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Research paper

Identifying clinical net benefit of psychotropic medication use with latent variable techniques: Evidence from Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD)

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ABSTRACT

Background: Poor medication adherence is common among individuals with Bipolar Disorder (BD). Understanding the sources of heterogeneity in clinical net benefit (CNB) and how it is related to psychotropic medications can provide new insight into ways to improve adherence.
Methods: Data come from the baseline assessments of the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD). Latent class analysis identified groups of CNB, and validity of this construct was assessed using the SF-36. Adherence was defined as taking 75% or more of medications as prescribed. Associations between CNB and adherence were tested using multiple logistic regression adjusting for socio-demographic characteristics.
Results: Five classes of CNB were identified: High (24%), Moderately high (12%), Moderate (26%), Moderately low (27%) and Low (12%). Adherence to psychotropic medications did not differ across classes (71% to 75%, $\chi^2 = 3.43$, $p = 0.488$). Medication regimens differed by class: 57% of the High CNB were taking ≤ 2 medications, whereas 49% of the Low CNB were taking ≥ 4. CNB classes had good concordance with the SF-36.
Limitations: Missing data limited measures used to define CNB. Participants' perceptions of their illness and treatment were not assessed.
Conclusions: This novel operationalization of CNB has construct validity as indicated by the SF-36. Although CNB and polypharmacy regimens are heterogeneous in this sample, adherence is similar across CNB. Studying adherent individuals, despite suboptimal CNB, may provide novel insights into aspects influencing adherence.

1. Introduction

Bipolar Disorder (BD) is among the leading causes of disability-adjusted life-years lost worldwide (Bloom et al., 2011). Effective treatment with psychotropic medication, often in combination with psychotherapy, can help individuals with BD manage their illness (Yatham et al., 20052013,2018).

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 (Clatworthy et al., 2009). Approximately 20–60% of individuals with BD will be non-adherent to their medication at some point in their treatment (Kutzelnigg et al., 2014); medication non-adherence contributes to elevated relapse, suicidal behavior and greater healthcare costs (Svarstad et al., 2001; Velligan et al., 2010). Poor adherence is thought to stem from multiple sources, including effects of the illness itself (e.g., "lack of insight" about the condition (Crowe et al., 2011; Ketter, 2010), adverse effects of medications (e.g., heart disease, somnolence (Bates et al., 2010; Clatworthy et al., 2009; Kemp, 2014)), and complexity of medication regimens (e.g., multiple pills taken

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multiple times per day (Ketter, 2010; Vieta, 2005)). In addition, individuals' attitudes toward their continued risks of exacerbated symptoms and perceived benefits and burdens of treatments for BD effect whether individuals will adhere to their medications (Sajatovic et al., 2008). Adapting self-management strategies to include the individual's desired locus of control (e.g., active or passive roles in the patient-provider relationship) may be considered as additional support for adherence (Berk et al., 2004). Psychological reactance has been suggested as a response to the need for adherence to prescribed medication because it can be considered a reduction of freedom of choice, resulting in non-adherence (De Las Cuevas et al., 2014).

When considering prescribing medications, practitioners routinely weigh the benefits versus risks of each treatment, seeking a positive balance between expected benefits and risk of adverse effects (Yatham et al., 2013). For example, the Canadian Network for Mood and Anxiety Treatments (CANMAT) clinical guidelines (Yatham et al., 2018) provide hierarchical rankings of medications for first-, second-, and third-line recommendations during acute mania, acute depression and maintenance treatment for BD. Recommendations are supported by levels of evidence for efficacy, tolerability profiles and treatment emergent switch risks informed by previous research. Changes between medications are driven by inefficacy of symptom management and tolerability. Sedation and weight gain are frequent reasons for medication non-adherence in BD. Close monitoring is recommended for possible metabolic or other adverse effects; replacing a high metabolic risk medication with a lower metabolic risk medication is recommended if the efficacy is similar. At the population level, this concept of benefit versus risk is quantified in two main ways: (1) Number Needed to Treat (i.e., if the outcome is a desirable, number of persons to be treated with Treatment 1 in order to find one more preferred response than the same number of persons treated with Treatment 2, and (2) Number Needed to Harm (i.e., if the outcome is harmful, negative number needed to treat (Kraemer et al., 2011)). However, these existing notions of benefit versus risk are limited in two important ways. First, although clinical guidelines for maintenance treatment identify the importance of preventing relapse and promoting quality of life and functioning (Yatham et al., 2005), their practical focus is on efficacious symptom management. This approach, along with Number Needed to Treat, reduces the benefit-risk ratio to a single unidimensional quantity (Kraemer et al., 2011). This does not appropriately capture the complexity of what benefit versus risk objectively looks like for the patient; Clinical Net Benefit (CNB) of treatment can be conceptualized as the complex intersection between psychiatric symptoms, adverse effects, and overall functioning.

Second, there has been only limited discussion of how the experience of CNB for individuals with BD relates to their medication *adherence*. Instead, focus has been on how to remedy non-adherence with clinician-administered psychoeducation (Vieta, 2005) and identifying individual's perception of their providers' confidence in their medication regimen as some of the possible methods (Cochran and Gitlin, 1988). Much research has focused on why people *do not* adhere, but new insight can be found by focusing in individuals who *do* adhere. A handful of studies explored how perspectives of individuals with BD relate to medication adherence. Using the Beliefs about Medication Questionnaire (Horne et al., 1999), Clatworthy et al. (2009) found that perceptions of higher concern and lower necessity regarding medication were associated with lower adherence. Using components of the Rating of Medication Influences Scale (ROMI) (Weiden et al., 1994), Adams and Scott (2000) found that participants' perceived benefits-to-risks for medications differentiated those who were highly adherent and partially adherent. 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 (Morselli et al., 2003; Yatham et al., 2013). These reports were also limited in scope (i.e., small samples, limited to one type of medication) and one relied on self-administered mail-in questionnaires with lower validity relative to clinical assessments (Bowling, 2005; McIntyre, 2009; Morselli et al., 2003).

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 clinical trial (RCT) designed to test the utility of different treatment modalities (medications and psychotherapy) for individuals with BD. Participants were also given a battery of clinician- and self-administered psychological assessments as well as detailed clinician-determined medication adherence measures (Sachs et al., 2003).

The objective of this study was to use STEP-BD 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 BD treatment (Lanza et al., 2007). Latent variable modeling is ideal for quantifying a complex construct such as CNB (Krueger et al., 2007; Woolston et al., 2012), and can effectively classify people into discrete subgroups. Classes of CNB were characterized according to objective indicators of symptom management, adverse effects, and overall functioning. Validity of the CNB construct was analyzed using the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36; (McHorney et al., 1993)), a commonly used self-report metric of health and 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 objective characteristics of CNB. We also hypothesized that these distinct classes will be differentially associated with medication adherence.

2. Methods

2.1. Sample

All eligible participants in the STEP-BD trial aged 18 years and older, who completed baseline assessments, and were taking medication were included in the current study, as medications taken by STEP-BD participants were only approved for this population when the study began (Smarty and Findling, 2007; Thomas et al., 2011). The details of the original study design were described elsewhere (Sachs et al., 2003). 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). At baseline, participants who met the symptom inclusion criteria for one of the three RCPs (i.e., acute depression, refractory depression, or relapse prevention) could then choose to enter those pathways or stay in the 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 (i.e., treatment as usual). In addition, participants underwent a battery of clinician- and self-administered psychological assessments, including medication adherence. Although STEP-BD is a longitudinal trial, we are conducting a cross-sectional analysis with these data since we are only using data from the baseline assessments before individuals have participated in STEP-BD.

Although 4360 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 18 years of age. Missing data $<10\%$ was imputed using Full Information Likelihood Estimation (Dong and Peng, 2013). The final analytic sample size was 3738 (Supplemental Figure 1).