
Five or More Medications	668/3393 (19.69)	109/785 (13.89)	137/869 (15.77)	131/429 (30.54)	154/875 (17.60)	137/435 (31.49)	
Adhere – no./total no. (%)	2423/3347 (72.39)	557/769 (72.43)	626/862 (72.62)	315/424 (74.29)	620/862 (71.93)	305/430 (70.93)	0.854
Pathway							**<0.001**
Standardized Care	3344/3537 (94.54)	816/821 (99.39)	869/918 (94.66)	416/431 (96.52)	844/926 (91.14)	399/441 (90.48)	
Randomized Care	193/3537 (5.46)	5/821 (0.61)	49/918 (5.34)	15/431 (3.48)	82/926 (8.86)	42/441 (9.52)	
Predicting	**Adherence**						
Classes (Ref=High Benefit)	OR (95% CI)						
Moderately High Benefit	0.95 (0.74-1.21)						
Moderate Benefit	0.89 (0.65-1.20)						
Moderately Low Benefit	1.03 (0.81-1.32)						
Low Benefit	1.09 (0.81-1.47)						
* Adjusted for medication regimens, gender, education, marital status, lives alone, income, social security disability insurance, welfare, and employment							

Table 2.2. Results from Exploratory Factor Analysis. Factor loadings are in order of importance.

Measures	**Factor Loadings**
Psychiatric Symptoms	
MADRS	0.808
BHS	0.652
Panic	0.404
YMRS	0.312
Externalizing Disorders*	-0.199
Adverse Events	
Memory Difficulties	0.804
Dry Mouth	0.733
Sexual Dysfunction	0.678
Headache	0.644
Constipation	0.601
Sedation	0.600
Diarrhea	0.537
Tremor	0.535
Appetite Increase	0.487
EPS	0.230
Functioning	
QLESQ	0.703
LRIFT	0.629
GAF Past Week	0.557
Work Impact Score**	0.523

Bold=Kept in model
*Count that combined: Alcohol Abuse (Y/N); Current Substance Abuse or Dependence (Y/N); Binge Purge (Y/N); Caffeine Cups Per Day (cont.); Nicotine Packs Per Day (cont.)
**Weighted combination: Unable to work or carry out normal activities; Had to cut down on what you did; Extreme effort to perform usual level of normal activities

Supplemental Table 2.1. Fit Statistics from five and six class Latent Class Analyses.

Class	AIC	BIC	BIC_N	BLRT	Entropy
Five Classes	51734.203	52226.081	51975.057	181.755, p<0.001[a]	0.710
Six Classes	51692.095	52283.594	51981.730	74.108, p<0.001[b]	0.687

For each of these indices smaller values, and Entropy values closest to 1, indicate better relative fit.
AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion; BIC_N: Sample-Size Adjusted BIC; BLRT: Bootstrapped Likelihood Ratio Test
[a] BLRT for 4-class versus 5-class model
[b] BLRT for 5-class versus 6-class model

Supplemental Table 2.2. Overall five-class model from Latent Class Analysis, N=3,738. Higher scores indicate better outcomes.

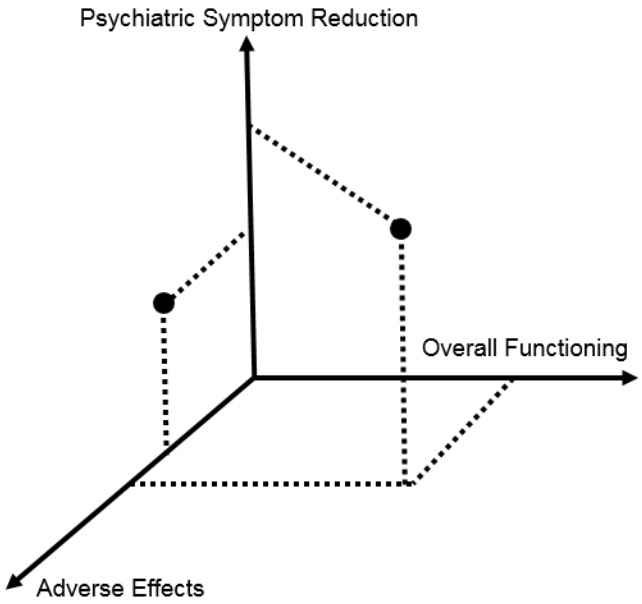
Clinical Net Benefit	**Class 1** *High Benefit*	**Class 2** *Moderately High Benefit*	**Class 3** *Moderate Benefit*	**Class 4** *Moderately Low Benefit*	**Class 5** *Low Benefit*
Predicted Probabilities of Symptom Endorsement					
Psychiatric Symptoms					
BHS	0.922	0.688	0.782	0.138	0.165
YMRS	0.825	0.607	0.698	0.516	0.522
MADRS	1.000	0.545	0.817	0.084	0.131
Adverse Effects					
Tremor	0.921	0.927	0.612	0.907	0.592
Dry Mouth	0.957	0.973	0.477	0.942	0.390
Sedation	0.924	0.910	0.467	0.911	0.487
Constipation	0.981	0.987	0.793	0.983	0.742
Diarrhea	0.968	0.976	0.775	0.967	0.743
Headache	0.955	0.958	0.635	0.943	0.477
Memory Difficulties	0.976	0.969	0.488	0.976	0.311
Sexual Dysfunction	0.982	0.976	0.690	0.969	0.577
Overall Functioning					
QLESQ	0.913	0.557	0.796	0.105	0.134
LRIFT	0.916	0.585	0.779	0.195	0.291
GAF Past Week	0.845	0.490	0.603	0.204	0.189
Work Impact Score	0.789	0.349	0.546	0.218	0.190

BHS: Beck Hopelessness Scale; YMRS: Young Mania Rating Scale; MADRS: Montgomery-Asberg Depression Rating Scale; QLESQ: Quality of Life Enjoyment and Satisfaction Questionnaire; LRIFT: Life Range of Impaired Functioning; GAF: Global Assessment of Functioning

Supplemental Table 2.3. Medication Types in each Regimen by Class.

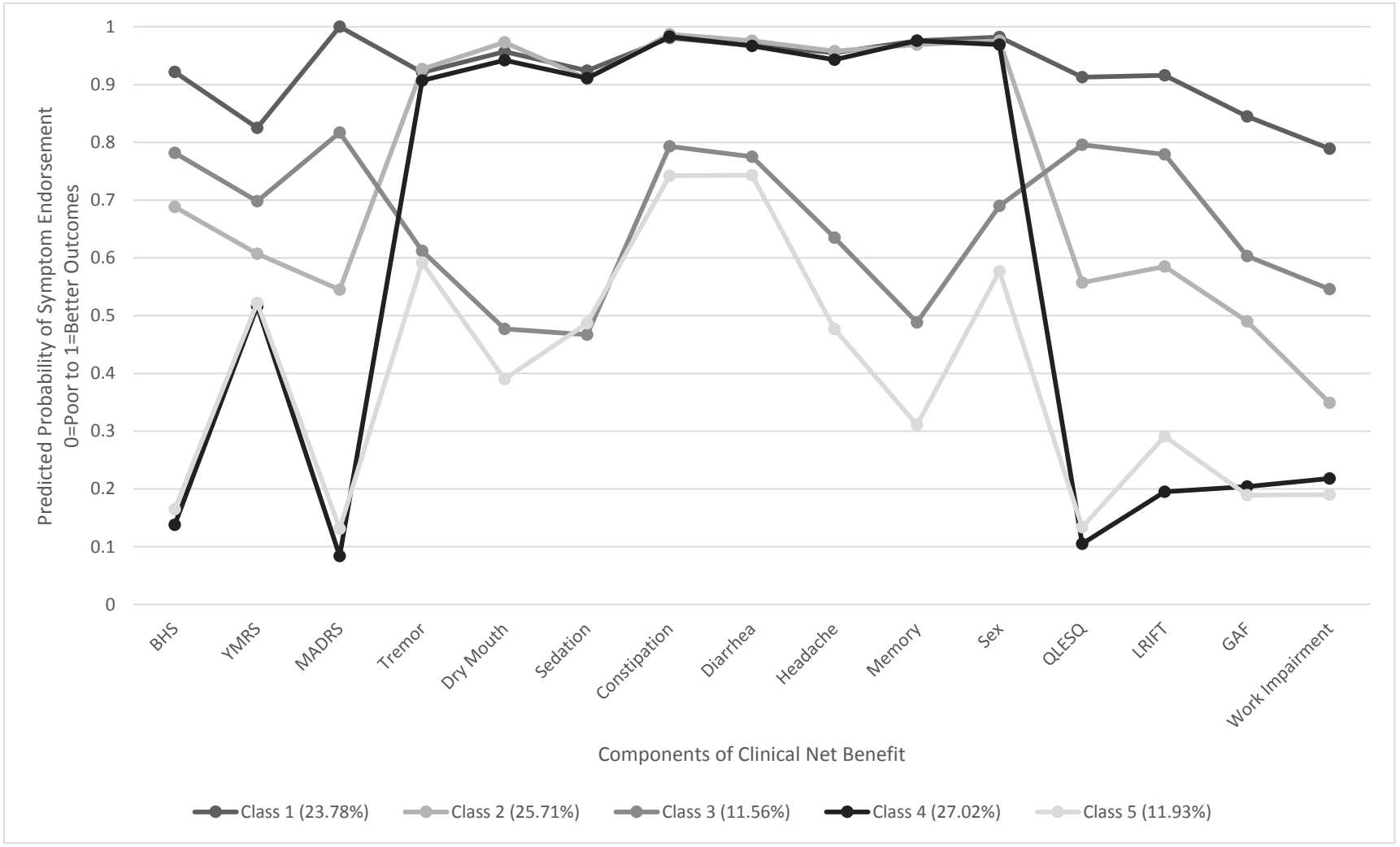
	Antidepressant	Mood Stabilizer	Antipsychotic	Sedative/Hypnotic	Stimulant	Other
Class 1 *High Benefit*						
Monotherapy (N=202)*	13 (6.44)	169 (83.66)	15 (7.43)	--	--	5 (2.48)
Two Medications (N=244)	93 (19.06)	255 (52.25)	72 (14.75)	17 (3.48)	2 (0.41)	49 (10.04)
Three Medications (N=145)	80 (18.39)	178 (40.92)	61 (14.02)	38 (8.74)	4 (0.92)	74 (17.01)
Four Medications (N=85)	54 (15.88)	120 (35.29)	44 (12.94)	34 (10.00)	2 (0.59)	86 (25.29)
Five + Medications (N=109)	85 (15.60)	155 (28.44)	54 (9.91)	57 (10.46)	8 (1.47)	186 (34.13)
Class 2 *Moderately High Benefit*						
Monotherapy (N=150)	11 (7.33)	119 (79.33)	13 (8.67)	3 (2.00)	--	4 (2.67)
Two Medications (N=249)	103 (20.68)	262 (52.61)	66 (13.25)	21 (4.22)	5 (1.00)	41 (8.23)
Three Medications (N=203)	135 (22.17)	268 (44.01)	85 (13.96)	60 (9.85)	7 (1.15)	54 (8.87
Four Medications (N=130)	81 (15.58)	191 (36.73)	58 (11.15)	54 (10.38)	8 (1.54)	128 (24.62)
Five + Medications (N=137)	100 (14.53)	221 (32.12)	82 (11.92)	86 (12.50)	8 (1.16)	191 (27.76)
Class 3 *Moderate Benefit*						
Monotherapy (N=57)	6 (10.53)	42 (73.68)	6 (10.53)	--	--	3 (5.26)
Two Medications (N=85)	31 (18.24)	83 (48.82)	30 (17.65)	13 (7.65)	--	13 (7.65)
Three Medications (N=86)	44 (17.05)	106 (41.09)	41 (15.89)	21 (8.14)	1 (0.39)	45 (17.44)
Four Medications (N=70)	64 (22.86)	95 (33.93)	39 (13.93)	31 (11.07)	2 (0.71)	49 (17.50)
Five + Medications (N=131)	106 (15.87)	195 (29.19)	78 (11.68)	61 (9.13)	3 (0.45)	225 (33.68)
Class 4 *Moderately Low Benefit*						
Monotherapy (N=158)	12 (7.59)	122 (77.22)	16 (10.13)	4 (2.53)	--	4 (2.53)
Two Medications (N=208)	93 (22.36)	207 (49.76)	50 (12.02)	26 (6.25)	1 (0.24)	39 (9.38)
Three Medications (N=210)	128 (20.32)	255 (40.48)	95 (15.08)	74 (11.75)	3 (0.48)	75 (11.90)
Four Medications (N=145)	107 (18.45)	212 (36.55)	69 (11.90)	92 (15.86)	7 (1.21)	93 (16.03)
Five + Medications (N=154)	126 (16.20)	228 (29.31)	96 (12.33)	126 (16.20)	10 (1.29)	192 (24.68)
Class 5 *Low Benefit*						
Monotherapy (N=53)	10 (18.87)	25 (47.17)	10 (18.87)	3 (5.66)	--	5 (9.43)
Two Medications (N=77)	28 (18.18)	69 (44.81)	19 (12.34)	13 (8.44)	1 (0.65)	24 (15.58)
Three Medications (N=93)	74 (26.52)	102 (36.56)	31 (11.11)	35 (12.54)	--	37 (13.26
Four Medications (N=75)	58 (19.33)	98 (32.67)	40 (13.33)	42 (14.00)	2 (0.67	60 (20.00)
Five + Medications (N=137)	142 (20.11)	187 (26.49)	88 (12.46)	106 (15.01)	6 (0.85)	177 (25.07)
*Monotherapy regimens are different between Classes (χ^2=39.8, p<0.001)						

Figure 2.1. Conceptual diagram of Clinical Net Benefit latent construct.



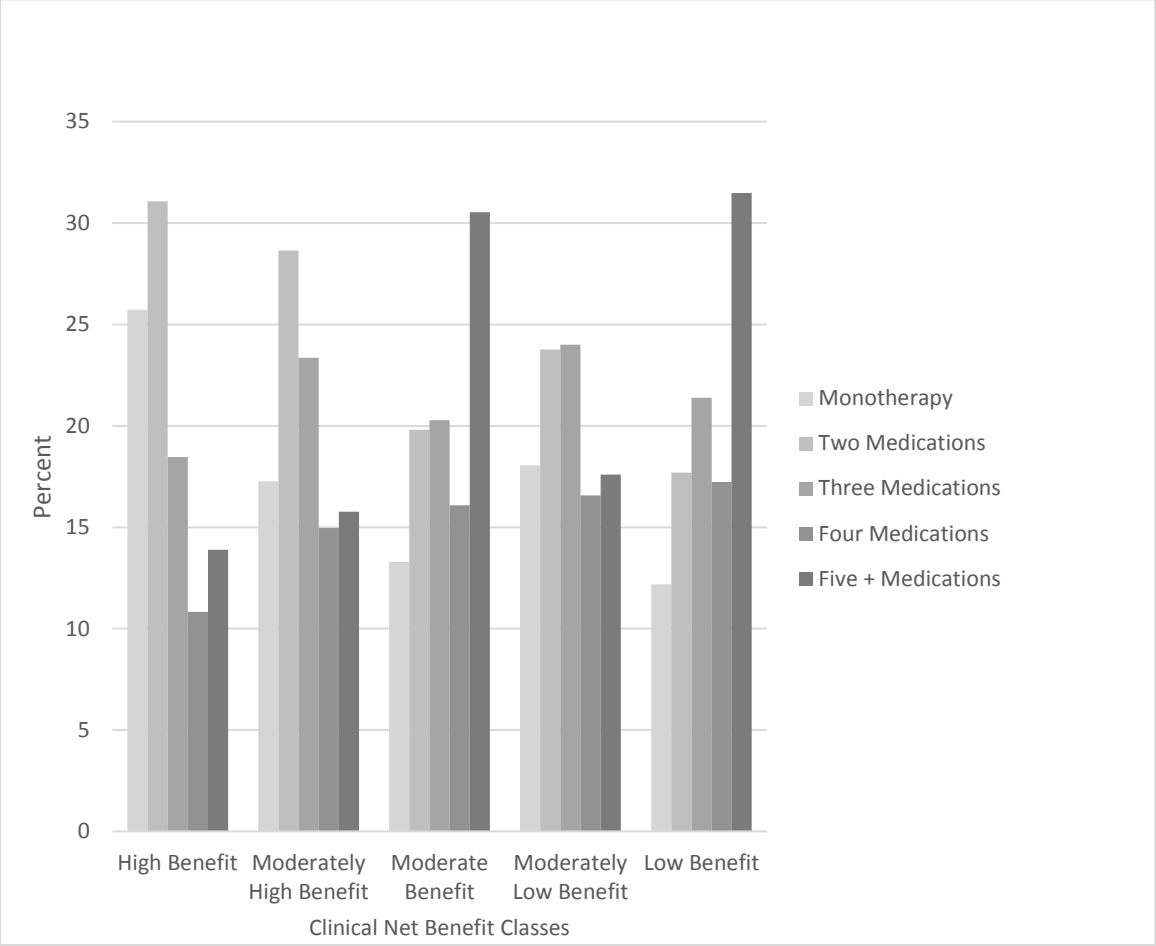
Caption: Dots represent different hypothetical CNB groups and their relative coordinates of psychiatric symptoms, adverse medication effects, and overall functioning.

Figure 2.2. Results of the Latent Class Analysis depicting the five classes of CNB.

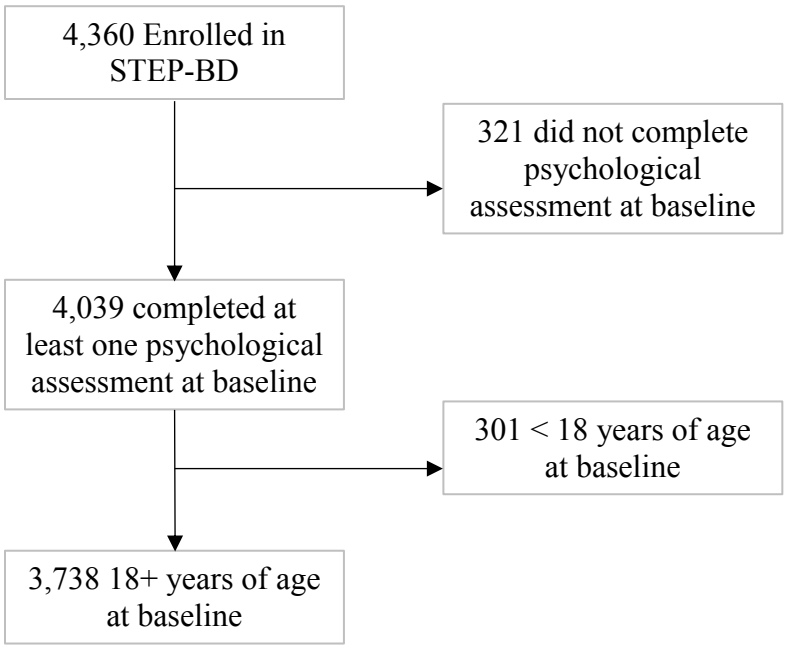


Caption: BHS, YMRS and MADRS are the Psychiatric Symptoms dimension. Tremor through Sex are the Adverse Effects dimension. QLESQ, LRIFT, GAF and Work Impairment are the Overall Functioning dimension.

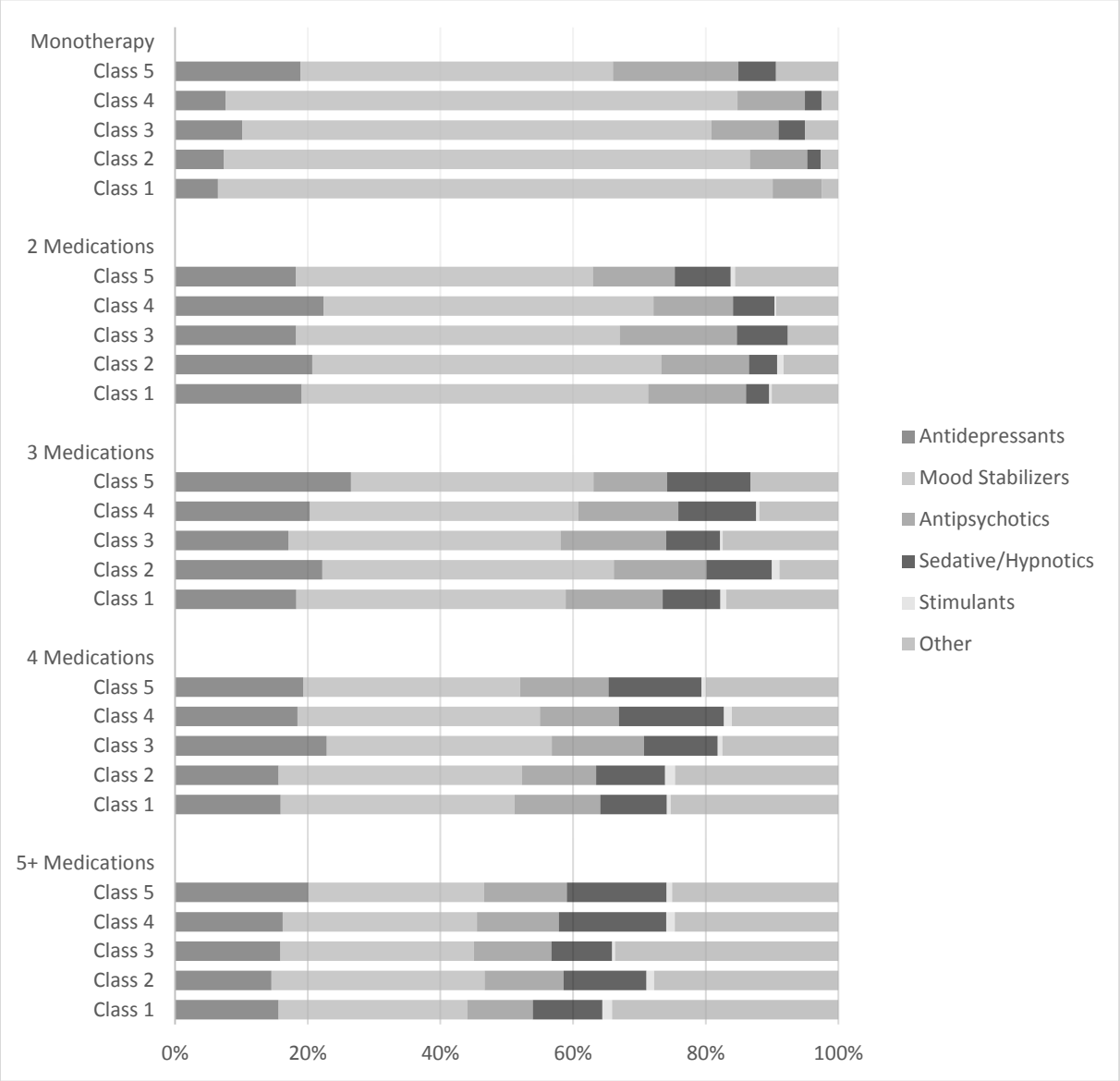
Figure 2.3. Psychotropic Regimens by Class.



Supplemental Figure 2.1. Flowchart from original sample to current analytical sample.



Supplemental Figure 2.2. Make up of Psychotropic Medication regimens by Class and Regimen Type.



CHAPTER 3

The Bi-directional Relationship between Clinical Net Benefit and Medication Adherence Over Time in Bipolar Disorder: A Latent Transition Analysis

ABSTRACT

Objectives: Poor adherence to psychotropic medication is a significant problem for individuals with bipolar disorder (BD), despite effective therapies. Clinicians report individuals who benefit from treatment over time become less adherent possibly due to perceptions that treatment is no longer necessary. Clinical net benefit (CNB) models the experiences individuals have while being treated for BD. We aimed to test whether transitions between classes of benefit occur over time and whether these changes are associated with adherence.

Methods: Data come from the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD), including two years of follow up (Time 1 through 5) of participants aged 18+ years. Latent class analysis identified distinct groups based on the intersection of the three factors of CNB: psychiatric symptoms (i.e., decrease in episodes), adverse effects (e.g., sedation), and functioning (i.e., employment, quality of life). Transitions between classes across the five time points was determined using latent transition analysis. Adherence was defined as taking 75% or more of medications as prescribed. Polypharmacy was categorized as number of medications taken concurrently. Associations between CNB classes, medication regimens, changes in both over time, and adherence were tested using multiple logistic regression adjusting for sociodemographic characteristics.

Results: Five classes of CNB were identified at each time point: High, Moderately high, Moderate, Moderately low and Low. The lower benefit classes transitioned to higher benefit classes by Time 5 (probability of low benefit at Time 4 to moderate benefit at Time 5=0.86), while the higher benefit classes transitioned to lower benefit classes by Time 5 (probability of high benefit at Time 4 to moderately low benefit at Time 5=0.96), but transitioning was not associated with adherence. Relative to monotherapy, taking less complex regimens (three or

fewer) while in the higher benefit classes, were associated with lower adherence (e.g., high benefit at Time 2 taking two medications: OR=0.40; 95% CI: 0.20-0.81), and more complex regimens (four or more) in the lower benefit classes were associated with higher adherence (e.g., moderately low benefit at Time 2 taking five + medications: OR=1.98; 95% CI: 1.05-3.76). Medication regimens were nonlinearly associated with adherence; taking 3 or fewer medications were associated with lower adherence (e.g., three medications at Time 2: OR=0.62; 95% CI: 0.46-0.83), taking 4 or more were associated with higher adherence (e.g., five + medications at Time 2: OR=1.60; 95% CI: 1.12-2.27). Adherence did not differ across classes at each time point.

Conclusions: Individuals initially experiencing low CNB from their medications transitioned to higher CNB classes over time, with few participants in the low benefit class by Time 5. However, individuals receiving high benefit early in the study transitioned to the lower benefit classes by Time 5. This supports reports from clinicians treating individuals with BD and suggests psychotherapeutic methods such as psychoeducation are possible ways to increase adherence in individuals who are experiencing high benefit from their medications.

INTRODUCTION

Bipolar disorder (BD) is a psychiatric condition characterized by cyclical periods of mania and depression that affects 1-4% of the United States population.[19, 126] It is one of the leading causes of disability adjusted life years lost in the U.S.[12, 14] Due to the debilitating, chronic and cyclical nature of this illness, symptomatic individuals often experience high levels of unemployment, disability, in-patient care, medical comorbidities, and increased mortality.[16, 127] Psychotropic medications can successfully treat symptoms of BD; for example, among individuals who are adherent to treatment, only 37% relapse into a depression after one year,[126] and lithium monotherapy symptom recurrence rates are 40% in long term follow-up studies.[30] These individuals can be treated on an outpatient basis and remain fully functioning members of the general population. However, between 20 and 60% of individuals with BD are non-adherent over long term treatment, defined as greater than one year.[36] Improving medical management of BD is key to reducing these negative consequences.

To identify determinants of non-adherence, the perspective of health care providers and individuals with BD themselves have been examined. Health care providers have identified aspects of the illness itself, such as feeling well or missing the highs experienced in mania,[22, 39, 40] as well as adverse effects [44, 108] and complex regimens of multiple psychotropic medications taken concurrently (i.e., polypharmacy)[127] as predictors of non-adherence. Predictors of non-adherence include negative attitudes toward medication in individuals with BD, for example with the notion that taking medication for their illness is not normal.[47] As individuals achieve remission, non-adherence may increase because individuals may incorrectly believe that they are cured or that they did not actually have BD.[39]

Providers weigh the benefits versus risks of specific medications when selecting a treatment regimen for individuals with BD, with symptom remission as the primary goal during acute episodes.[32] As individuals with BD achieve remission, they then enter the maintenance phase of treatment.[16] Guidelines indicate that effective treatments in the acute phase should be continued in the maintenance phase, with medication adjuncts as other symptoms arise (e.g., addition of an antipsychotic or antidepressant if symptoms of depression persist).[128] BD is a chronic disorder and thus adherence to treatment must be maintained indefinitely.[32] However, if during maintenance individuals with BD poorly adhere to their medications, this will lead to relapse and possible hospitalization.[19] It has been found that multiple relapses leads to not only more episodes, but more severe symptoms during those episodes.[33]

Three main factors are in play when considering the benefit of a particular medication or medication regimen for managing BD: psychiatric symptom reduction, low levels of adverse effects, and high functioning.[16] These factors work synergistically, and we have developed a novel construct of Clinical Net Benefit (CNB) to empirical model these elements, detailed previously.[129]

To fully explore the associations between the CNB of medication and adherence, individuals must be followed over time to test the stability of these associations. Using the five-year longitudinal Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD), and the latent construct of CNB identified in our previous analysis, there are three goals for the current study: (1) to determine if membership in the CNB classes changes over time, (2) to determine if there is an association between the classes of CNB and adherence over time, and (3) to determine if the complexity of medication regimens are associated with adherence over time. The primary hypothesis is that individuals who initially experience high CNB during treatment

will become less adherent over time, and that this change in adherence will in turn reduce CNB. The secondary hypothesis is that as the complexity of medication regimens increases, adherence to those regimens will decrease over time, regardless of CNB.

METHODS

Sample

Data come from the STEP-BD study analysis. Eligibility criteria for STEP-BD included diagnoses of bipolar spectrum disorders (meeting DSM-IV criteria for Bipolar I Disorder, Bipolar II Disorder, Bipolar Not Otherwise Specified, Cyclothymic Disorder, or Schizoaffective Disorder Bipolar Subtype), currently in outpatient treatment for BD at a STEP-BD treatment center, could meet with their clinicians as scheduled for the study and could complete all study registration forms within three months of registration. STEP-BD was a 5-year randomized clinical trial (RCT) of individuals treated for bipolar spectrum disorders. It was designed to simulate the "real world" experiences of treatment for individuals with BD. STEP-BD was not solely an RCT, as eligible participants could choose to enter either the Randomized Care Pathways (RCPs) or Standardized Care Pathway (SCP; i.e., treatment as usual). In the RCPs, participants were randomly assignment to specific medications (i.e., mood stabilizers, antipsychotics, antidepressants or placebos) to minimize self-selection bias. If initial regimens were ineffective, participants moved on to subsequent medications, either randomized or determined by the treating physician, until an effective regimen was reached. Participants routinely underwent a battery of clinician- and self-administered psychological assessments. In addition, at each meeting the treating clinicians assessed participants using the Clinical Monitoring Form (CMF). This form is used as a comprehensive tool for clinicians to use during follow-up assessments with participants and includes information on mood episodes, medication use, adverse events, mental status as well as medication adherence.[62] Additional details of the original study design are described elsewhere.[52]

STEP-BD enrolled 4,360 participants that met these eligibility criteria for the study. This analysis excluded 321 participants with less than five STEP-BD assessments (approximately two years of active study participation), as well as those missing data on all of the components of CNB, the main exposure for this analysis. In addition 399 participants were excluded who were less than age 18 at Time 1 and all follow-ups. The final analytic sample size was 3,996 (Supplemental Figure 3.1.). For those with incomplete data, missing values were imputed using Full Information Maximum Likelihood Estimation.[92]

Measures

Clinical Net Benefit

CNB incorporates three main effects of treatment on the individual: (1) psychiatric symptom reduction; (2) adverse effects; and (3) overall functioning. As we indicated in Chapter 1, CNB can be conceptualized as a 3-dimensional construct lying at the intersection of these axes. Individuals differentially experience these components of treatment, depicted as points in Figure 1.1. from Chapter 1. Our prior work in Chapter 2 used latent class analysis to empirically define and quantitatively measure these three dimensions of CNB, using baseline data from STEP-BD.

In the current study the *psychiatric symptoms* dimension consisted of the Montgomery-Asberg Depression Rating Scale (MADRS)[71] and the Young Mania Rating Scale (YMRS).[70] However, due to the small sample size of the Beck Hopelessness Scale relative to the other measures by Time 5, we removed this assessment from the *psychiatric symptoms* dimension. The *adverse effects* dimension included the measures of memory difficulties, dry mouth, sexual dysfunction, headache, constipation, sedation, diarrhea, and tremor from the CMF.[62] Finally, the

overall functioning dimension included the Quality of Life Enjoyment and Satisfaction Questionnaire (QLESQ),[72] LIFE Range of Impaired Functioning Tool (LRIFT)[73] three indicators from the Work Impact Form (WIF),[52] and past week Global Assessment of Functioning (GAF)[79] score from the CMF.

Medication

Supplemental Table 2.3. from Chapter 2 indicates the psychotropic medication families making up the different regimens that participants were taking at their baseline assessment in STEP-BD stratified by CNB class. These medications were listed by name (either generic or brand) on the CMF and were recorded at each of the five assessments. All medications were identified and grouped into six families: (1) antidepressants, (2) mood stabilizers, (3) antipsychotics, (4) sedatives/hypnotics, (5) stimulants, and (6) other using the U.S. Food & Drug Administration National Drug Code Directory.[121] Next, a medication count variable was created indicating whether a participant was taking one (monotherapy), two, three, four or five or more medications (polypharmacy).

Adherence

The CMF recorded both the milligrams prescribed as well as milligrams missed for each medication a participant was taking in the past seven days. We calculated adherence by first identifying whether participants were taking each of their medications as prescribed. Then they were defined as adherent if 75% or more of their regimens were taken as prescribed. For example, if individuals were prescribed four medications in their regimens, and if they were fully adherent to three of the four medications then they would be defined as adherent. Participants who missed more than 25% of the milligrams prescribed for one or more of the medications in

their regimens were defined as non-adherent. Adherence defined as missing less than 25% of an individual's regimen is consistent with definitions used in STEP-BD studies.[83]

Standard Care or Randomized Care Pathways

Identification of treatment pathway was also included. STEP-BD was designed to have both a SCP and three RCPs. The SCP was subsequently categorized into 15 distinct pathways and the RCP added an additional pathway.[62] Approximately 5% (N=195) of participants entered RCPs at Time 1, therefore we categorized entry into any SCP as one category and any RCP as the second category.

Demographic Characteristics

Demographic characteristics included age (in years); gender; race (White, Black, and Other); educational attainment (≤high school, high school diploma or General Education Development (GED), some college, Bachelor's degree, and Graduate or professional degree); current marital status (married or living as though married, divorced or separated, never married, or widowed); whether participants lived alone; primary residence (private home, group home or something else); income (greater or less than $50,000); whether participants received Social Security Disability Insurance (SSDI) and welfare; and employment status (employed, unemployed, disabled or retired/not in the labor force).

Analytic Approach

Analyses took place in two steps. First, five latent class analyses (LCAs) were conducted, one at each STEP-BD time point, to determine the number of classes that best fit the sample at each time point and the predicted probabilities of participant membership in each class at each of these time points. Second, a Latent Transition Analysis (LTA) was conducted to confirm fit for

the number of classes at each time point, and to identify participants' movement between classes at each time point.

Latent Class Analysis

As described in Chapter 2, the values of the measured indicators for CNB, whether ordinal or continuous, were dichotomized at all time-points based on the participants' mean scores at those time points, with 1=above the mean (better outcomes). Then the number of distinct latent classes of CNB were determined by conducting the LCA with these measures at each time point. To determine model fit, we compared the Akaike Information Criterion (AIC), Bayesian Information Criterion (BIC), Sample-Size Adjusted BIC (BIC_N), Bootstrapped Likelihood Ratio Test (BLRT) and Entropy; for each of these indices smaller values, and Entropy values closest to 1, indicate better relative fit.[100] Measures of model fit, prevalence of class membership and model interpretability were all used to determine the final number of classes for each time point.[125] Finally, most likely class membership at each time point for each participant was determined from their posterior probabilities identified in these LCAs.[97]

Latent Transition Analysis

The goal of LTA is to determine whether individuals in one latent class at a particular time point remain in the same class or transition to another latent class at a subsequent time point.[99] The goal of this analysis is to determine if the CNB classes are static or change over time; for example, whether individuals in the low benefit class stay in that class over time or move to higher benefit classes over the course of the trial.

The primary outcome of LTAs are transition probabilities, which are akin to posterior probabilities of individuals' class membership generated from an LCA. However, in this case,

the transition probabilities quantify the likelihood of moving from one class to another across two time points.[99] LTA was used to quantify three aspects of CNB change over time: (1) the best fitting number of latent classes, (2) the change in values of the measured indicators for each class, and (3) the probability of participant class membership change at each time point. LCA is a cross sectional analysis that determines the best fit of the number of classes at each time point. However, it lacks the additional information regarding probability of participants' changing classes over time.[99] This can result in different numbers or characteristics of classes. Therefore, the LCA fit for each time point was confirmed when conducting the LTA using the AIC, BIC, and BIC_N.

We also wanted to allow for changes in values in each of the measured indicators at each time point in addition to participant class membership change. Therefore we did not impose parameter restrictions to hold the item-response probabilities equal across each time point, which is often done but not necessary for an LTA.[99, 102] For example, a parameter restriction would hold the MADRS scores in the high benefit class constant over time, and would not give us the additional insight into whether and which direction MADRS scores changed for the high benefit class at subsequent time points.

LTA is preferable to other analytical approaches for examining change over time (such as Repeated Measures Latent Class Analysis) because we not only wanted to determine class membership at each time point, but also the probability of participants changing class membership (i.e., transitioning) at each consecutive time point. This additional measure of transitioning probabilities can most effectively be determined in LTA.[99, 102]

Characterizing the Latent Classes of CNB

The demographic characteristics, adherence to medication regimens, types of medication regimens (i.e., monotherapy versus polypharmacy) and membership in the SCPs or RCPs of the Time 1 latent classes of CNB were compared using ANOVA for continuous measures and Chi-square analyses for categorical measures.

Predictors of Adherence

To determine predictors of adherence, multiple logistic regression analyses, adjusted for demographic characteristics, were conducted at each of the five time points. The primary predictors of adherence were: (1) CNB class membership at each time point from the LCAs, and (2) number of medications in participants' regimens at each time point. An additional predictor was changes in medication regimens from the previous time point.

Descriptive statistics and regressions were calculated using SAS version 9.4 (SAS Institute Inc.). LCA and LTA were conducted using Mplus version 7.[91]

RESULTS

Table 3.1. describes the characteristics of the analytic sample at Time 1. The mean age was 40 years, 58% were female, and 91% were non-Hispanic white. The majority had an income less than $50,000, 15% had income from SSDI, and 23% were unemployed. Most participants lived with at least one other person (73%), and only 1% lived in group homes. Three out of ten participants took five or more medications. Three quarters of participants were adherent to their medication regimen at the Time 1 assessment.

Fitting the Latent Class Analysis for Clinical Net Benefit

Model fit statistics indicated that both the four- and five-class models of CNB had comparable fit across the five time points (Supplemental Table 3.1.). At Time 1 and 4, the AIC, BIC_N and BLRT indicated better fit for the five-class model, however, at Time 2 and 3 the BIC, BIC_N and Entropy indicated better fit for the four-class model. At Time 5 , both the four- and five-class models had equivalent fit, although the smallest class prevalence at Time 5 for the four-class model was 12% (N=322) compared with the smallest class in the five-class model of only 2% (N=47). The best fitting model when confirmed via the LTA, was the five-class model at each time point with an AIC, BIC, BIC_N greater than the four-class model (Supplementary Table 3.1.). In addition, keeping the number of classes the same at each time point in the LTA aided the interpretability of class membership change. For example, if prevalence of a class reduced in size at each time point, and a greater percentage of individuals moved from that class to a higher benefit class, this may support the notion that over time participants' CNB increased.

Characteristics of the Classes of Clinical Net Benefit

Characteristics for the five-class model of CNB are shown in Figure 3.1. The five classes of CNB were: (1) *high benefit* (characterized by low psychiatric symptoms, low adverse effects, and high functioning); (2) *moderately high benefit* (moderate psychiatric symptoms, low adverse effects and moderate functioning); (3) *moderate benefit* (moderate psychiatric symptoms, moderate adverse effects and moderate functioning); (4) *moderately low benefit* (high psychiatric symptoms, low adverse effects and low functioning); and (5) *low benefit* (high psychiatric symptoms, moderate adverse effects, and low functioning). Finally, participation in the SCPs versus the RCPs differed across CNB classes at Time 1. Consistent with the notion that individuals deriving the most benefit from their current medication regimens would choose to stay with their current treatment, almost all (99%) of those in the *high benefit* class elected to stay in the SCPs; in contrast, 10% of the *low benefit* class elected to enter an RCP.

Table 3.2. describes the CNB class prevalence and medication adherence for each CNB class across the five time points as well as the differences in adherence across classes at each time point. This table illustrates three key points: First, the *high benefit* class grows substantially over the 2-year follow up period, from 19% to 36%. These findings are consistent with the fact that these data are derived from a stepped treatment trial, and it is expected that providers and participants will make treatment changes to improve the outcomes if participants do not appear to be benefiting from their current medication regimens.[52] Second, they are also consistent with the notion that individuals who are not deriving much benefit from their medications are more likely to drop out of the trial. At Time 1, when compared to participants who stayed through Time 5, those who ever dropped out during the study were less likely to have at least a Bachelor's degree (N=258, 24%), less likely to have an income of $50,000 or greater (N=333,

33%), more likely to be unemployed (N=291, 27%), and more likely to live in a group home (N=17, 2%). In addition, adherence was less in individuals who ever dropped out of the study (71% versus 76%) and almost 42% were taking five or more medications compared with 25% who stayed in the study (Table 3.3.). Medication adherence ranged from 72% to 80% across classes and time points, and did not differ across classes at each time point, with the exception of Time 2 (Table 3.2.).

Clinical Net Benefit, Medication Regimens, and Medication Adherence at Time 1

On average, participants were taking 3 (range 1 – 12) medications at Time 1. Medication adherence did not differ across the classes ($\chi2=2.96$, $p=0.57$) at Time 1, ranging between 72% and 77%. However, medication regimens did differ between classes ($\chi2=75.18$, $p<0.001$). In the high benefit class over 60% were taking three or fewer medications. In contrast, in the low benefit class almost 50% were taking four or more medications.

Latent Transition Analysis: Changes in Clinical Net Benefit over Time

Characteristics of the different measured indicators of CNB are also in Figure 3.1. In general the scores for the three dimensions of CNB remained consistent across time, with the greatest variability seen in the psychiatric symptoms dimension and the overall functioning dimension. The values on the three dimensions remained relatively stable for the *high benefit*, the *moderate benefit* and the *low benefit* classes. The *moderately high benefit* class saw a decrease in symptoms over time, while the other two dimensions remained consistent. The *moderately low benefit* class saw decreased symptoms and increased functioning over time.

Latent Transition Analysis: Movement between Classes of Clinical Net Benefit over Time

Table 3.4. illustrates the latent transition probabilities of moving between classes at each consecutive time point. Each column and each row sum to a probability of 1.0.[99] For example, the transitions between Time 1 and 2 illustrate that most of the movement between classes occurred among the *moderate*, *moderately high* and *high benefit* classes. For example, there was an 80% probability of moving from the *moderate* to the *moderately high benefit* class, and an 85% probability of moving from the *moderately high* to the *high benefit* class. In contrast, the *moderately low* and *low benefit* classes were generally stable, with about a 75% probability of remaining in these classes. Somewhat unexpected, the *high benefit* class had a 79% probability of transitioning to the *moderate benefit* class; this represents the precariousness of ideal outcomes for this population.

From Time 2 to 3, most of the movement between classes happened with the *moderately high* to *moderately low benefit* classes. The probability of moving to a lower benefit class ranged from 81% to 86% for these three classes. The *high benefit* class remained stable with a 93% probability of remaining in this class. The *low benefit* class was the only class that had an increase in benefit, with a probability of 84% moving to the *moderately high benefit* class.

Movement from Time 3 to 4 was most notable for the increase in benefit of the two lower benefit classes, with an 85% probability of the *low benefit* class moving to the *high benefit* class, and an 88% probability of the *moderately low benefit* class moving up to the *moderate benefit* class. The three highest classes had probabilities of between 84% and 89% movement to a lower benefit class.

Finally, from Time 4 to 5 the three lowest benefit classes had probabilities between 86% and 92% of moving to higher benefit classes However, the two highest benefit classes at Time 4 had probabilities of moving to lower benefit classes at Time 5; the *high benefit* class had a 96%

probability of moving to the *moderately low benefit* class and the *moderately high benefit* class had a 92% probability of moving to the *low benefit* class.

Additionally, change in a participant's regimen was associated with movement between classes at Time 4 and 5 with 34% odds of moving to a lower benefit class at Time 4, and a 28% odds of moving to a lower class at Time 5. In addition, a regimen change was associated with 32% odds of moving to a higher benefit class at Time 5 (Figure 3.2.).

Changes in Clinical Net Benefit, Medication Regimens, and Medication Adherence

Table 3.5. shows the relative odds of adherence across the five CNB classes over time. At Time 1, class membership was not associated with adherence. Over time, however, several patterns emerged in the relationship between CNB and adherence. Relative to the *high benefit* class, most classes had lower adherence over time. For example, compared to the *high benefit* class, the *low* and *moderately low benefit* classes had approximately 30% lower odds of adherence at Time 2, a trend that continued to Time 4. At Time 5, the *moderately high benefit* class had 24% lower odds of adherence when compared with the *high benefit* class.

Across all time points, there was a non-linear relationship between polypharmacy and adherence. Compared to monotherapy, taking three or fewer medications was associated with lower adherence, however taking four or more medications was associated with higher adherence. At Time 2, 3 and 5 taking two or three medications was associated with lower adherence as compared to monotherapy. However, changing medication regimens, including adding, removing or changing a medication, was not associated with adherence over time (Time 2: OR=0.86; 95% CI: 0.72-1.03; Time 3: OR=0.95; 95% CI: 0.78-1.16; Time 4: OR=1.07; 95% CI: 0.87-1.32; Time 5: OR=0.84; 95% CI: 0.68-1.04).

Post-hoc analysis

Medication regimens were significantly different between the classes at Time 1, participants in the *low benefit* class were the most likely to be taking complex polypharmacy (four or more medications). Additionally, at Time 1 adherence across all classes of benefit did not differ. Therefore to further examine the association between classes of CNB and their medication regimens with adherence, a post hoc analysis of the association between medication regimens and adherence stratified by class was conducted (Table 3.6.). The post hoc analysis revealed that the *high benefit* class had a trend of lower odds of adherence over time, reaching significance at Time 2, 3 and 5, when prescribed less complex regimens (three medications or less). The *low benefit* class had a trend of higher odds of adherence over time, with the odds reaching significance at Time 1 to 3 with more complex regimens of 4 or more medications.

Due to the high rates of dropout by Time 5, we also compared the demographic characteristics at Time 1 of participants who stayed in the study through Time 5 to those who ever dropped out of the study before Time 5. Those who dropped out of the study were different from those who stayed in almost all demographic and study characteristics. In addition to the differences noted above, individuals who dropped out of the study were also less adherent, taking more medications concurrently, were less likely to be in a RCP, but were actually more likely to be in a higher benefit class (Table 3.6.).

DISCUSSION

The primary finding from this study is that membership in the classes of CNB changes over time even in this sample of BD patients being actively treated. On a positive note, participants who were receiving less benefit from their medications at the start of the trial transitioned to classes of increased benefit over time. This is anticipated, as the purpose of a stepped-treatment trial is to increase the benefit participants are receiving from their treatment.[52] However, the initial higher benefit classes transitioned to lower benefit classes over time. The relationship between changes in CNB and changes in adherence is complex even during this relatively short 2-year period. Finally, toward the conclusion of the trial, changes to medication regimens were associated with both positive and negative changes to CNB. These findings broadly support clinicians' reported experiences while working with individuals with BD. The individuals who benefit from their treatment become less adherent over the long term, leading to less benefit from their medications, likely due to their belief that they have been cured, or never had BD.[130]

Medication regimens were associated with adherence across time, as expected, although this relationship was bi-directional. Our post hoc analysis of the association between medication regimens and adherence stratified by class revealed that the *high benefit* class had lower odds of adherence over time. This provides further support that individuals with higher benefit over time become less adherent, leading to less benefit from their treatment.[41]

A notable finding was that the *low benefit* class had a trend of higher odds of adherence over time in participants who were taking more complex regimens of 4 or more medications. It is highly likely that only when it was absolutely necessary did participants' treating psychiatrists prescribe complex polypharmacy, taking into account that under-dosing has been associated with

higher non-adherence.[16] This may also be due to differential drop out, because individuals who dropped out of the study were taking more complex polypharmacy regimens than those who remained. Nevertheless, this finding adds support to previous analyses suggesting that adherence likely results in better outcomes because these medications are effective treatments of BD.[30, 126]

Overall adherence across classes slightly increased over time although at each time point adherence across classes was not different, with the exception of Time 2. This indicates that individuals who are receiving low benefit of their medication had the same prevalence of adherence as those with high benefit from their medication. This lends support to the theory of the association between adherence and individuals' perspectives of necessity versus concerns of their treatment.[43] Although participants are not greatly benefiting from their medications at Time 1, their high levels of adherence are likely associated with their movement to higher benefit classes.

Strengths and Limitations of the Study

Strengths of this study include the use of a randomized controlled trial that was large and actively followed individuals at multiple time points over two years. In addition to the randomized pathways, treatment as usual was also allowed which more closely replicated the circumstances in naturalistic studies. The wealth of rigorous psychological assessments allowed for detailed LCAs at each time point. Detailed information on psychotropic medications gathered at each time point allowed us to determine the number and make up of medication regimens prescribed to participants in the study. The inclusion criteria allowing for bipolar spectrum disorders, comorbidities, different stages of the illness, and continuation of current medications increased the generalizability of the results. Finally, the use of both LCA to identify the indicators of CNB, and LTA to quantify the likelihood of moving from one class to another

across time points gave us empirical results rather than a reliance on theoretical conceptualizations.

These results must be tempered by the limitations of this study. The primary limitation is that nearly one in three participants dropped out of the trial by Time 5, and this attrition was differential based on medication regimen and Time 1 adherence. These individuals were less educated, had lower socioeconomic status, and were taking more complex medication regimens than individuals who remained in the study. However, this is a comparable rate of retention with other longitudinal RCTs.[131, 132] Despite the dropout rates, by Time 5 the sample size was almost 2,800, which indicates a very high level of power for conducting latent analysis techniques.[103] Additionally, indications of adherence by the treating clinician were not confirmed by pill bottle counts or blood serum levels.[38] In large clinical trials, this is a common measurement of adherence, which makes comparison between studies easier.[47] Finally, participant perceptions of their illness, medication treatment, and their preferences for treatment were not assessed in this study (e.g. Beliefs about Medicines Questionnaire).[63] Therefore we can only infer participants' perceptions of the benefit they are receiving from their medications by their symptom and functional outcomes used in the psychological assessments.

Conclusions

Our findings support continued collaborative, person-centered care to optimize adherence for individuals with BD. Consistent with practitioners' experiences, we found that individuals who initially benefit from their medication are likely to become less adherent over time, possibly due in part to remission and the concept of being cured.[46] This also suggests that becoming well is not as difficult as staying well. This is surprising to find in a study such as STEP-BD which is designed as the "best-case" scenario with regards to support, and in which participants agreed

upon participation. Our findings were also consistent with the reported experiences of individual being treated for BD that necessity versus concerns are associated with adherence.[43] Individuals were adherent despite low benefit from their medications, and if they maintained adherence were likely to experience an increase in benefit from their medications over time. Education regarding the course of BD as well as psychotherapy with a focus on shared decision making and positive alliances between individuals and their practitioners have been suggested as a way to support adherence in populations with BD.[45, 133] However, this may need to play a greater role in helping individuals who are successfully recovering from BD symptoms and benefiting from their medications as well. Further insight into whether adherence and CNB is maintained in a naturalistic setting can add to our results, which may be limited due to active study participation.

Table 3.1. Time 1 Demographic Characteristics of the full sample and by clinical net benefit class. Includes between group significant differences using ANOVA or chi-square analyses.

	Full Sample	**High Benefit**	**Moderately High Benefit**	**Moderate Benefit**	**Moderately Low Benefit**	**Low Benefit**	**P value**
N (%)	3,996	744 (18.62)	940 (23.52)	410 (10.26)	1,450 (36.29)	452 (11.31)	
Age (M, SD)	40.25 (12.82)	41.99 (14.37)	39.01 (13.58)	40.99 (13.04)	39.84 (11.54)	40.55 (11.87)	**<0.001**
Female - no./total no. (%)	2,206/3814 (57.84)	363/710 (51.13)	508/895 (56.76)	250/397 (62.97)	818/1383 (59.15)	267/429 (62.24)	**<0.001**
Race - no./total no. (%)							0.356
White	2725/3008 (90.59)	456/510 (89.41)	659/718 (91.78)	277/299 (92.64)	1028/1144 (89.86)	305/337 (90.50)	
African American	176/3008 (5.85)	32/510 (6.27)	37/718 (5.15)	10/299 (3.34)	79/1144 (6.91)	18/337 (5.34)	
Other	107/3008 (3.56)	22/510 (4.31)	22/718 (3.06)	12/299 (4.01)	37/1144 (3.23)	14/337 (4.15)	
Education - no./total no. (%)							**<0.001**
Less than High School	113/3692 (3.06)	16/677 (2.36)	22/873 (2.52)	5/383 (1.31)	59/1343 (4.39)	11/416 (2.64)	
High School/GED	553/3692 (14.98)	85/677 (12.56)	114/873 (13.06)	45/383 (11.75)	232/1343 (17.27)	77/416 (18.51)	
Some College	1398/3692 (37.87)	196/677 (28.95)	343/873 (39.29)	132/383 (34.46)	550/1343 (40.95)	177/416 (42.55)	
Bachelor's Degree	979/3692 (26.52)	206/677 (30.43)	251/873 (28.75)	113/383 (29.50)	318/1343 (23.68)	91/416 (21.88)	
Graduate Degree	649/3692 (17.58)	174/677 (25.70)	143/873 (16.38)	88/383 (22.98)	184/1343 (13.70)	60/416 (14.42)	
Marital Status - no./total no. (%)							**<0.001**
Currently Married	1381/3780 (36.53)	279/707 (39.46)	288/886 (32.51)	163/393 (41.48)	472/1368 (34.50)	179/426 (42.02)	
Previously Married	954/3780 (25.24)	145/707 (20.51)	204/886 (23.02)	93/393 (23.66)	410/1368 (29.97)	102/426 (23.94)	
Never Married	1385/3780 (36.64)	275/707 (38.90)	374/886 (42.21)	134/393 (34.10)	469/1368 (34.28)	133/426 (31.22)	
Widowed	60/3780 (1.59)	8/707 (1.13)	20/886 (2.26)	3/393 (0.76)	17/1368 (1.24)	12/426 (2.82)	
Lives Alone - no./total no. (%)	1008/3775 (26.70)	175/707 (24.75)	254/885 (28.70)	108/394 (27.41)	370/1364 (27.13)	101/425 (23.76)	0.260
Income - no./total no. (%)							**<0.001**
<$50,000	2108/3484 (60.51)	346/648 (53.40)	499/816 (61.15)	193/363 (53.17)	829/1261 (65.74)	241/396 (60.86)	
$50,000 +	1376/3484 (39.49)	302/648 (46.60)	317/816 (38.85)	170/363 (46.83)	432/1261 (34.26)	155/396 (39.14)	
SSDI - no./total no. (%)	554/3642 (15.21)	69/668 (10.33)	110/859 (12.81)	54/377 (14.32)	238/1325 (17.96)	83/413 (20.10)	**<0.001**
Welfare - no./total no. (%)	67/3642 (1.84)	6/668 (0.90)	4/859 (0.47)	7/377 (1.86)	36/1325 (2.72)	14/413 (3.39)	**<0.001**
Employment - no./total no. (%)							**<0.001**
Employed	1747/3754 (46.54)	412/697 (59.11)	427/880 (48.52)	190/395 (48.10)	567/1358 (41.75)	151/424 (35.61)	
Unemployed	874/3754 (23.28)	119/697 (17.07)	211/880 (23.98)	81/395 (20.51)	340/1358 (25.04)	123/424 (29.01)	
Disabled	665/3754 (17.71)	63/697 (9.04)	126/880 (14.32)	63/395 (15.95)	313/1358 (23.05)	100/424 (23.58)	
Other	468/3754 (12.47)	103/697 (14.78)	116/880 (13.18)	61/395 (15.44)	138/1358 (10.16)	50/424 (11.79)	
Type of Residence - no./total no. (%)							**0.047**
Private Home	3543/3705 (95.63)	650/680 (95.59)	829/875 (94.74)	357/382 (93.46)	1304/1350 (96.59)	403/418 (96.41)	
Group Home	40/3705 (1.08)	3/680 (0.44)	15/875 (1.71)	5/382 (1.31)	13/1350 (0.96)	4/418 (0.96)	
Other	122/3705 (3.29)	27/680 (3.97)	31/875 (3.54)	20/382 (5.24)	33/1350 (2.44)	11/418 (2.63)	
Adhere - no./total no. (%)	2,468/3282 (75.20)	456/597 (76.38)	555/734 (75.61)	297/387 (76.74)	857/1145 (74.85)	303/419 (72.32)	0.565

Medication Regimens - no./total no. (%)							**<0.001**
Monotherapy	631/3977 (15.87)	173/744 (23.25)	136/938 (14.50)	51/406 (12.56)	214/1445 (14.81)	57/444 (12.84)	
Two Medications	875/3977 (22.00)	191/744 (25.67)	210/938 (22.39)	96/406 (23.65)	309/1445 (21.38)	69/444 (15.54)	
Three Medications	760/3977 (19.11)	115/744 (15.46)	180/938 (19.19)	78/406 (19.21)	288/1445 (19.93)	99/444 (22.30)	
Four Medications	519/3977 (13.05)	71/744 (9.54)	118/938 (12.58)	67/406 (16.50)	194/1445 (13.43)	69/444 (15.54)	
Five + Medications	1,192/3977 (29.97)	194/744 (26.08)	294/938 (31.34)	114/406 (28.08)	440/1445 (30.45)	150/444 (33.78)	
Pathway - no./total no. (%)							
Standardized Care	3418/3613 (94.60)	650/658 (98.78)	810/830 (97.59)	397/408 (97.30)	1156/1269 (91.10)	405/448 (90.40)	**<0.001**
Randomized Care	195/3613 (5.40)	8/658 (1.22)	20/830 (2.41)	11/408 (2.70)	113/1269 (8.90)	43/448 (9.60)	

Table 3.2. Class prevalence and prevalence of adherence at each time point, with indications of differences in adherence across classes at each time point from chi-square analyses.

	Time 1	**Time 2**	**Time 3**	**Time 4**	**Time 5**
N (%)	3996	3530	3240	2988	2785
Class (N, %)					
High Benefit Class	744 (18.62)	590 (16.71)	776 (23.95)	1174 (39.29)	1003 (36.01)
Adherence	*456 (76.38)*	*429 (80.94)*	*535 (78.45)*	*848 (79.55)*	*723 (79.54)*
Moderately High Benefit	940 (23.52)	1204 (34.11)	433 (13.36)	767 (25.67)	1033 (37.09)
Adherence	*555 (75.61)*	*813 (77.06)*	*323 (80.55)*	*538 (76.42)*	*731 (76.23)*
Moderate Benefit	410 (10.26)	367 (10.40)	443 (13.67)	311 (10.41)	372 (13.36)
Adherence	*297 (76.74)*	*260 (76.02)*	*324 (76.24)*	*236 (78.15)*	*272 (77.49)*
Moderately Low Benefit	1450 (36.29)	934 (26.46)	1277 (39.41)	496 (16.60)	332 (11.92)
Adherence	*857 (74.85)*	*606 (73.54)*	*871 (75.35)*	*337 (74.56)*	*244 (76.25)*
Low Benefit	452 (11.31)	435 (12.32)	311 (9.60)	240 (8.03)	45 (1.62)
Adherence	*303 (72.32)*	*308 (74.04)*	*225 (75.76)*	*175 (76.42)*	*34 (79.07)*
P-value	*0.565*	***0.023****	*0.213*	*0.239*	*0.493*

Table 3.3. Characteristics at Time 1 of individuals who remained in the trial for at least five time points compared with those who ever dropped out before Time 5. Includes between group significance using ANOVA and chi-square analyses.

Time 1	**Time 5**		
	Ever Dropped out	**Stayed**	**P-value**
N, %	1211 (30.31)	2785 (69.69)	
Age (M, SD)	38.51 (12.95)	40.95 (12.71)	**<0.001**
Female - no./total no. (%)	628/1104 (56.88)	1578/2710 (58.23)	0.446
Race - no./total no. (%)			**0.009**
White	950/1066 (89.12)	1775/1942 (91.40)	
African American	81/1066 (7.60)	95/1942 (4.89)	
Other	35/1066 (3.28)	72/1942 (3.71)	
Education - no./total no. (%)			**<0.001**
Less than High School	52/1079 (4.82)	61/2613 (2.33)	
High School/GED	173/1079 (16.03)	380/2613 (14.54)	
Some College	443/1079 (41.06)	955/2613 (36.55)	
Bachelor's Degree	258/1079 (23.91)	721/2613 (27.59)	
Graduate Degree	153/1079 (14.18)	496/2613 (18.98)	
Marital Status - no./total no. (%)			**<0.001**
Currently Married	340/1089 (31.22)	1041/2691 (38.68)	
Previously Married	304/1089 (27.92)	650/2691 (24.15)	
Never Married	426/1089 (39.12)	959/2691 (35.64)	
Widowed	19/1089 (1.74)	41/2691 (1.52)	
Lives Alone - no./total no. (%)	283/1086 (26.06)	725/2689 (26.96)	0.570
Income - no./total no. (%)			**<0.001**
<$50,000	666/999 (66.67)	1442/2485 (58.03)	
>=$50,000	333/999 (33.33)	1043/2485 (41.97)	
SSDI - no./total no. (%)	143/1061 (13.48)	411/2581 (15.92)	0.062
Welfare - no./total no. (%)	25/1061 (2.36)	42/2581 (1.63)	0.137
Employment Status - no./total no. (%)			**0.009**
Employed	476/1079 (44.11)	1271/2675 (47.51)	
Unemployed	291/1079 (26.97)	583/2675 (21.79)	
Disabled	181/1079 (16.77)	484/2675 (18.09)	
Other	131/1079 (12.14)	337/2675 (12.60)	
Residence - no./total no. (%)			**0.041**
Private Home	1022/1083 (94.37)	2521/2622 (96.15)	
Group Home	17/1083 (1.57)	23/2622 (0.88)	
Other	44/1083 (4.06)	78/2622 (2.97)	
Adherence - no./total no. (%)	546/768 (71.09)	1922/2514 (76.45)	**0.003**
Pathway - no./total no. (%)			**<0.001**
Standard Care	871/881 (98.86)	2547/2732 (93.23)	
Randomized Care	10/881 (1.14)	185/2732 (6.77)	
Medication Regimens - no./total no. (%)			**<0.001**
Monotherapy	203/1211 (16.76)	428/2766 (15.47)	
Two Medications	234/1211 (19.32)	641/2766 (23.17)	
Three Medications	166/1211 (13.71)	594/2766 (21.48)	
Four Medications	106/1211 (8.75)	413/2766 (14.93)	
Five + Medications	502/1211 (41.45)	690/2766 (24.95)	

Classes - no./total no. (%)			**<0.001**
High Benefit	258/1211 (21.30)	486/2785 (17.45)	
Moderately High Benefit	316/1211 (26.09)	624/2785 (22.41)	
Moderate Benefit	84/1211 (6.94)	326/2785 (11.71)	
Moderately Low Benefit	471/1211 (38.89)	979/2785 (35.15)	
Low Benefit	82/1211 (6.77)	370/2785 (13.29)	

Table 3.4. a-d. Probabilities of transitions between latent classes of CNB for each pair of time points. Bold indicates highest probability of movement to subsequent class.

a.	**Time 2**				
Time 1	**High Benefit**	**Moderately High Benefit**	**Moderate Benefit**	**Moderately Low Benefit**	**Low Benefit**
High Benefit	0.087	0.000	**0.788**	0.084	0.041
Moderately High Benefit	**0.849**	0.000	0.108	0.000	0.043
Moderate Benefit	0.005	**0.805**	0.016	0.062	0.112
Moderately Low Benefit	0.009	0.027	0.206	**0.721**	0.038
Low Benefit	0.064	0.086	0.025	0.049	**0.776**

b.	**Time 3**				
Time 2					
High Benefit	**0.932**	0.025	0.003	0.040	0.000
Moderately High Benefit	0.000	0.100	**0.812**	0.000	0.087
Moderate Benefit	0.058	0.026	0.001	**0.849**	0.066
Moderately Low Benefit	0.000	0.015	0.036	0.093	**0.855**
Low Benefit	0.080	**0.840**	0.017	0.000	0.062

c.	**Time 4**				
Time 3					
High Benefit	0.007	**0.894**	0.088	0.000	0.012
Moderately High Benefit	0.003	0.033	0.044	0.050	**0.871**
Moderate Benefit	0.079	0.000	0.000	**0.880**	0.041
Moderately Low Benefit	0.039	0.113	**0.835**	0.000	0.014
Low Benefit	**0.850**	0.000	0.100	0.025	0.025

d.	**Time 5**				
Time 4					
High Benefit	0.026	0.006	0.003	**0.957**	0.008
Moderately High Benefit	0.000	0.038	0.038	0.000	**0.924**
Moderate Benefit	0.000	**0.918**	0.019	0.063	0.000
Moderately Low Benefit	**0.874**	0.000	0.078	0.048	0.000
Low Benefit	0.011	0.045	**0.863**	0.052	0.030

Table 3.5. Results from logistic regression analyses with class membership, medication regimens and medication regimen change predicting adherence at each time point.

Predicting Adherence at	**Time 1**	**Time 2**	**Time 3**	**Time 4**	**Time 5**
	(OR, 95% CI)	(OR, 95% CI)	(OR, 95% CI)	(OR, 95% CI)	(OR, 95% CI)
Class (ref=High Benefit Class)					
Moderately High Benefit	0.99 (0.74-1.31)	0.81 (0.61-1.09)	1.08 (0.77-1.52)	0.84 (0.65-1.09)	0.76 (0.59-0.97)*
Moderate Benefit	1.16 (0.83-1.64)	0.77 (0.54-1.12)	0.95 (0.68-1.32)	0.92 (0.65-1.31)	0.79 (0.57-1.10)
Moderately Low Benefit	0.91 (0.70-1.19)	**0.69 (0.51-0.93)***	0.80 (0.62-1.03)‡	0.79 (0.59-1.06)	0.77 (0.55-1.09)
Low Benefit	0.87 (0.63-1.21)	**0.71 (0.50-0.99)***	0.75 (0.52-1.08)	0.70 (0.48-1.01)‡	0.87 (0.37-2.05)
Medication Regimen (ref=1)					
Two Medications	0.86 (0.65-1.12)	**0.69 (0.51-0.91)****	**0.51 (0.37-0.71)****	0.94 (0.67-1.31)	**0.58 (0.40-0.85)****
Three Medications	**0.63 (0.48-0.82)****	**0.62 (0.46-0.83)****	**0.53 (0.38-0.74)****	**0.71 (0.50-0.99)***	**0.49 (0.34-0.72)****
Four Medications	**1.41 (1.01-1.96)***	**1.45 (1.01-2.09)***	1.24 (0.83-1.84)	**1.43 (0.97-2.11)‡**	1.17 (0.76-1.80)
Five + Medications	1.28 (0.93-1.75)	**1.60 (1.12-2.27)****	0.88 (0.61-1.27)	**1.44 (0.99-2.09)‡**	1.04 (0.69-1.57)
Regimen Change (ref=No)		0.86 (0.72-1.03)	0.95 (0.78-1.16)	1.07 (0.87-1.32)	0.84 (0.68-1.04)
Values are adjusted for care pathway, age, gender, education, marital status, income, SSDI, Welfare, Employment, Residence					

Table 3.6. Post-hoc analysis results: Odds of adherence predicted by medication regimens stratified by class for each time point.

Predicting Adherence at	**Time 1**	**Time 2**	**Time 3**	**Time 4**	**Time 5**
	(OR, 95% CI)	(OR, 95% CI)	(OR, 95% CI)	(OR, 95% CI)	(OR, 95% CI)
High Benefit					
Regimen (ref=Monotherapy)					
Two medications	0.70 (0.39-1.24)	**0.40 (0.20-0.81)***	**0.31 (0.16-0.59)****	0.91 (0.56-1.49)	**0.61 (0.34-1.08)‡**
Three medications	0.63 (0.33-1.23)	**0.36 (0.16-0.80)***	**0.35 (0.17-0.70)****	0.70 (0.42-1.17)	**0.46 (0.25-0.85)***
Four Medications	1.30 (0.55-3.10)	0.85 (0.32-2.28)	0.70 (0.29-1.67)	1.30 (0.68-2.48)	0.94 (0.44-2.01)
Five + Medications	1.05 (0.47-2.34)	1.37 (0.44-4.26)	1.68 (0.52-5.47)	1.15 (0.61-2.19)	0.71 (0.35-1.42)
Moderately High Benefit					
Regimen (ref=Monotherapy)					
Two medications	1.01 (0.58-1.77)	**0.56 (0.35-0.89)***	0.67 (0.25-1.81)	0.71 (0.36-1.41)	0.92 (0.50-1.67)
Three medications	0.76 (0.43-1.35)	0.70 (0.43-1.15)	0.51 (0.19-1.40)	0.80 (0.40-1.60)	0.76 (0.42-1.37)
Four Medications	1.37 (0.69-2.71)	1.41 (0.76-2.63)	0.78 (0.25-2.46)	1.28 (0.61-2.73)	**2.71 (1.31-5.62)****
Five + Medications	**2.30 (1.08-4.88)***	**2.47 (1.15-5.33)***	0.42 (0.14-1.26)	**2.09 (0.90-4.86)‡**	1.52 (0.77-3.00)
Moderate Benefit					
Regimen (ref=Monotherapy)					
Two medications	0.94 (0.36-2.47)	0.73 (0.23-2.28)	0.52 (0.17-1.55)	1.31 (0.33-5.27)	0.37 (0.10-1.32)
Three medications	0.87 (0.31-2.39)	0.39 (0.12-1.27)	0.51 (0.17-1.51)	0.65 (0.16-2.63)	0.64 (0.18-2.35)
Four Medications	1.44 (0.46-4.48)	2.33 (0.61-8.98)	0.90 (0.28-2.91)	2.23 (0.47-10.65)	0.82 (0.21-3.17)
Five + Medications	1.14 (0.41-3.14)	1.11 (0.33-3.74)	1.38 (0.45-4.27)	1.38 (0.36-5.30)	1.23 (0.32-4.65)
Moderately Low Benefit					
Regimen (ref=Monotherapy)					
Two medications	0.80 (0.50-1.27)	1.08 (0.61-1.91)	**0.55 (0.33-0.91)***	1.59 (0.62-4.12)	--
Three medications	**0.54 (0.34-0.85)****	0.84 (0.48-1.47)	**0.58 (0.34-0.98)***	0.78 (0.31-1.96)	--
Four Medications	**1.67 (0.94-2.94)‡**	**2.62 (1.28-5.35)****	**2.02 (1.06-3.84)***	**2.48 (0.87-7.06)‡**	--
Five + Medications	0.85 (0.49-1.46)	**1.98 (1.05-3.76)***	0.96 (0.54-1.70)	2.16 (0.80-5.86)	--
Low Benefit					
Regimen (ref=Monotherapy)					
Two medications	1.12 (0.42-2.99)	1.30 (0.45-3.77)	1.25 (0.30-5.09)	1.93 (0.25-15.23)	--
Three medications	0.61 (0.25-1.51)	0.77 (0.27-2.18)	2.23 (0.56-8.87)	1.09 (0.17-7.12)	--
Four Medications	1.43 (0.52-3.92)	1.34 (0.44-4.10)	**3.67 (0.88-15.39)‡**	2.71 (0.42-17.66)	--
Five + Medications	**2.35 (0.91-6.08)‡**	**2.60 (0.89-7.64)‡**	2.53 (0.70-9.10)	4.27 (0.69-26.40)	--

Values are adjusted for care pathway, age, gender, education, marital status, income, SSDI, Welfare, Employment, Residence
-- Sample size too small for analysis

Supplemental Table 3.1. Fit statistics for 4 and 5 class LCAs and 4 and 5 class LTA.

	AIC	BIC	BIC_N	BLRT	Entropy	Smallest Class (%)
Time 1						
4 classes	48234.41	48605.7	48418.23	408.883	0.728	11.7
5 classes	48156.63	48622.32	48387.18	107.781	0.646	12.3
Time 2						
4 classes	41246.95	41610.94	41423.47	305.253	0.689	12
5 classes	41180.28	41636.81	41401.68	96.668	0.611	12.4
Time 3						
4 classes	36059.46	36418.38	36230.91	323.342	0.676	11
5 classes	36044.69	36494.85	36259.72	44.776	0.602	10.6
Time 4						
4 classes	31421.84	31775.98	31588.51	288.119	0.65	11.5
5 classes	31376.04	31820.21	31585.09	75.799	0.593	8.2
Time 5						
4 classes	28224.47	28574.46	28387	172.43	0.598	11.6
5 classes	28175.8	28614.77	28379.64	78.677	0.624	1.7
LTA						
4 classes	175454.4	177537.5	176485.8	--	--	--
5 classes	174223.6	176954.9	175575.8	--	--	--

AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion; BIC_N: Sample-Size Adjusted BIC; BLRT: Bootstrapped Likelihood Ratio Test

Figure 3.1. Classes of CNB over the course of the study. From left to right, Time 1 (a), 2 (b), 3 (c), 4 (d) and 5 (e) at the bottom.

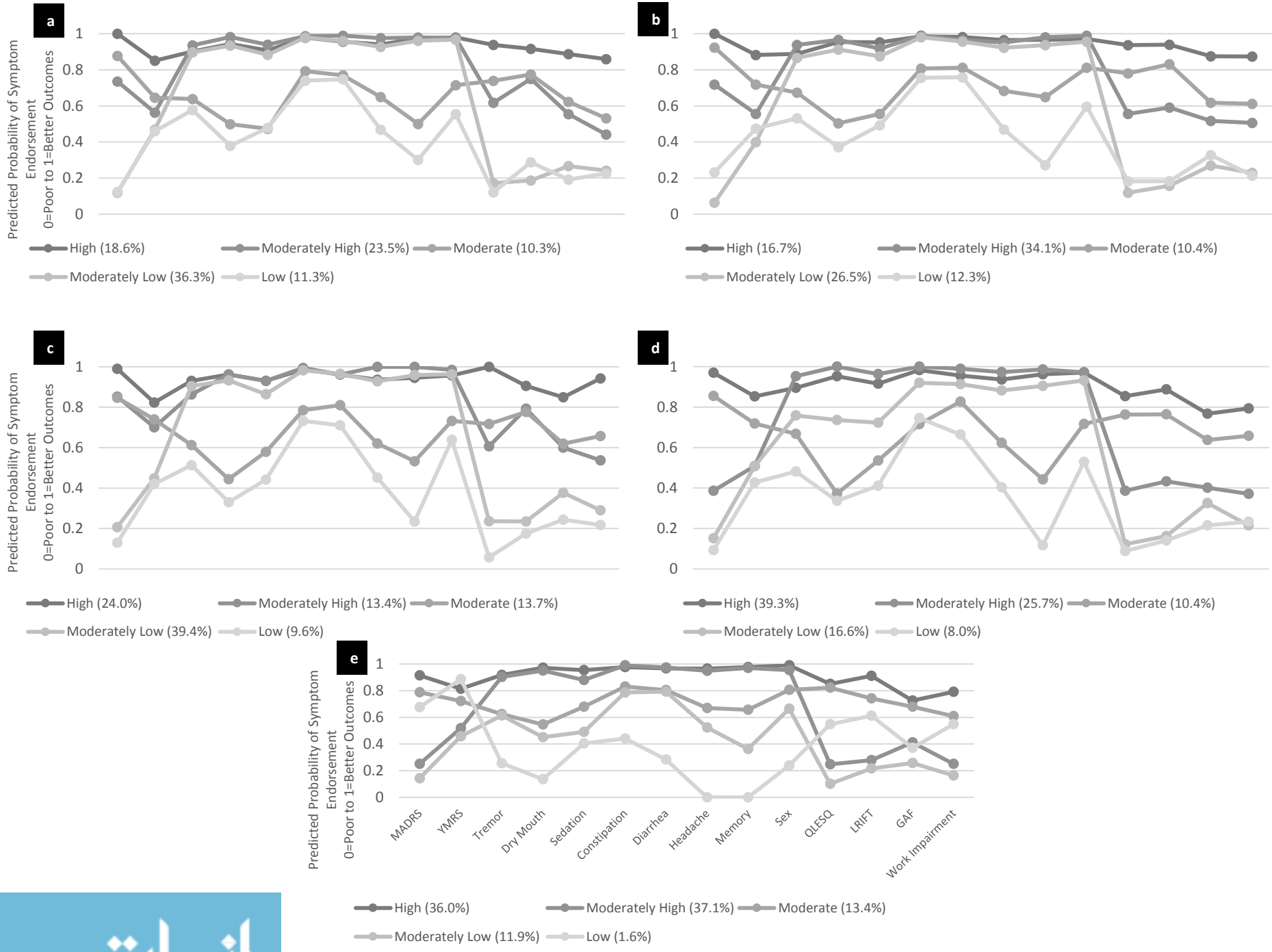
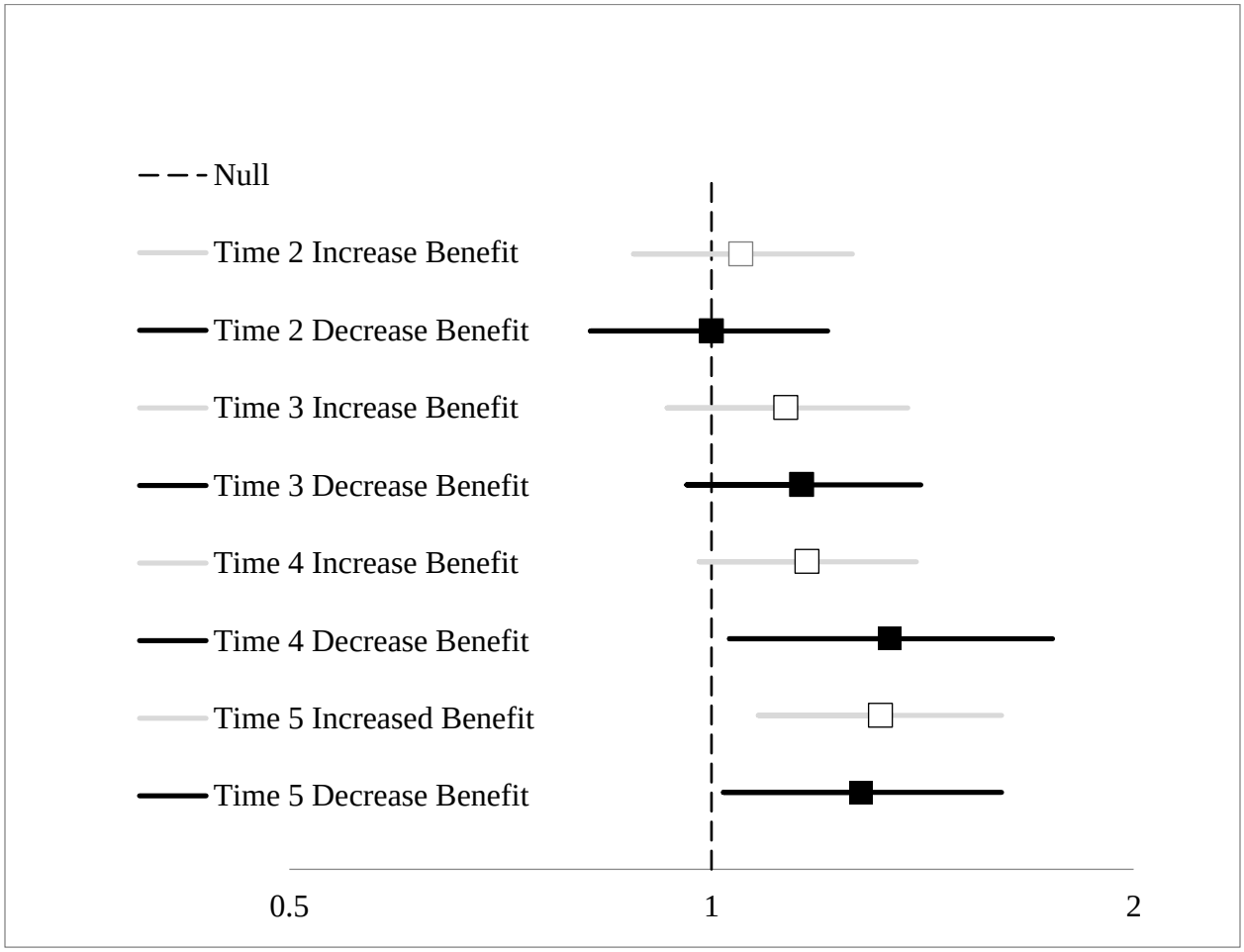
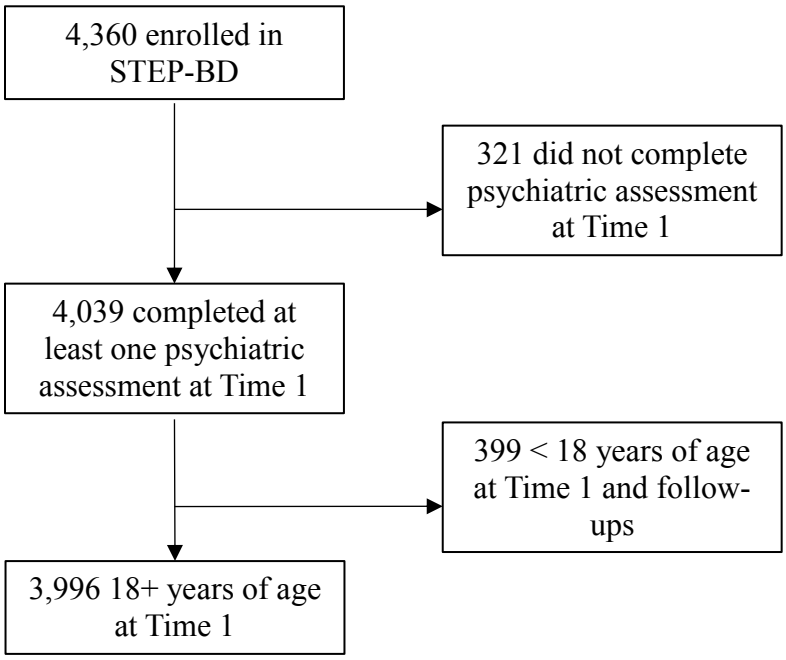


Figure 3.2. Medication regimen change and the subsequent odds of changing to an increased or decreased CNB class at each time point.



Supplemental Figure 3.1. Flowchart from original sample to current analytical sample.



CHAPTER 4

The Bi-directional Relationship between Clinical Net Benefit and Medication Adherence Long Term in Bipolar Disorder: A Latent Transition Analysis

ABSTRACT

Objectives: Treatment for bipolar disorder (BD) is chronic, yet medication adherence is poor. Research into the long-term efficacy of psychotropic medication treatment of BD largely focuses on remission or relapse rather than adherence. Long-term studies rarely follow individuals more than two years, which does not accurately represent treatment of BD that may extend 20 years. Using the empirically quantified latent construct of clinical net benefit (CNB) and a three-year naturalistic follow-up, or treatment as usual, of individuals with BD, we tested whether classes of CNB changed over time and were associated with adherence to the same extent as occurred during two years of the active participation.

Methods: Data come from the Systematic Treatment Enhancement Program for Bipolar Disorder's (STEP-BD) 3-year naturalistic follow up (Time 5 to 8) of participants aged 18+ years, following two years of active participation. Latent class analysis identified distinct groups based on the intersection of the three factors of CNB: psychiatric symptoms (i.e., decrease in episodes), adverse effects (e.g., sedation), and functioning (i.e., employment, quality of life). Transitions between classes across the four time points was determined using latent transition analysis. Adherence was defined as taking 75% or more of medications as prescribed. Polypharmacy was categorized as number of medications taken concurrently. Associations between CNB classes, medication regimens, changes in both over time, and adherence were tested using multiple logistic regression adjusting for sociodemographic characteristics.

Results: Four classes of CNB were identified at each time point: High, Moderate, Moderately low and Low. The lower benefit classes transitioned to higher benefit classes at each time point (e.g., probability of low benefit at Time 5 to moderate benefit at Time 6=0.93), while the higher benefit classes transitioned to lower benefit classes by Time 8 (e.g., probability of high benefit at

Time 7 to moderately low benefit at Time 8=0.79). Medication regimens were associated with both positive and negative changes in class (e.g., Time 7 taking 5+ medications predicted Time 8 higher class: OR=3.75; 95% CI: 1.07-13.17). Neither the CNB classes, nor transitioning between them were associated with adherence, and adherence did not differ across classes at each time point. Relative to monotherapy, taking less complex regimens (three or fewer) was associated with lower adherence across Time 5 to 7 (e.g., Time 5 taking two medications: OR=0.32; 95% CI: 0.14-0.74).

Conclusions: Individuals experiencing low CNB from their medications at Time 5 transitioned to higher CNB classes over time, while individuals receiving high benefit transitioned to the lower benefit classes by Time 8. This is consistent with our findings from the active participation phase of STEP-BD. However, class membership was not associated with adherence, and adherence was equivalent across classes and time points. This suggests that although CNB does represent experiences people are having during treatment, it does not explain why individuals adhere to their medications. Using CNB, individuals with low benefit from treatment can be identified by their clinicians and focus together on changing their treatment to increase their benefit, with high probability of success due to their adherence.

INTRODUCTION

Bipolar disorder (BD) only affects 4% of adults,[126] but is one of the leading causes of disability adjusted life years lost in the U.S.[12] The first line treatment for individuals experiencing onset or acute episodes of BD is psychotropic medication.[16] Due the chronic and cyclical nature of BD, medication adherence is not only necessary but must often be maintained indefinitely. However, medication adherence to treatment is a continuing problem for individuals with BD, ranging from 20-70% during long term treatment (i.e., greater than one year).[36, 37] Non-adherence is associated with increasing numbers and severity of episodes leading to increased health care costs, disability and mortality.[134, 135]

There are multiple factors believed to influence medication non-adherence for individuals with BD. One factor is adverse effects from medications (e.g., sedation, sexual dysfunction).[43, 44] However, the prevalence of adherence has remained relatively consistent even with the advent of newer generation medications (i.e., atypical antipsychotics, selective serotonin reuptake inhibitors, and antiepileptics) with fewer severe adverse effects, compared with older medications (i.e., monoamine oxidase inhibitors and typical antipsychotics).[43] Another factor concerns the complexity of medication regimens (taking more than one medication concurrently or polypharmacy). Baldessarini, et al. (2008), found that 40% of individuals with BD covered by a large commercial health care plan were prescribed polypharmacy (defined as two or more psychotropic medications concurrently) between the years of 2001 and 2005.[127] Finally, aspects of the illness itself ("feeling well", "missing highs") have also been identified as possibly associated with lower levels of adherence.[22] Specifically, individuals with BD indicate that non-adherence is related to their need to find balance between necessity of treatment versus concerns

about medications.[43] In sum, non-adherence has multiple, intersecting determinants, and novel methodological approaches are needed to examine this complex relationship.

While the imperative of clinical trials is to demonstrate the efficacy of medications, studies of "long term" use of medications used to treat BD (e.g., mood stabilizers or atypical antipsychotics) have an average length of 6 months to two years.[30, 136, 137] Additionally, non-adherence is generally not the primary end point of interest for these studies. Instead they focus on time to relapse/recurrence (i.e., rehospitalization rates, time to any mood episode, total number of relapses) or remission (i.e., first stabilized with active drug after mood episode, duration of neutral mood).[128, 136, 137] The studies that have identified non-adherence use multiple definitions of non-adherence (i.e., time to premature discontinuation for any clinical reason, treatment discontinuation), making comparisons difficult.[49]

Individuals with BD are often diagnosed in their early twenties,[15] and thus most individuals will be taking medications for many decades as they age.[14] Rather than evaluating efficacy for a relatively short period of time, to fully understand the outcomes of a typical treatment regimen for individuals with BD it is necessary to follow them for multiple years. The Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) trial was designed to fill this gap. STEP-BD followed participants for five years. The active participation phase occurred during the first two years, followed by a naturalistic follow-up for three years with treatment-as-usual to simulate experiences by individuals with BD being treated in the general population.[52]

In addition to medication efficacy, providers weigh the benefits versus risks of any medication they prescribe to individuals they treat. This follows the treatment guidelines for individuals with BD,[16] which identifies three overarching goals of treatment: psychiatric

symptom reduction, low levels of adverse effects, and improved functioning. As detailed in Chapter 2, we have created a novel model of these aspects of treatment for BD as three intersecting dimensions of a latent variable we call Clinical Net Benefit (CNB). Each of these dimensions work synergistically and reflect the heterogeneity in benefit (and harm) experienced by individuals undergoing treatment for BD.

From our previous analyses (Chapter 3), we identified that while a substantial proportion of STEP-BD participants attained a high level of CNB at some point during the trial, most individuals did not maintain this status consistently over time. We also identified that for individuals with low initial levels of CNB, those who maintained adherence to their medications experienced an increase in their CNB over time. However, our previous study only followed individuals during the active-trial component of STEP-BD, over approximately two years. To add to the knowledge gained in our previous work, we extended this to the naturalistic follow-up during the final three years of STEP-BD. The overarching aims for this study are to determine if, during the naturalistic follow-up of STEP-BD, (1) membership in classes of CNB change over time, (2) the CNB classes are associated with adherence over time, and (3) the complexity of the medication regimens are associated with adherence over time.

METHODS

Sample

Data come from the STEP-BD study. Eligibility criteria for STEP-BD included diagnoses of bipolar spectrum disorders (meeting DSM-IV criteria for Bipolar I Disorder, Bipolar II Disorder, Bipolar Not Otherwise Specified, Cyclothymic Disorder, or Schizoaffective Disorder Bipolar Subtype), receiving outpatient treatment for BD at a STEP-BD treatment center at the time of study entrance, participants' ability to meet with their clinicians as scheduled for the study and their ability to complete all study registration forms within three months of registration. STEP-BD was a 5-year RCT designed to simulate the "real world" experiences of treatment for individuals with BD. The first two years of study participation included active monitoring and regular meetings occurring approximately every three months. The last three years of the study were designed to be a naturalistic follow up, with at least one appointment per year during those subsequent years. Eligible participants could choose to enter either the Randomized Care Pathways (RCPs) where participants were randomly assignment to specific medications (i.e., mood stabilizers, antipsychotics, antidepressants or placebos) or Standardized Care Pathways (SCPs; i.e., treatment as usual). If initial regimens were ineffective, participants moved on to subsequent medications, either randomized or determined by their treating physicians, until an effective regimen was reached. Participants underwent a battery of clinician- and self-administered psychological assessments at each scheduled meeting that included the Clinical Monitoring Form (CMF). In addition to tracking psychiatric symptoms and functioning, this form also included clinicians' indications of participants' medication adherence.[62] Additional details of the original study design are described elsewhere.[52]

This study used data from the naturalistic follow up, starting with the final active participation assessment and three follow ups during the last three years. STEP-BD enrolled 4,360 participants that met eligibility criteria for the study. This analysis excluded 1,555 participants with less than five STEP-BD assessments, and missing data on all the components of CNB, the main exposure for this analysis. In addition, 1,234 participants were excluded because they were less than 18 years of age at all time points. The final analytic sample size was 1,571 (Supplemental Figure 4.1.). For those with incomplete data on some variables, missing values were imputed using Full Information Maximum Likelihood Estimation.[92]

Measures

Clinical Net Benefit

As detailed in Chapter 2, CNB incorporates three main effects of treatment on the individual: (1) psychiatric symptoms; (2) adverse effects; and (3) overall functioning. CNB can be conceptualized as a 3-dimensional construct lying at the intersection of these axes. Individuals differentially experience these components of treatment and our prior work used latent class analysis to empirically define and quantitatively measure these three dimensions of CNB using baseline data from the STEP-BD.[129]

The *psychiatric symptoms* dimension consisted of the Montgomery-Asberg Depression Rating Scale (MADRS)[71] and the Young Mania Rating Scale (YMRS).[70] The *adverse effects* dimension included the measures of memory difficulties, dry mouth, sexual dysfunction, headache, constipation, sedation, diarrhea, and tremor from the CMF.[62] Finally, the *overall functioning* dimension included the LIFE Range of Impaired Functioning Tool (LRIFT)[73] three indicators from the Work Impact Form (WIF) and past week Global Assessment of Functioning (GAF)[79] score. However, due to the small sample size of the Quality of Life Enjoyment and

Satisfaction Questionnaire (QLESQ)[72] relative to the other measures by the eighth time point, we removed this assessment from the *overall functioning* dimension.

Medication

Psychotropic medications were listed by name (either generic or brand) on the CMF and were recorded at each of the assessments. All medications were identified and grouped into six families: (1) antidepressants, (2) mood stabilizers, (3) antipsychotics, (4) sedatives/hypnotics, (5) stimulants, and (6) other using the U.S. Food & Drug Administration's National Drug Code Directory. [121] Next, a medication count variable was created indicating whether a participant was taking one (monotherapy), two, three, four or five or more medications (polypharmacy).

Adherence

The CMF was completed by the study psychiatrist at each assessment. The CMF recorded both the milligrams prescribed as well as milligrams missed for each medication a participant was taking in the past seven days.[62] We calculated adherence by first identifying whether participants were taking each of their medications as prescribed. Then they were defined as adherent if less than 25% of their regimens were not taken as prescribed. For example, if an individual was prescribed four medications in his/her regimen, if s/he was fully adherent to four of the five medications then she would be defined as adherent. Participants who missed more than 25% of the milligrams prescribed for one or more of the medications in their regimens were defined as non-adherent. Adherence defined as missing less than 25% of an individual's regimen is consistent with definitions used in STEP-BD studies.[83]

Demographic Characteristics

Demographic characteristics included age (in years); gender; race (White, Black, and Other); educational attainment (≤high school, high school diploma or GED, some college, Bachelor's degree, and Graduate or professional degree); current marital status (married or living as though married, divorced or separated, never married, or widowed); whether participants lived alone; primary residence (private home, group home or something else); income (greater or less than $50,000); whether participants received Social Security Disability Insurance (SSDI) and welfare; and employment status (employed, unemployed, disabled or retired/not in the labor force).

Standardized Care or Randomized Care Pathways

Individuals could choose to enter the SCPs or RCPs if they met inclusion criteria. As we previously found in Chapters 2 and 3, individuals who chose these different pathways were characteristically different. Therefore, we combined all of the RCPs into one category and all of the SCPs into a second category and indicated membership in either of these categories across the classes and time points.

Analytic Approach

Analyses were similar to those conducted in Chapter 3 and took place in two steps. First, latent class analyses (LCAs) were conducted, one for each time point, to determine the number of classes that best fit the sample at each time point and the predicted probabilities of participant membership in each class. Second, a Latent Transition Analysis (LTA) was conducted to confirm fit for the number of classes at each time point, and to identify participants' movement between classes across adjacent time points.

Latent Class Analysis

We used the same process to create the binary indicators of CNB for the LCAs as detailed in Chapter 2. LCA is an empirical method to determine the number of subgroups, or classes, of a latent variable (i.e., CNB) that exist in a sample of participants. The LCA also assigns individuals' membership in these classes according to their posterior probabilities of symptom endorsement for each of the measures.[97] To determine the number of classes that best fit the model at each time point, we compared the Akaike Information Criterion (AIC), Bayesian Information Criterion (BIC), Sample-Size Adjusted BIC (BIC_N), Bootstrapped Likelihood Ratio Test (BLRT) and Entropy;[100] for each of these indices smaller values, and Entropy values closest to 1, indicate better relative fit. Measures of model fit, prevalence of class membership and model interpretability were all used to determine the final number of classes for each time point.[97, 125]

Latent Transition Analysis

Following the methods described in Chapter 3, we conducted the LTA to determine whether individuals in one latent class at each time point transition to the same class or another latent class at a subsequent time point. Primary outcomes of an LTA are transition probabilities, akin to posterior probabilities of the LCAs. These transition probabilities quantify the likelihood of moving from one class to another class across time points.[99] The time span for this analysis is over a 3-year period, covering visits 5 through 8 which occurred approximately 6-12 months apart.[52] LTA quantified three aspects of CNB change over time: (1) confirmation of the best fitting number of latent classes, (2) the change in values of the measured indicators for each class, and (3) the probability of participant class membership change at each time point. Confirmation of the number of classes found in the LCAs that best fit the sample, taking

transition between classes into account, was determined via the LTA using the AIC, BIC, and BIC_N. We allowed for changes in values in each of the measured indicators at each time point by not imposing parameter restrictions to hold the item-response probabilities equal across each time point,[99, 102] as detailed in Chapter 3.

Characterizing the latent classes of CNB

The demographic characteristics, adherence to medication regimens, types of medication regimens (i.e., monotherapy versus polypharmacy), and whether participants were in the SCPs or RCPs of the latent classes of CNB at Time 5 were compared using ANOVA for continuous measures and Chi-square analyses for categorical measures.

Predictors of Adherence

To determine predictors of adherence, multiple logistic regression analyses, adjusted for demographic characteristics, were conducted at each of the four time points. The primary predictors of adherence were: (1) CNB class membership at each time point from the LCAs, and (2) the number of medications in participants' regimens at each time point. Additional predictors were: (3) change in CNB class membership from the previous time point, and (4) changes in medication regimens from the prior time point.

Descriptive statistics and regressions were calculated using SAS version 9.4 (SAS Institute Inc.). LCA and LTA were conducted using Mplus version 7.[91]

RESULTS

Table 4.1. describes the characteristics of the analytic sample at Time 5 of STEP-BD, the end of active study participation. The mean age of participants was 43 years, 58% were female, and 94% were non-Hispanic white. The majority had an income less than $50,000 (56%), 17% had income from SSDI, and 19% were unemployed. Most participants lived with at least one other person (74%), and less than 1% lived in group homes (0.88%). Three out of ten participants took five or more medications. Over three quarters of participants were adherent to their medication regimen at Time 5 (78%).

Fitting the Latent Class Analysis for Clinical Net Benefit

Model fit statistics indicated that the four-class models of CNB had better fit than the five-class models across Times 6-8, although fit was comparable between the four- and five-class models at Time 5 (Supplemental Table 4.1.). Additionally, the smallest class prevalence at Times 5-7 were larger for the four-class model than the five-class model (9.3% versus 2.3% at Time 5; 10.6% versus 6% at Time 6; and 9.4% versus 6.4% at Time 7). Class prevalence at Time 8 was the same for both the four- and five-class models (4.2%). However, the best fitting model when confirmed via the LTA, was the five-class model at each time point with an AIC, BIC, BIC_N greater than the four-class model (Supplementary Table 4.1.). Due to better interpretability of the four-class model because of higher class prevalence, and the utility of keeping the number of classes the same at each time point in the LTA to more easily identify class membership change, we decided to use the four-class model for the LTA.

Characteristics of the Classes of Clinical Net Benefit

Characteristics for the four-class model of CNB are shown in Figure 4.1. In following with our nomenclature from Chapters 2 and 3, the four classes of CNB were: (1) *high benefit*

(characterized by low psychiatric symptoms, low adverse effects, and high functioning); (2) *moderate benefit* (characterized by moderate psychiatric symptoms, moderate adverse effects and moderate functioning); (3) *moderately low benefit* (characterized by high psychiatric symptoms, low adverse effects and low functioning); and (4) *low benefit* (characterized by high psychiatric symptoms, moderate adverse effects, and low functioning). Finally, participation in the SCPs versus the RCPs differed across CNB classes at Time 5. As we found in Chapter 3, individuals deriving the most benefit from their current medication regimens would choose to stay with their current treatment, over 90% of those in the *high benefit* class elected to remain in the SCPs; in contrast, 18% of the *moderately low benefit* class elected to enter an RCP.

Table 4.2. describes the CNB class prevalence and medication adherence for each CNB class across the four time points as well as the differences in adherence across classes at each time point. This table illustrates two key points: First, the *high benefit* class grew in size over the 3-year naturalistic follow up, going from 35% to almost half (49%) of participants. These findings are consistent with the trajectories seen in Chapter 3, and are expected even during this naturalistic follow up because clinicians and participants were continuing to make treatment changes to improve the outcomes if participants did not appear to be benefiting from their medications. Second, we also see that the *low benefit* class is greatly reduced by Time 8, which suggests that individuals who are deriving less benefit from their medications may be modifying their regimens and seeing increased benefit from their regimens. This may also indicate that individuals who are not deriving benefit are dropping out of the trial, since only 33% remained in the trial from Time 5 through Time 8. However, there were no differences between the group that dropped out and those who remained except for their pathway membership at Time 5 (Table 4.3.). Although overall adherence remained high across all time points and classes (between 75%

and 85%), we did see a great reduction in adherence in the *low benefit* class, ranging from 80% at Time 5 to 53% at Time 8. This corresponded with a great reduction in membership in this class, with only 10 people in this class at Time 8, supporting the notion that people who do not adhere do not derive benefit from their medications and thus remain in the *low benefit* class.

Clinical Net Benefit, Medication Regimens, and Medication Adherence at Baseline

On average, participants were taking 3.4 (range 1 – 8) medications at Time 5. Medication adherence did not differ across the classes (χ^2=2.35, p=0.50) at Time 5, ranging between 76% and 80%. However, medication regimens did differ between classes (χ^2=111.37, p<0.001). In the *high benefit* class 52% were taking three or fewer medications. In contrast, in the *low benefit* class over 50% were taking five or more medications.

Latent Transition Analysis: Changes in Clinical Net Benefit over Time

Characteristics of the different measured indicators of CNB are in Figure 4.1. In general, scores for the three dimensions of CNB remained consistent across time, with the greatest variability seen in the adverse effects dimension and to a lesser degree in the overall functioning dimension. The values on the three dimensions remained relatively stable for the *high benefit*, the *moderately low benefit* and the *low benefit* classes. The *low benefit* class saw an increase in adverse effects over time, while the other two dimensions remained relatively consistent. The *moderate benefit* class saw the greatest change, with decreased adverse effects and decreased psychiatric symptoms by Time 8.

Latent Transition Analysis: Movement between Classes of Clinical Net Benefit over Time

Table 4.4. illustrates the latent transition probabilities of moving between classes at each consecutive time point. Each column and each row sum to a probability of 1.0. Overall, at each time point individuals in the *low benefit* class had a high probability of moving to the *moderate*

benefit class, and by Time 8 those in the *moderately low benefit* class had a high probability of moving to the *high benefit* class. By Time 8, individuals in both of the higher benefit classes had a high probability of moving to the lower benefit classes.

Between Times 5 and 6 participants in the *moderate* and *moderately low benefit* classes had high probabilities of moving to lower benefit classes; 90% from the *moderate* to *moderately low*, and 92% from the *moderately low* to *low benefit* classes. However, participants in the *low benefit* class had a high probability (93%) of moving to the *moderate benefit* class. Those in the *high benefit* class had a 91% probability of staying in that class.

Between Time 6 and Time 7, movement of the *high* and *low benefit* classes were the same as the previous time point; 91% of those in the *high benefit* class stayed in that class and 92% of those in the *low benefit* class moved to the *moderate benefit* class. Those in the *moderate benefit* class at Time 6 again had a high probability of moving to a lower benefit class; however, the probability of remaining in the *moderately low benefit* class was 87%.

Finally, between Times 7 and 8, members of the *low benefit* and the *moderately low benefit* class had a high probability of moving to a higher benefit class; 87% moving from the *moderately low* to the *high benefit* class and 97% moving from *low* to *moderate benefit* class. Both the *high* and *moderate benefit* classes had high probabilities of moving to lower benefit classes.

Changes in Clinical Net Benefit, Medication Regimens, and Medication Adherence

Table 4.5. shows the relative odds of adherence across the four CNB classes over time. In general, class membership was not associated with adherence, with the exception of the *low benefit* class at Time 7 which had lower odds of adherence when compared to the *high benefit* class (OR=0.32; 95% CI: 0.15-0.68). Also, changing to a lower benefit class from Time 6 to

Time 7 was also associated with lower adherence (OR=0.49; 95% CI: 0.26-0.91). At Time 5, 6 and 7 taking 2 or 3 medications was associated with lower adherence compared with monotherapy. However, regimen change was only significantly associated with lower adherence at Time 7 (OR=0.64; 95% CI: 0.44-0.93).

Post-hoc analysis

The probabilities of movement between the classes was not explained by changing medication regimens. However, medication regimens were significantly different between the classes at Time 5; participants in the *low benefit* class were the most likely to be taking complex polypharmacy (five or more medications). Additionally, less complex medication regimens were associated with lower adherence. Therefore, to further explore the drivers associated with transitions between classes, we conducted a post hoc analysis testing whether medication regimens taken at each time point were associated with moving to a higher or lower benefit class at a subsequent time point. This post hoc analysis revealed that at Time 5 having a regimen of three medications and at Time 6 of five or more medications was associated with changes to a subsequently lower benefit class. However, at Time 7, having a medication regimen of 4 or more medications was associated with movement to a higher benefit class at Time 8 (Table 4.6.).

DISCUSSION

The primary finding from this study is that there is heterogeneity in CNB change over time during this three-year naturalistic follow-up of STEP-BD participants. The number of individuals in the *high benefit* class increased at each time point, and the prevalence of the *low benefit* class declined substantially over time. In many ways this was expected, since the goal of a treatment is to modify medication regimens if symptoms are not improving or adverse effects are not tolerable over time. However, we also observed that at the conclusion of follow-up individuals in the two highest benefit classes had moved to lower benefit classes, with the *moderate benefit* class moving to lower benefit classes at each time point. This suggests that even when a person achieves high benefit from their medical treatment, this benefit can decline over time.[41] Finally, number of medications taken concurrently (i.e., polypharmacy) explained some of the transition between classes, with more complex regimens (3 or more medications) predicting change to either a higher or lower benefit class.

In general, changes in CNB classes were not associated with adherence during this phase of the study, contrary to our primary hypothesis. These results parallel our prior findings in that individuals with less CNB have the same level of adherence as individuals with high CNB (Chapter 2 and 3). Lower numbers of medications taken concurrently (two or three medications) were associated with lower adherence relative to monotherapy at Times 5, 6 and 7. However, changes in medication regimen (i.e., adding a medication, removing a medication or changing from one medication to another) was not associated with adherence.

These findings suggest that this metric of CNB, while informed by guidelines for treatment of BD, do not directly drive individual differences in adherence. While this may be seen as a weakness of the CNB concept, there is good external validity of the CNB construct

(described in detail in Chapter 2); for example, individuals in the *low benefit* class have the highest prevalence of Social Security Disability Insurance (SSDI; 22%), lowest prevalence of employment (32%), and lowest prevalence of a Bachelor's or graduate degree (40%). This suggests that individual level factors we were unable to assess in this study, such as individuals' attitudes and perspectives toward treatment,[43, 112] social support of family and friends,[47] psychotherapy support,[45] and patient-clinician relationship,[47] may have more direct impact on medication adherence for individuals with BD, as has been suggested in other work.

Strengths and Limitations

Strengths of this study include not only the use of a randomized clinical trial, but also the length of time people were followed during this trial. Individuals were followed for close to the three years during the naturalistic follow-up. The wealth of objective information from the psychological assessments helped us create a robust model of CNB. In addition, information on medication prescriptions and adherence were recorded by clinicians using standardized assessments. Unlike more traditional randomized clinical trials, the inclusion criteria were very broad (bipolar spectrum disorders, any comorbidities, any age over 15), with numerous sites across the U.S., leading to greater generalizability of the results. Using LCA to identify classes of CNB experienced by participants in the trial and LTA to quantify the likelihood of changing to different classes of benefit over time, helped us rely on empirical results rather than theoretical conceptualizations.

However, there were limitations to this study that cannot be overlooked. The greatest limitation is the high levels of participant drop out. By the end of this analysis only 500 participants remained, from an initial sample at Time 5 of almost 1,600. Although this is not uncommon for clinical trials,[131, 132] this is poor when compared with observational cohort studies

such as the Health and Retirement Study (N=20,000, response rate=85% to 95%).[138] However, according to the most cited guidelines 500 participants gave us enough power to complete the LCAs and LTA analyses which require a minimum sample size of 200.[103] In addition, those who remained in the study from Time 5 to Time 8 did not differ when compared to those who dropped out of the study, therefore the findings for this cohort are not strongly influenced by differential loss to follow-up. This level of dropout, and missing data from the QLESQ, restricted the measures we could use for the LCA. Finally, participants' perspectives of their medications were not analyzed in this study. We can only infer that they are receiving benefit or lack thereof, but do not know if they perceive they are subjectively doing "better", and whether they associate that with their treatment.

Conclusions

Our findings suggest more research into person-centered factors will likely shed light on aspects of adherence not easily measured through psychological assessments. Other studies have suggested additional factors such as personality, locus of control, perceptions of one's illness and treatment, and rapport between clinicians and individuals they treat may play a significant role in driving adherence.[47] This is most obvious in our findings that individuals who are experiencing low benefit from their medications are adherent to the same extent as individuals experiencing high benefit. Subjective reports from individuals achieving different levels of benefit from their medications would be a highly valuable next step. Further examination into the drivers of adherence in individuals who are not benefiting from their treatment will inform future treatment strategies improving the experiences of outcomes of these individuals.

Table 4.1. Demographic characteristics of the sample at Time 5 and by clinical net benefit class, at the end of active monitoring. Includes between group differences from ANOVA and chi-square analyses at P-values

	Full Sample	**High Benefit**	**Moderate Benefit**	**Moderately Low Benefit**	**Low Benefit**	**P value**
N (%)	1571	549 (34.95)	134 (8.53)	681 (43.35)	207 (13.18)	
Age (M, SD)	42.60 (12.29)	42.42 (13.06)	44.28 (12.93)	42.20 (11.92)	43.35 (10.84)	0.255
Female - no./total no. (%)	901/1556 (57.90)	315/544 (57.90)	77/132 (58.33)	378/676 (55.92)	131/204 (64.22)	0.218
Race - no./total no. (%)						0.143
White	871/928 (93.86)	265/288 (92.01)	65/70 (92.86)	430/449 (95.77)	111/121 (91.74)	
African American	31/928 (3.34)	12/288 (4.17)	1/70 (1.43)	13/449 (2.90)	5/121 (4.13)	
Other	26/928 (2.80)	11/288 (3.82)	4/70 (5.71)	6/449 (1.34)	5/121 (4.13)	
Education - no./total no. (%)						**0.002**
Less than High School	24/1481 (1.62)	7/519 (1.35)	2/120 (1.67)	10/646 (1.55)	5/196 (2.55)	
High School/GED	213/1481 (14.38)	59/519 (11.37)	15/120 (12.50)	105/646 (16.25)	34/196 (17.35)	
Some College	505/1481 (34.10)	156/519 (30.06)	33/120 (27.50)	237/646 (36.69)	79/196 (40.31)	
Bachelor's Degree	427/1481 (28.83)	164/519 (31.60)	40/120 (33.33)	180/646 (27.86)	43/196 (21.94)	
Graduate Degree	312/1481 (21.07)	133/519 (25.63)	30/120 (25.00)	114/646 (17.65)	35/196 (17.86)	
Marital Status - no./total no. (%)						**0.035**
Currently Married	643/1551 (41.46)	228/543 (41.99)	65/131 (49.62)	252/673 (37.44)	98/204 (48.04)	
Previously Married	377/1551 (24.31)	122/543 (22.47)	28/131 (21.37)	173/673 (25.71)	54/204 (26.47)	
Never Married	505/1551 (32.56)	181/543 (33.33)	36/131 (27.48)	239/673 (35.51)	49/204 (24.02)	
Widowed	26/1551 (1.68)	12/543 (2.21)	2/131 (1.53)	9/673 (1.34)	3/204 (1.47)	
Lives Alone - no./total no. (%)	407/1551 (26.24)	144/543 (26.52)	27/131 (20.61)	188/674 (27.89)	48/203 (23.65)	0.281
Income - no./total no. (%)						**<0.001**
<$50,000	808/1435 (56.31)	242/503 (48.11)	60/124 (48.39)	398/619 (64.30)	108/189 (57.14)	
$50,000 +	627/1435 (43.69)	261/503 (51.89)	64/124 (51.61)	221/619 (35.70)	81/189 (42.86)	
SSDI - no./total no. (%)	251/1465 (17.13)	49/508 (9.65)	18/120 (15.00)	140/641 (21.84)	44/196 (22.45)	**<0.001**
Welfare - no./total no. (%)	23/1465 (1.57)	1/508 (0.20)	2/120 (1.67)	14/641 (2.18)	6/196 (3.06)	**0.014**
Employment - no./total no. (%)						**<0.001**
Employed	754/1543 (48.87)	326/541 (60.26)	76/129 (58.91)	287/671 (42.77)	65/202 (32.18)	
Unemployed	293/1543 (18.99)	95/541 (17.56)	16/129 (12.40)	138/671 (20.57)	44/202 (21.78)	
Disabled	279/1543 (18.08)	38/541 (7.02)	20/129 (15.50)	156/671 (23.25)	65/202 (32.18)	
Other	217/1543 (14.06)	82/541 (15.16)	17/129 (13.18)	90/671 (13.41)	28/202 (13.86)	
Type of Residence - no./total no. (%)						0.0940
Private Home	1437/1485 (96.77)	501/519 (96.53)	116/121 (95.87)	630/649 (97.07)	190/196 (96.94)	
Group Home	13/1485 (0.88)	2/519 (0.39)	0	7/649 (1.08)	4/196 (2.04)	
Other	35/1485 (2.36)	16/519 (3.08)	5/121 (4.13)	12/649 (1.85)	2/196 (1.02)	
Adhere - no./total no. (%)	1115/1432 (77.86)	392/493 (79.51)	99/129 (76.74)	466/612 (76.14)	158/198 (79.80)	0.503

Medication Regimens - no./total no. (%)						**<0.001**
Monotherapy	137/1550 (8.84)	73/546 (13.37)	7/131 (5.34)	45/670 (34.35)	11/203 (5.42)	
Two Medications	338/1550 (21.81)	162/546 (29.67)	19/131 (14.50)	137/670 (20.45)	20/203 (9.85)	
Three Medications	331/1550 (21.35)	106/546 (19.41)	30/131 (22.90)	167/670 (24.93)	28/203 (13.79)	
Four Medications	280/1550 (18.06)	77/546 (14.10)	30/131 (22.90)	133/670 (19.85)	40/203 (19.70)	
Five + Medications	464/1550 (29.94)	128/546 (23.44)	45/131 (34.35)	187/670 (27.91)	104/203 (51.23)	
Pathway - no./total no. (%)						**<0.001**
Standardized Care	1299/1503 (86.43)	474/521 (90.98)	119/133 (89.47)	525/642 (81.78)	181/207 (87.44)	
Randomized Care	204/1503 (13.57)	47/521 (9.02)	14/133 (10.53)	117/642 (18.22)	26/207 (12.56)	

Table 4.2. Class prevalence and prevalence of adherence at each time point, with significance of differences in adherence across classes at each time point.

	Time 5	**Time 6**	**Time 7**	**Time 8**
N (%)	1571	1152	802	515
Class (N, %)				
High Benefit	549 (34.95)	483 (41.93)	366 (45.64)	253 (49.13)
Adherence	*392 (79.51)*	*351 (80.69)*	*274 (84.57)*	*173 (75.22)*
Moderate Benefit	134 (8.53)	104 (9.03)	64 (7.98)	88 (17.09)
Adherence	*99 (76.74)*	*79 (79.00)*	*50 (80.65)*	*66 (79.52)*
Moderately Low Benefit	681 (43.35)	448 (38.89)	248 (30.92)	153 (29.71)
Adherence	*466 (76.14)*	*320 (79.01)*	*185 (79.06)*	*109 (74.66)*
Low Benefit	207 (13.18)	117 (10.16)	124 (15.46)	21 (4.08)
Adherence	*158 (79.80)*	*94 (82.46)*	*81 (69.23)*	*10 (52.63)*
P-value	*0.503*	*0.833*	***0.005****	*0.113*

Table 4.3. Characteristics of individuals who remained in the trial for at least eight time points compared with those who ever dropped out after Time 5. Between group differences from ANOVA and chi-square analyses are indicated as P-values.

Time 5	**Time 8**		
	Dropped out	**Stayed**	**P-value**
N, %	1056 (67.22)	515 (32.78)	
Age (M, SD)	42.18 (12.42)	43.45 (11.98)	0.055
Female - no./total no. (%)	595/1044 (56.99)	306/512 (59.77)	0.298
Race - no./total no. (%)			0.839
White	550/585 (94.02)	321/343 (93.59)	
African American	20/585 (3.42)	11/343 (3.21)	
Other	15/585 (2.56)	11/343 (3.21)	
Education - no./total no. (%)			0.091
Less than High School	20/1022 (1.96)	4/459 (0.87)	
High School/GED	150/1022 (14.68)	63/459 (13.73)	
Some College	361/1022 (35.32)	144/459 (31.37)	
Bachelor's Degree	292/1022 (28.57)	135/459 (29.41)	
Graduate Degree	199/1022 (19.47)	113/459 (24.62)	
Marital Status - no./total no. (%)			0.794
Currently Married	432/1038 (41.62)	211/513 (41.13)	
Previously Married	252/1038 (24.28)	125/513 (24.37)	
Never Married	339/1038 (32.66)	166/513 (32.36)	
Widowed	15/1038 (1.45)	11/513 (2.14)	
Lives Alone - no./total no. (%)	280/1038 (26.97)	127/513 (24.76)	0.350
Income			0.496
<$50,000	546/959 (56.93)	262/476 (55.04)	
>=$50,000	413/959 (43.07)	214/476 (44.96)	
SSDI - no./total no. (%)	172/1010 (17.03)	79/455 (17.36)	0.876
Welfare - no./total no. (%)	18/1010 (1.78)	5/455 (1.10)	0.330
Employment Status - no./total no. (%)			0.129
Employed	503/1032 (48.74)	251/511 (49.12)	
Unemployed	210/1032 (20.35)	83/511 (16.24)	
Disabled	185/1032 (17.93)	94/511 (18.40)	
Other	134/1032 (12.98)	83/511 (16.24)	
Residence - no./total no. (%)			0.301
Private Home	988/1026 (96.30)	449/459 (97.82)	
Group Home	10/1026 (0.97)	3/459 (0.65)	
Other	28/1026 (2.73)	7/459 (1.53)	
Adherence - no./total no. (%)	736/958 (76.83)	379/474 (79.96)	0.179
Pathway - no./total no. (%)			**<0.001**
Standard Care	949/999 (94.99)	350/504 (69.44)	
Randomized Care	50/999 (5.01)	154/504 (30.56)	
Medication Regimens - no./total no. (%)			0.267
Monotherapy	102/1052 (9.70)	35/498 (7.03)	
Two Medications	221/1052 (21.01)	117/498 (23.49)	
Three Medications	219/1052 (20.82)	112/498 (22.49)	
Four Medications	186/1052 (17.68)	94/498 (18.88)	
Five + Medications	324/1052 (30.80)	140/498 (28.11)	

Classes - no./total no. (%)			0.148
High Benefit	381/1056 (36.08)	168/515 (32.62)	
Moderate Benefit	98/1056 (9.28)	36/515 (6.99)	
Moderately Low Benefit	443/1056 (41.95)	238/515 (46.21)	
Low Benefit	134/1056 (12.69)	73/515 (14.17)	

Table 4.4. a-c. Probabilities of latent transitions between classes of CNB for each pair of time points. Bold indicates highest probabilities of transitioning.

a.	**Time 6**			
Time 5	**High Benefit**	**Moderate Benefit**	**Moderately Low Benefit**	**Low Benefit**
High Benefit	**0.905**	0.000	0.000	0.095
Moderate Benefit	0.052	0.051	**0.897**	0.000
Moderately Low Benefit	0.005	0.079	0.000	**0.916**
Low Benefit	0.002	**0.928**	0.024	0.046

b.	**Time 7**			
Time 6				
High Benefit	**0.911**	0.062	0.000	0.027
Moderate Benefit	0.029	0.056	0.006	**0.908**
Moderately Low Benefit	0.067	0.005	**0.872**	0.056
Low Benefit	0.019	**0.918**	0.005	0.059

c.	**Time 8**			
Time 7				
High Benefit	0.173	0.023	**0.794**	0.009
Moderate Benefit	0.000	0.008	0.000	**0.992**
Moderately Low Benefit	**0.866**	0.134	0.000	0.000
Low Benefit	0.016	**0.966**	0.000	0.018

Table 4.5. Results of logistic regression analyses predicting adherence at each time point. Also shown is prediction of class change when medication regimens changed (either an increase or decrease in number of medications taken, or a change of medication).

Predicting Adherence at	**Time 5**	**Time 6**	**Time 7**	**Time 8**
	(OR, 95% CI)	(OR, 95% CI)	(OR, 95% CI)	(OR, 95% CI)
Class (ref=High Benefit Class)				
Moderate Benefit	0.63 (0.33-1.21)	0.67 (0.30-1.54)	0.63 (0.23-1.70)	1.41 (0.61-3.29)
Moderately Low Benefit	1.07 (0.70-1.66)	0.86 (0.52-1.43)	0.66 (0.34-1.28)	1.35 (0.71-2.58)
Low Benefit	1.22 (0.65-2.28)	1.14 (0.51-2.54)	**0.32 (0.15-0.68)****	0.51 (0.14-1.80)
Change in Class (ref=No)				
Higher Benefit	--	0.92 (0.53-1.57)	1.42 (0.64-3.16)	0.91 (0.49-1.71)
Lower Benefit	--	1.35 (0.67-2.74)	**0.49 (0.26-0.91)***	0.75 (0.32-1.75)
Medication Regimen (ref=1)				
Two Medications	**0.32 (0.14-0.74)****	**0.46 (0.20-1.04)‡**	0.84 (0.36-1.96)	0.68 (0.32-1.44)
Three Medications	**0.35 (0.15-0.81)***	0.54 (0.24-1.23)	**0.50 (0.22-1.12)‡**	0.55 (0.27-1.14)
Four Medications	1.20 (0.46-3.12)	0.90 (0.37-2.16)	0.95 (0.40-2.23)	1.64 (0.73-3.64)
Five + Medications	0.71 (0.30-1.71)	0.93 (0.39-2.17)	0.82 (0.36-1.86)	0.90 (0.43-1.87)
Regimen Change (ref=No)		1.08 (0.28-4.20)	**0.64 (0.44-0.93)***	0.87 (0.60-1.25)
Values are adjusted for care pathway, age, gender, race, education, marital status, income, SSDI, Welfare, Employment, Residence				

Table 4.6. Results of logistic regression predicting change to a higher or lower benefit class by prior time point medication regimen.

Prior Time Point Medication Regimen (ref=1)	**Time 6**		**Time 7**		**Time 8**	
	Higher	Lower	Higher	Lower	Higher	Lower
Two Medications	1.43 (0.51-3.99)	2.33 (0.48-11.38)	1.11 (0.34-3.62)	3.64 (0.42-31.50)	2.47 (0.66-9.33)	2.39 (0.41-14.05)
Three Medications	1.68 (0.61-4.63)	**3.82 (0.82-17.84)‡**	1.07 (0.34-3.43)	4.42 (0.52-37.28)	2.27 (0.63-8.21)	2.40 (0.43-13.35)
Four Medications	1.70 (0.61-4.78)	2.33 (0.47-11.52)	1.62 (0.50-5.21)	4.65 (0.54-40.29)	**3.52 (0.94-13.23)‡**	2.19 (0.36-13.30)
Five + Medications	1.79 (0.66-4.88)	2.30 (0.48-10.96)	0.93 (0.29-2.97)	**6.75 (0.81-56.20)‡**	**3.75 (1.07-13.17)***	2.70 (0.50-14.42)
Values are adjusted for care pathway, age, gender, race, education, marital status, income, SSDI, Welfare, Employment, Residence						

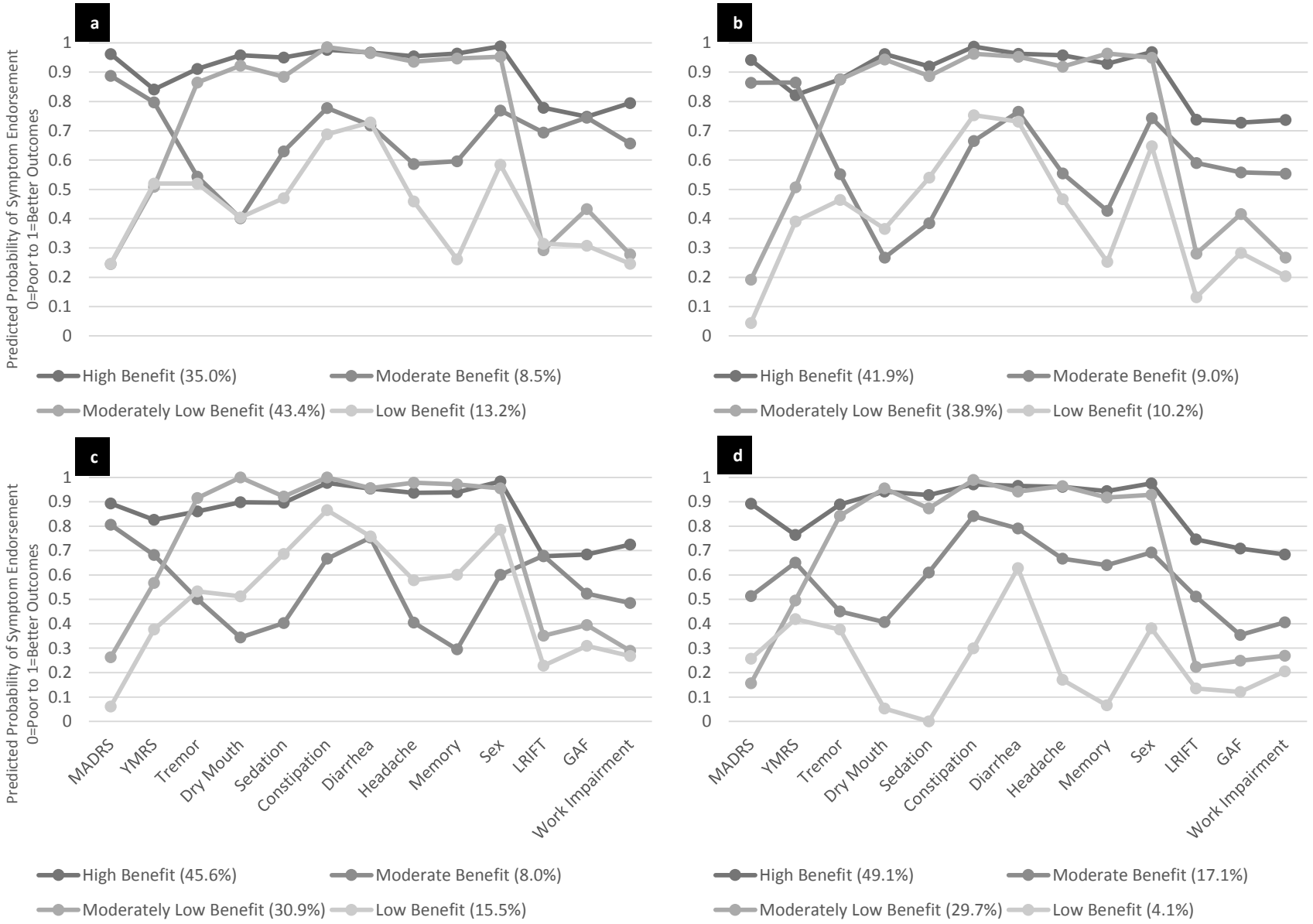
Supplemental Table 4.1. Fit statistics for 4 and 5 class LCAs at each time point, and 4 and 5 class LTA.

	AIC	BIC	BIC_N	BLRT	Entropy	Smallest Class (%)
Time 5						
4 classes	18108.410	18403.181	18228.458	69.889	0.700	9.30
5 classes	18073.861	18443.664	18224.466	62.550	0.703	2.30
Time 6						
4 classes	13312.03	13589.74	13415.04	90.728	0.733	10.60
5 classes	13303.97	13652.37	13433.21	36.058	0.699	6.00
Time 7						
4 classes	9369.76	9627.551	9452.895	49.037	0.661	9.40
5 classes	9355.647	9679.058	9459.944	42.113	0.682	6.40
Time 8						
4 classes	5915.012	6148.441	5973.861	42.817	0.719	4.20
5 classes	5919.633	6212.481	5993.463	23.379	0.729	4.20
LTA						
4 classes	44627.21	45951.00	45166.34	--	--	--
5 classes	44393.54	46130.01	45100.73	--	--	--

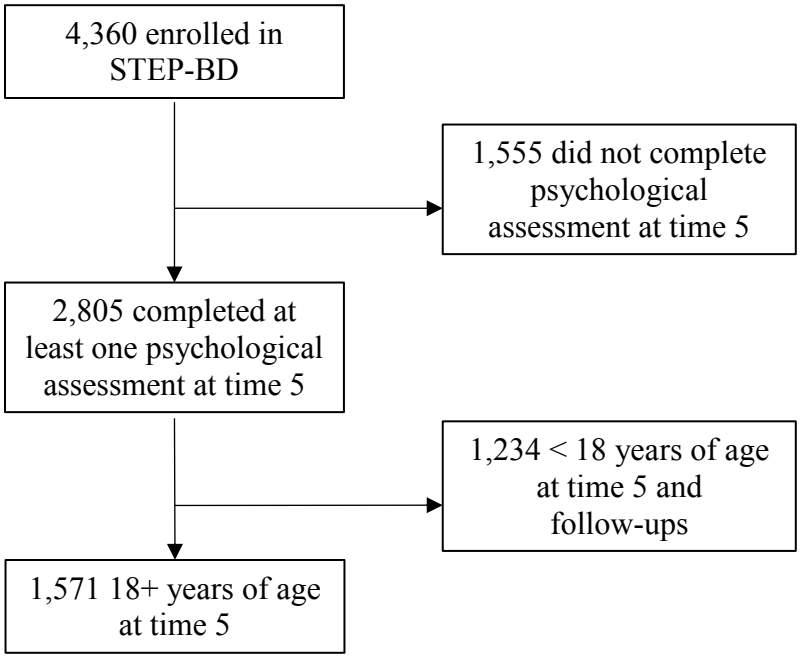
Supplemental Table 4.2. Families of medications making up different regimens taken by each class at Time 5.

	Antidepressant	Mood Stabilizer	Antipsychotic	Sedative/Hypnotic	Stimulant	Other
High Benefit						
Monotherapy (N=73)	9 (12.33)	55 (75.34)	4 (5.48)	--	--	5 (6.85)
Two Medications (N=162)	54 (16.67)	178 (54.94)	50 (15.43)	12 (3.70)	3 (0.93)	27 (8.33)
Three Medications (N=106)	62 (19.50)	139 (43.71)	39 (12.26)	24 (7.55)	6 (1.89)	48 (15.09)
Four Medications (N=77)	50 (16.13)	116 (37.42)	46 (14.84)	33 (10.65)	2 (0.65)	63 (20.32)
Five + Medications (N=98)	64 (13.06)	139 (28.37)	55 (11.22)	52 (10.61)	6 (1.22)	186 (34.13)
Moderate Benefit						
Monotherapy (N=7)	1 (14.29)	6 (85.71)	--	--	--	--
Two Medications (N=19)	8 (21.05)	22 (57.89)	2 (5.26)	1 (2.63)	--	5 (13.16)
Three Medications (N=30)	12 (13.33)	38 (42.22)	15 (16.67)	5 (5.56)	--	20 (22.22)
Four Medications (N=30)	22 (18.33)	44 (36.67)	8 (6.67)	12 (10.00)	1 (0.83)	33 (27.50)
Five + Medications (N=45)	24 (10.67)	67 (29.78)	24 (10.67)	22 (9.78)	2 (0.89)	86 (38.22)
Moderately Low Benefit						
Monotherapy (N=46)	2 (4.35)	30 (65.22)	11 (23.91)	1 (2.17)	--	2 (4.35)
Two Medications (N=137)	48 (17.52)	157 (57.30)	29 (10.58)	14 (5.11)	--	26 (9.49)
Three Medications (N=167)	101 (20.16)	211 (42.12)	81 (16.17)	46 (9.18)	6 (1.20)	56 (11.18)
Four Medications (N=133)	108 (20.30)	212 (39.85)	68 (12.78)	54 (10.15)	5 (0.94)	85 (15.98)
Five + Medications (N=146)	108 (14.79)	225 (30.82)	88 (12.05)	100 (13.70)	4 (0.55)	205 (28.08)
Low Benefit						
Monotherapy (N=11)	--	8 (72.73)	2 (18.18)	--	--	1 (9.09)
Two Medications (N=20)	12 (30.00)	20 (50.00)	2 (5.00)	5 (12.50)	--	1 (2.50)
Three Medications (N=28)	16 (19.05)	36 (42.86)	7 (8.33)	13 (15.48)	--	12 (14.29)
Four Medications (N=40)	30 (18.75)	59 (36.88)	16 (10.00)	21 (13.13)	--	34 (21.25)
Five + Medications (N=104)	87 (16.73)	175 (33.65)	68 (13.08)	67 (12.88)	3 (0.58)	120 (23.08)

Figure 4.1. a-d. CNB LCAs for Time 5 (a), Time 6 (b), Time 7 (c) and Time 8 (d).



Supplemental Figure 4.1. Flowchart from original sample to current analytical sample.



CHAPTER 5

Afterword

This chapter provides a brief overview of the results from each of the three empirical papers, discusses the clinical and public health implications of these findings, and provides guidance for next steps in research.

Chapter 2: Identifying clinical net benefit among individuals being treated for bipolar disorder

The objective of this first analysis was to create the Clinical Net Benefit (CNB) construct and determine its external validity using the baseline data from the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD). In this analysis we used baseline measures from STEP-BD to create a latent of the three dimensions of CNB: psychiatric symptoms, adverse effects and overall functioning. This latent construct of CNB was created using a two-step procedure. First, exploratory factor analysis (EFA) was used to reduce the number of measures in the CNB construct to only those necessary to define each of the three dimensions. Second, latent class analysis (LCA) was used to empirically identify distinct classes of CNB based on the clustering of responses on these three dimensions. This construct illustrated the heterogeneity in CNB experienced by individuals being treated for BD, with five classes (*high benefit* [N=889, 23.8%], *moderately high benefit* [N=961, 25.7%], *moderate benefit* [N=432, 11.6%], *moderately low benefit* [N=1010, 27.0%], and *low benefit* [N=446, 11.93%]) identified as the best fit to the data. These classes appeared externally valid in that individuals differed in terms of sociodemographic characteristics such as education (*high benefit* class: highest level of graduate degree (23.6%); highest employment (57.1%); *low benefit* class: highest SSDI (21.3%); highest unemployment (27.8%)). An unexpected finding was that the prevalence of medication adherence did not differ across the classes at baseline. This indicates that even

groups of individuals with low apparent CNB are just as likely to adhere to their medications as people with high apparent CNB.

Chapter 3: Change in clinical net benefit and short-term medication adherence

The objectives of this second analysis were to examine whether the classes of CNB changed over time, whether individuals transitioned between classes, and whether these changes affected adherence. In this analysis we used latent transition modeling to estimate change in CNB over the active treatment phase of STEP-BD (approximately two years). We found that transitioning between CNB classes was common, and that individuals in the lowest benefit classes moved to higher benefit classes as the trial progressed. However, by the end of the 2-year period individuals in the higher benefit classes were transitioning to lower benefit classes. We also found that as time passed, the higher benefit classes had lower odds of adherence when taking fewer medications concurrently when compared to monotherapy, and the lower benefit classes had higher odds of adherence when taking more medications concurrently when compared to monotherapy. An unexpected finding was that when compared to monotherapy, individuals taking 4 or more medications had higher odds of adherence than individuals taking three or fewer medications. Finally, as we saw in Chapter 2, the classes of CNB were similar in their adherence rates at each time point, contrary to our expectations.

Chapter 4: Change in clinical net benefit and long-term medication adherence

The objective of this third analysis was to determine whether our findings of CNB classes changing over time, and their association with adherence found in Chapter 3 held during the naturalistic follow-up in STEP-BD (approximately 3 years). This analysis showed that transitions between CNB classes were similar in the 3-year naturalistic follow-up period to those in the

active participation phase of the study. Individuals in the lower benefit classes transitioned to higher benefit classes by the conclusion of the study. As with the earlier chapters, classes of CNB were not associated with adherence in a systematic way. Medication regimens were associated with adherence in much the same manner as in Chapter 3, with individuals taking three or fewer medications concurrently having lower odds of adherence relative to monotherapy. Complexity of medication regimens predicted change to higher or lower benefit classes.

Implications and Limitations

Through the identification, creation, and testing of the CNB construct we have looked beyond the factors of psychiatric symptoms, adverse effects and overall functioning experienced by individuals with BD. By integrating these three concepts and applying that construct to a large sample of participants, we have identified individuals who adhere but are not benefitting from their treatment. We can postulate that these individuals may perceive they are currently benefitting from their treatment as compared to previous experiences before entering STEP-BD, which could be supporting their adherence. These individuals also may not be aware that there are newer medications with fewer side effects to which they could switch for their quality of life to increase.

If we want a more person-centered approach to treating individuals with BD that will lead to a higher quality of life, we need to identify and work with individuals such as these. They have a wealth of insight to provide clinicians as to why they adhere and what they perceive as benefits from their treatment. They can inform person-centered treatment that may lead to higher

levels of adherence and quality of life for a broader range of individuals. Increasing public health for individuals with BD can start by focusing on what we can learn from these individuals. These individuals were more likely to be taking 4 or more medications concurrently, which puts them at high risk for development of chronic conditions such as obesity and cardiovascular disease. With a focus on the health of these individuals and involving them in their care, we can test and enhance our understanding and use of person-centered care for individuals with BD.

Latent variable modeling is a flexible analytic approach to quantifying multiple aspects (i.e., psychiatric symptoms, adverse effects, and overall functioning) of the individual's experience while being treated for BD. The latent construct of CNB was informed by clinical guidelines and research on clinical impressions and patient insights to treatment. This construct highlights the substantial heterogeneity in CNB for this disorder. Using this novel construct, we identified a group of individuals who experienced low benefit from their treatment, but were adherent to the same extent as those with high benefit. This group that may have distinct clinical needs from others treated for BD, including the need for more attention to medication dosage or more rapid regimen changes to achieve a clinical response.

As has been suggested by clinicians treating individuals with BD, those who initially benefitted from their treatment experienced a decrease in CNB over time. This may be due in part to lower adherence when individuals in the high CNB class were taking fewer medications concurrently, as was found in Chapter 3, or changes in aspects of CNB itself, such as increases in adverse effects as can be seen in the lower benefit classes at each time point in Chapter 3 Figure 3.1. However, this decrease in CNB may also be due to decreased effectiveness of the treatment they are receiving (e.g., tachyphylaxis: developing tolerance to antidepressant medication, or narrow therapeutic indices that restrict continued titration of the medication to retain

effectiveness).[31, 139] This was suggested during the naturalistic follow up where adherence rates were the same across classes and time points, there was no association between medication regimen change and class change, yet individuals in the higher benefit classes moved to lower benefit classes by the end of this phase.

However, due to the longer time intervals between follow-up assessments during the naturalistic phase of the trial (i.e., assessments occurred every 12 months instead of every 3 months as during the active phase of the trial), our measure of adherence may have been less valid for this portion of the analysis. Participants were asked about their medication use for the *past week*, which likely overestimated the prevalence of adherence when the time between appointments was from six and twelve months.

The dropout rates during the active phase of the trial (Time 1 through 5) and the many differences between individuals who dropped out and individuals who remained also tempers the conclusions that can be made from our findings. Overall high dropout rates lead to bias toward the null. However, missingness was not at random. Individuals who dropped out before Time 5 were less likely to be adherent, more likely to be taking 5 + medications concurrently, and more likely to be in the *high benefit* class. This biases our results away from the null with regards to adherence in the overall sample, and away from the null with regards to adherence in the *high benefit* class. In addition, relationships between adherence and medication regimens would be biased away from the null for individuals taking 5 + medications concurrently. There was a high dropout rate during the naturalistic follow-up (Time 5 through 8) as well, although there were no demographic differences between participants who stayed and who dropped out during that time period. This non-differentially biases our results toward the null.

Finally, despite being theoretically grounded in clinical guidelines for CNB and having external validity, the construct of CNB was generally not related to medication adherence. This was contrary to expectations, but even though this core hypothesis was not supported, these null results do provide important information. Foremost, they suggest that something outside of CNB is driving adherence, at least in our sample. As discussed previously, there are many aspects of clinical care that could not be examined in this study, including subjective measures of participants' opinions about taking their medications, the relationship between clinicians and those they treat for BD, and past changes in relative functioning before they began the trial. This may be particularly true with participants in our analyses who were approximately 40 years of age. Onset of BD takes place when people are approximately 20 years of age. This suggests that our sample may have been receiving treatment for BD for 20 years or more before STEP-BD began, and those care experiences and history may be stronger determinants of contemporary adherence than concurrent symptoms, adverse effects, and functioning.

Selection bias is also a concern in any RCT. Individuals who participate in clinical trials are different from those who do not in a myriad of ways, which reduces the generalizability of the results. In addition, even though this was technically a RCT, the vast majority of participants elected to remain in the Standard Care Pathways (i.e., treatment as usual); this suggests they were satisfied with their medication regimens at baseline, since they were unwilling to "roll the dice" so to speak and make a change. It is also unlikely that individuals who were not adherent would be receiving regular outpatient care.

Next Steps

A number of directions could be pursued to further test the utility of the CNB construct For example, qualitative research of individuals with BD, stratified by CNB class, may provide important new insight into the patients' perspective of their treatment, relationships with their provider, and their perspectives of the benefit versus risks of their treatment. This would lend support, or suggest there is limited utility, of the subgroups identified by CNB. In addition, other measures of adherence such as pill bottle counts, blood serum levels, and self-report questionnaires of adherence (e.g., Medication Adherence Rating Scale) may be more sensitive measures than the metric of adherence used here.

Additionally, the CNB construct could be tested in different clinical populations, such as with individuals diagnosed with schizophrenia (e.g., CATIE Schizophrenia trial) or major depression (e.g., STAR*D trial), to understand the heterogeneity in these dimensions across a range of psychiatric disorders. These RCTs have similar designs to STEP-BD. If we are able to identify distinct subgroups of CNB in these populations, this would further support the utility of the CNB construct in understanding heterogeneity in treated populations with psychiatric disorders, regardless of whether that heterogeneity predicts adherence. Finally, it would be important to explore the construct of CNB in observational, rather than clinical trial, data (e.g., population surveys such as the Medical Expenditures Panel Survey), which have superior external validity to RCTs.

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Appendix

Diagnostic Criteria for Bipolar I Disorder

For a diagnosis of bipolar I disorder, it is necessary to meet the following criteria for a manic episode. The manic episode may have been preceded by and may be followed by hypomanic or major depressive episodes.

Manic Episode

A. A distinct period of abnormally and persistently elevated, expansive, or irritable mood and abnormally and persistently increased activity or energy, lasting at least 1 week and present most of the day, nearly every day (or any duration if hospitalization is necessary).

B. During the period of mood disturbance and increased energy or activity, three (or more) of the following symptoms (four if the mood is only irritable) are present to a significant degree and represent a noticeable change from usual behavior:

    1. Inflated self-esteem or grandiosity.
    2. Decreased need for sleep (e.g., feels rested after only 3 hours of sleep).
    3. More talkative than usual or pressure to keep talking.
    4. Flight of ideas or subjective experience that thoughts are racing.
    5. Distractibility (i.e., attention too easily drawn to unimportant or irrelevant external stimuli), as reported or observed.
    6. Increase in goal-directed activity (either socially, at work or school, or sexually) or psychomotor agitation (i.e., purposeless non-goal-directed activity).

7. Excessive involvement in activities that have a high potential for painful consequences (e.g., engaging in unrestrained buying sprees, sexual indiscretions, or foolish business investments).

C. The mood disturbance is sufficiently severe to cause marked impairment in social or occupational functioning or to necessitate hospitalization to prevent harm to self or others, or there are psychotic features.

D. The episode is not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication, other treatment) or another medical condition.

- **Note:** A full manic episode that emerges during antidepressant treatment (e.g., medication, electroconvulsive therapy) but persists at a fully syndromal level beyond the physiological effect of that treatment is sufficient evidence for a manic episode and, therefore, a bipolar I diagnosis.

Note: Criteria A–D constitute a manic episode. At least one lifetime manic episode is required for the diagnosis of bipolar I disorder.

Hypomanic Episode

A. A distinct period of abnormally and persistently elevated, expansive, or irritable mood and abnormally and persistently increased activity or energy, lasting at least 4 consecutive days and present most of the day, nearly every day.

B. During the period of mood disturbance and increased energy and activity, three (or more) of the following symptoms (four if the mood is only irritable) have persisted, represent a noticeable change from usual behavior, and have been present to a significant degree:

1. Inflated self-esteem or grandiosity.

2. Decreased need for sleep (e.g., feels rested after only 3 hours of sleep).
3. More talkative than usual or pressure to keep talking.
4. Flight of ideas or subjective experience that thoughts are racing.
5. Distractibility (i.e., attention too easily drawn to unimportant or irrelevant external stimuli), as reported or observed.
6. Increase in goal-directed activity (either socially, at work or school, or sexually) or psychomotor agitation.
7. Excessive involvement in activities that have a high potential for painful consequences (e.g., engaging in unrestrained buying sprees, sexual indiscretions, or foolish business investments).

C. The episode is associated with an unequivocal change in functioning that is uncharacteristic of the individual when not symptomatic.

D. The disturbance in mood and the change in functioning are observable by others.

E. The episode is not severe enough to cause marked impairment in social or occupational functioning or to necessitate hospitalization. If there are psychotic features, the episode is, by definition, manic.

F. The episode is not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication, other treatment) or another medical condition.

- **Note:** A full hypomanic episode that emerges during antidepressant treatment (e.g., medication, electroconvulsive therapy) but persists at a fully syndromal level beyond the physiological effect of that treatment is sufficient evidence for a hypomanic episode diagnosis. However, caution is indicated so that one or two symptoms (particularly increased irritability, edginess, or agitation following antidepressant use)

are not taken as sufficient for diagnosis of a hypomanic episode, nor necessarily indicative of a bipolar diathesis.

Note: Criteria A–F constitute a hypomanic episode. Hypomanic episodes are common in bipolar I disorder but are not required for the diagnosis of bipolar I disorder.

Major Depressive Episode

A. Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure.
    - **Note:** Do not include symptoms that are clearly attributable to another medical condition.
        1. Depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad, empty, or hopeless) or observation made by others (e.g., appears tearful). (**Note:** In children and adolescents, can be irritable mood.)
        2. Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation).
        3. Significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day. (**Note:** In children, consider failure to make expected weight gain.)
        4. Insomnia or hypersomnia nearly every day.

5. Psychomotor agitation or retardation nearly every day (observable by others; not merely subjective feelings of restlessness or being slowed down).
6. Fatigue or loss of energy nearly every day.
7. Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick).
8. Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others).
9. Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.

B. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

C. The episode is not attributable to the physiological effects of a substance or another medical condition.

Note: Criteria A–C constitute a major depressive episode. Major depressive episodes are common in bipolar I disorder but are not required for the diagnosis of bipolar I disorder.

Note: Responses to a significant loss (e.g., bereavement, financial ruin, losses from a natural disaster, a serious medical illness or disability) may include the feelings of intense sadness, rumination about the loss, insomnia, poor appetite, and weight loss noted in Criterion A, which may resemble a depressive episode. Although such symptoms may be understandable or considered appropriate to the loss, the presence of a major depressive episode in addition to the normal response to a significant loss should also be carefully considered. This decision

inevitably requires the exercise of clinical judgment based on the individual's history and the cultural norms for the expression of distress in the context of loss.

In distinguishing grief from a major depressive episode (MDE), it is useful to consider that in grief the predominant affect is feelings of emptiness and loss, while in an MDE it is persistent depressed mood and the inability to anticipate happiness or pleasure. The dysphoria in grief is likely to decrease in intensity over days to weeks and occurs in waves, the so-called pangs of grief. These waves tend to be associated with thoughts or reminders of the deceased. The depressed mood of an MDE is more persistent and not tied to specific thoughts or preoccupations. The pain of grief may be accompanied by positive emotions and humor that are uncharacteristic of the pervasive unhappiness and misery characteristic of an MDE. The thought content associated with grief generally features a preoccupation with thoughts and memories of the deceased, rather than the self-critical or pessimistic ruminations seen in an MDE. In grief, self-esteem is generally preserved, whereas in an MDE, feelings of worthlessness and self-loathing are common. If self-derogatory ideation is present in grief, it typically involves perceived failings vis-à-vis the deceased (e.g., not visiting frequently enough, not telling the deceased how much he or she was loved). If a bereaved individual thinks about death and dying, such thoughts are generally focused on the deceased and possibly about "joining" the deceased, whereas in an MDE such thoughts are focused on ending one's own life because of feeling worthless, undeserving of life, or unable to cope with the pain of depression.

Bipolar I Disorder

A. Criteria have been met for at least one manic episode (Criteria A–D under "Manic Episode" above).

B. The occurrence of the manic and major depressive episode(s) is not better explained by schizoaffective disorder, schizophrenia, schizophreniform disorder, delusional disorder, or other specified or unspecified schizophrenia spectrum and other psychotic disorder.

Vita

EDUCATION

Master of Science, Social Work 2011 – 2013
Advanced Generalist Practice and Programming, Contemporary Social Issues
Columbia University School of Social Work, New York, NY

Bachelor of Arts, Psychology – *Honors: Cum Laude* 1998 – 2007
Psychology Department, College of Science and Engineering
San Francisco State University, San Francisco, CA

AWARDS, PROFESSIONAL MEMBERSHIPS, LICENSURE

School of Medicine Phi Kappa Phi Scholarly Achievement Award, Virginia Commonwealth University, Richmond, VA 2017

Phi Kappa Phi Susan E. Kennedy Scholarship, Nominee, Virginia Commonwealth University, Richmond, VA 2017

International Society for Bipolar Disorders, Member, Richmond, VA 2016 – Present

International Society for Affective Disorders, Member, Richmond, VA 2016 – Present

Licensed Master Social Worker 2014 – Present
The University of the State of New York, License 091216, New York, NY

American Public Health Association, Member, Richmond, VA 2013 – Present

Paige E. Cook Jr. Fellowship, Columbia University School of Social Work 2012 – 2013
Competitive award given on the basis of excellence to a student with career interests in substance abuse, world of work, men's issues, and cross-cultural practice in clinical practice.

National Association of Social Workers, Member, New York, NY 2012 – Present

RELEVANT PROFESSIONAL EXPERIENCE AND EMPLOYMENT

Graduate Research Assistant 2013 – Present
Division of Epidemiology, Department of Family Medicine and Population Health, School of Medicine, Virginia Commonwealth University

Mood and Immune Regulation in Twins Study (K01-MH093642, PI: Mezuk)
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Richmond Stress and Sugar Study (RSASS) (ADA 1-16-ICTS-082, PI: Mezuk)
Project testing the contribution of stress reactivity to diabetes disparities. .
- Conduct intake and in-person interviews with participants
- Assist with development of survey instruments

- Participate as confederate in Trier Social Stress Test.

Social Work Intern: Year 2 Placement 2012 – 2013
Social Intervention Group (SIG), Columbia University School of Social Work

Connect 'N Unite (CNU) (R01-DA030296, PI: Wu)
Couples harm reduction intervention for African American Men who have Sex with Men to decrease risky behaviors leading to HIV and STI infection.

- Conduct participant screenings, intakes and outreach evaluations.
- Trained to facilitate manualized interventions with couples

HIV Intervention Science Training Program for Underrepresented New Investigators (HISTP) (R25-MH080665, PIs: El-Bassel and Wu)
Mentorship project to increase the number and success of NIH PIs from underrepresented groups who are highly-trained HIV scientists.

- Event logistics including marketing, recording, evaluations.
- Maintain internet-based mentorship portal.

Social Work Intern: Year 1 Placement 2011 – 2012
Bowery Residents Committee (BRC) Reception Center, New York, NY
Shelter serving severely mentally ill, chronically homeless adults as they attain mental and physical health and apply for permanent supportive housing.

- Submit housing applications to the Human Resources Administration.
- Obtain identification, benefits, and entitlements for clients.
- Training in activities of daily living including laundry, budgeting, and independent travel to medical and housing appointments.

Analyst II 2006 – 2011
Center for Imaging of Neurodegenerative Diseases (CIND), San Francisco, CA
Magnetic Resonance Imaging (MRI) lab at San Francisco VA Medical Center.

- Proofed and edited grant proposals funded by the NIH, DOD, and VA.
- Proofed and submitted manuscripts to journals and conferences.
- Designed and maintained lab website.
- Trained staff in NIH submission requirements.
- Co-produced Alzheimer's Disease Neuroimaging Initiative promotional film.

PEER-REVIEWED PUBLICATIONS AND PUBLISHED ABSTRACTS

Bareis N and Mezuk B. (2016). The relationship between childhood poverty, military service, and later life depression among men: Evidence from the Health and Retirement Study. Journal of Affective Disorders, 206:1-7. doi: 10.1016/j.jad.2016.07.018.

Bareis N. (2016). Client centered treatment to optimize psychiatric medication adherence. Bipolar Disorders, 18(Suppl 1): S96-S97. (Poster Abstract)

Bareis N and Mezuk B. (2015). Psychiatric polypharmacy and implications for obesity. Bipolar Disorders, 17(Suppl 1): 131. (Poster Abstract)

Bareis N. (2015). Relationship between childhood poverty and military service on late life depression among men: A life course perspective. The American Journal of Geriatric Psychiatry, 23(3, Suppl 1): S75-S76. (Poster Abstract)

Needham BL, Mezuk B, **Bareis N**, Lin J, Blackburn EH and Epel ES. (2015). Depression, anxiety and telomere length in young adults: Evidence from the National Health and Nutrition Examination Survey. Molecular Psychiatry, 20:520-528. doi: 10.1038/mp.2014.89

Bareis N, Needham B, and Mezuk B. (2014). Depression, anxiety, and telomere length: Evidence from the National Health and Nutrition Examination Survey. Comprehensive Psychiatry, 55(8): e45. (Poster Abstract)

Bareis N, Sando TA, Mezuk B, and Cohen SA. (In-Preparation). Use of psychotropic medication polypharmacy is associated with balance impairment among middle-aged adults: Results from the National Health and Nutrition Examination Survey.

Bareis N, Lu J, Kirkwood CK, Kornstein S, Wu E, and Mezuk B. (Submitted). Identifying Clinical Net Benefit of Psychotropic Medication Use with Latent Variable Techniques: Evidence from Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD). Bipolar Disorders.

PRESENTATIONS AT SCIENTIFIC MEETINGS

Bareis N and Mezuk B. (May, 2017) The Bi-Directional Relationship Between Clinical Net Benefit and Medication Adherence Over Time in Bipolar Disorder: A Latent Transition Analysis
19th Annual Conference of the International Society for Bipolar Disorders, Washington, DC (Poster)

Bareis N. (March, 2017). Psychiatric Medication Polypharmacy is Associated with Balance Impairment in Middle-Aged Adults: Evidence from the National Health and Nutrition Examination Survey (NHANES).
107th Annual Meeting of the American Psychopathological Association, New York, NY (Poster)

Bareis N. (July, 2016). Client-Centered Treatment to Optimize Psychiatric Medication Adherence.
18th Annual Conference of the International Society for Bipolar Disorders Amsterdam, The Netherlands (Poster)

Bareis N, Sando TA, and Cohen SA. (October, 2015). Psychiatric medication use is associated with increased impairments in balance and fall risk. 32nd Daniel T. Watts Research Poster Symposium Richmond, VA (Poster)

Bareis N and Mezuk B. (June, 2015). Psychiatric polypharmacy and implications for obesity. International Society for Bipolar Disorders 2015 Annual Conference Toronto, Canada (Poster)

Bareis N and Mezuk B. (March, 2015). Relationship between childhood poverty and military service on late-life depression among men: A life course perspective.
2015 American Association for Geriatric Psychiatry Annual Meeting New Orleans, LA (Poster)

Bareis N, Mezuk B, and Needham B. (March, 2014). Depression, Anxiety and Telomere Length: Evidence from the National Health and Nutrition Examination Survey.
American Psychopathological Association 2014 Annual Meeting New York, NY (Poster)

LECTURES

Bareis N. (December 7, 2016) *Stigma.*
Epidemiology of Psychiatric and Substance Use Disorders (VCU EPID 646) Richmond, VA

Bareis N. (September 20, 2016). *Clinical Net Benefit of Psychiatric Medication Use and Adherence.*
VCU School of Medicine, Department of Family Medicine and Population Health, Epidemiology Division Seminar Series Richmond, VA

Bareis N. (September 14, 2016). *The Role of Data in Public Health.*
Introduction to Public Health (VCU DENH 411) Richmond, VA

Bareis N. (February 2, 2016). *Psychiatric Medication Use is Associated with Impairments in Balance.*
VCU School of Medicine, Department of Family Medicine and Population Health, Epidemiology Division Seminar Series Richmond, VA

Bareis N. (December 2, 2015) *Stigma and the Future of Psychiatric Epidemiology.*
Epidemiology of Psychiatric and Substance Use Disorders (VCU EPID 646) Richmond, VA

Bareis N. (September 30, 2014). *Does Depression Accelerate Aging? Telomeres May Provide Answers.*
VCU School of Medicine, Department of Family Medicine and Population Health, Epidemiology Division Seminar Series Richmond, VA

TEACHING

Graduate Teaching Assistant Fall 2015, Fall 2016
Division of Epidemiology, Department of Family Medicine and Population Health, School of Medicine, Virginia Commonwealth University
Epidemiology of Psychiatric And Substance Use Disorders (VCU EPID 646)

- Classification, nosology and operational case definitions of disorders and measurement techniques for field surveys and risk-factor research.

SERVICE

Data Analyst and Moderator Trainer, Datapalooza 2014 2014
Community-based participatory research event to present results from the *East End Residents Community Survey* to community members.

PhD Student Representative, Faculty Promotion Committee 2014
Department of Family Medicine and Population Health, School of Medicine, VCU

Judge, Physical Science 2014
2014 Virginia Junior Academy of Science (VJAS) Research Symposium

PhD Student Representative, Curriculum Committee 2013 – Present
Division of Epidemiology, Department of Family Medicine and Population Health, School of Medicine, Virginia Commonwealth University

CUSSW Student Membership Associate 2012 – 2013

National Association of Social Workers (NASW), New York, NY

Student Representative, Ethics Board 2012 – 2013
Columbia University School of Social Work, New York, NY

Mentor Advocate Peer (MAP) Leader 2012 – 2013
Columbia University School of Social Work, New York, NY

Student Facilitator, Professional Development Self Awareness Orientation 2012
Columbia University School of Social Work, New York, NY

Volunteer Facilitator Removing the Bars: TAKE ACTION Conference 2012
Criminalization of People with Mental Illness Session, New York, NY