Is the collaborative chronic care model effective for patients with bipolar disorder and co-occurring conditions?

Amy M. Kilbourne,⁎ Kousick Biswas, Paul A. Pirraglia, Martha Sajatovic, William O. Williford, Mark S. Bauer

VA Ann Arbor Serious Mental Illness Treatment Research and Evaluation Center and Department of Psychiatry, University of Michigan; Ann Arbor, MI, USA

Cooperative Studies Program Coordinating Center at the VA Maryland Health Care System at Perry Point, MD, USA

Providence VA Medical Center and Brown University; Providence, RI, USA

Case Western Reserve University School of Medicine, University Hospitals of Cleveland; Cleveland, OH, USA

VA Boston Healthcare System; Boston, MA, USA

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Summary

Background: The effectiveness of bipolar collaborative chronic care models (B-CCMs) among those with co-occurring substance use, psychiatric, and/or medical conditions has not specifically been assessed. We assessed whether B-CCM effects are equivalent comparing those with and without co-occurring conditions.

Methods: We reanalyzed data from the VA Cooperative Study #430 (n=290), an 11-site randomized controlled trial of the B-CCM compared to usual care. Moderators included common co-occurring conditions observed in patients with bipolar disorder, including substance use disorders (SUD), anxiety, psychosis; medical comorbidities (total number), and cardiovascular disease-related conditions (CVD). Mixed-effects regression models were used to determine interactive effects between moderators and 3-year primary outcomes.

Results: Treatment effects were comparable for those with and without co-occurring substance use and psychiatric conditions, although possibly less effective in improving physical quality of life in those with CVD-related conditions (Beta = −6.11; p=0.04).

Limitations: Limitations included multiple comparisons and underpowered analyses of moderator effects.

Conclusions: B-CCM effects were comparable in patients with co-occurring conditions, indicating that the intervention may be generally applied. Specific attention to physical quality of life in those with CVD maybe warranted.

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1. Introduction

Bipolar disorder is common and associated with substantial functional impairment, health care costs, and premature mortality (Bauer, 2003). Co-occurring...
conditions (i.e., medical and/or substance use disorders) are the rule rather than the exception in this group. Prevalence rates for co-occurring psychiatric and substance use disorders ranged from 57.3% to 74.3%, with 30% having three or more conditions (Bauer et al., 2005; Otto et al., 2006). Co-occurring substance use disorders can occur in over 60% of some clinical samples (Bauer et al., 1997, 2005). Medical comorbidity occurs frequently, with over 80% of some samples having at least one active medical disorder, 19–23% having two such conditions, and 35–50% having three or more (Kilbourne et al., 2004; Fenn et al., 2005). Patients with co-occurring conditions are more likely to experience worse outcomes than those without comorbidity (Strakowski et al., 1998; Tsai et al., 2005).

Not surprisingly, outcomes for patients with bipolar disorder are suboptimal despite the availability of efficacious medications (APA, 2002). Adjunctive psychosocial treatments, such as cognitive-behavioral therapy (CBT) (Lam et al., 2005), family therapy (Clarkin et al., 1998; Miklowitz et al., 2000), and psychoeducation (Perry et al., 1999; Colom et al., 2003) trials have yielded promising results.

Nonetheless, in the few trials that have that included patients with co-occurring conditions, psychosocial treatments have only minimal effect (Scott et al., 2006; Nierenberg et al., 2006) while nothing is known about the effects of medical comorbidities on such treatment effects. In a recent trial of CBT in a sample of patients with co-occurring psychiatric conditions (Scott et al., 2006), lack of significant effect was associated with psychiatric severity in the sample, though others have questioned that explanation (Lam, 2006).

Recently, two long-term trials of over 700 participants (Bauer et al., 2006a,b; Simon et al., 2006) demonstrated that collaborative chronic care models for bipolar disorder (B-CCMs) can improve outcome in this chronic mental illness much as they do in chronic medical illnesses and depression treated in primary care (Badamgarav et al., 2003). Notably, B-CCMs had significant effects despite the trials enrolling patients with co-occurring conditions.

Kraemer and Wilson (2002) have devised a framework to address this issue by assessing the effect of moderators on treatment effect. This framework defines moderators as those characteristics present at the time of treatment initiation (and uncorrelated with treatment assignment) that have an interactive effect on the intervention to affect its impact on outcome. They can also represent different subgroups of patients within the population who have different effect sizes. Moderators analysis is critical both for optimal dissemination of the intervention to clinical practice and/or for further intervention adaptation, since it confirms whether the intervention is equally effective across different subgroups, and also identifies subgroups in which intervention effects may be blunted so that it can be modified.

Analysis of whether co-occurring conditions might moderate effects of medical interventions has not been available in part due to limited numbers of patients with highly severe or comorbid illness represented in clinical trials (Glasgow et al., 2003). Effectiveness-oriented clinical trials, which seek to enroll a heterogeneous sample of participants with severe or comorbid illness can provide the opportunity to identify potential moderators. Using outcome data from a long-term multi-site effectiveness trial of a B-CCM in a sample of veterans with bipolar disorder which was characterized by high rates of psychiatric (e.g. anxiety, psychosis), substance use, and medical comorbidity, we determined whether such putative moderators blunted the effect of the B-CCM on the primary trial outcome and select secondary outcomes. We hypothesized that B-CCM would be less effective for patients with bipolar disorder and co-occurring psychiatric or medical comorbidity compared to those without co-occurring conditions.

2. Methods

2.1. Study design

VA Cooperative Study Program (CSP) #430 was a 3-year, 11-site, randomized controlled trial in 306 veterans randomized of B-CCM vs. usual VA care. Study design and main results have been reported elsewhere (Bauer et al., 2006a,b). Briefly, participants were randomized at discharge from index hospitalization for bipolar disorder to 3 years of follow-up under B-CCM treatment or usual care. B-CCM treatment consisted of three components: evidence-based pharmacotherapy via simplified practice guidelines, augmented patient self-management skills through group-based psychoeducation, and enhanced access to and continuity of care using nurse care managers. Usual care included the dissemination of practice guidelines to providers but no active management or self-management sessions for the patient. Original trial primary analysis demonstrated significant reduction in weeks in affective episode with the B-CCM compared to usual care, subserved primarily by significant reduction in weeks manic; secondary analyses showed significant improvement in social role function and mental health quality of life but no difference in physical health-related quality of life (Bauer et al., 2006b). All participants provided informed
consent, and the study was approved by the Institutional Human Subjects Review Boards at each site.

2.2. Measures

Potential moderators were identified prior to this reanalysis based on the prior literature, which identified characteristics associated with poor outcome in bipolar disorder (Scott et al., 2006; Bauer, 2003; Fenn et al., 2005). We focused on co-occurring psychiatric, substance use, and medical conditions, which have been associated with non-response to other types of treatment (Nierenberg et al., 2006).

Data on co-occurring baseline substance use disorders (SUD; excluding nicotine), anxiety disorders, and psychosis at baseline were collected via Structured Clinical Interview for DSM-IV (SCID) (First et al., 1996). Co-occurring active medical conditions at baseline were identified from a structured chart review method of established validity and reliability (Fenn et al., 2005). Using this method, we identified participants with three or more general medical conditions given that the modal number of conditions was one and because having three or more signified substantial medical burden (Fenn et al., 2005). In addition, we identified those with a current diagnosis of any of the following CVD-related conditions present in the patient’s medical record: type 2 diabetes, hypertension, hyperlipidemia, coronary artery disease, or angina.

Prospective trial outcome data were collected by Survey Coordinators who were blinded to randomization assignment. Outcomes included the Longitudinal Interval Follow-Up Examination (LIFE) every 8 weeks, with primary outcome variable for the trial being weeks in affective episode (Keller et al., 1987). The LIFE utilizes time-line follow-back methodology to provide weekly Psychiatric Symptom Ratings (PSRs) for mania and depression based on the number of DSM-IV criteria endorsed: no/minimal symptoms (PSR=1–2), subthreshold symptoms (PSR=3–4), or episode (PSR=5–6). Prior to trial outcome we summarized symptom outcomes as the mean percentage of weeks each of the 3 years in manic, depressive, or any episode (PSR=5–6). The secondary outcomes of mental and physical quality of life data were collected every 6 months using, respectively, the mental (MCS) and physical (PCS) component scores of the SF-36 (Stewart et al., 1988), both of which have a range 0–100 and population mean±SD of 50±10. All original trial analyses utilized intention-to-treat mixed-effects regression models with weeks-in-episode square root-transformed to stabilize variance.

2.3. Analyses

Moderators can be defined by determining the interactive effect between the treatment and a baseline variable of interest (Kraemer and Wilson, 2002). For each candidate moderator we reapplied the same mixed-effect regression models used in the original CSP #430 analyses for each outcome, but added the candidate moderator and the interaction term for the moderator and B-CCM treatment effect as described below. We applied this strategy separately for each of the following characteristics, which we hypothesized a priori to be potential moderators: current substance use disorder, current anxiety disorder, psychosis, three or more active medical comorbidities, and CVD-related comorbidity. Because the B-CCM was designed to improve mental health-related outcomes, we focused our moderator analyses on the three main outcomes that were improved among patients in the B-CCM intervention compared to usual care overall: percent weeks in affective episodes, percent weeks in manic episodes, and mental health-related quality of life. We also assessed moderator effects for physical health-related quality of life given that we also chose to examine medical comorbidities as potential moderators.

For each mixed-effects regression model we included the interaction effect between B-CCM and the potential moderator of interest, adjusting for the main effect of the B-CCM, the moderator, time, time*B-CCM effect, and site. For all analyses, F-statistics were used and two-sided tests were applied for significance (p<0.05). A significant overall interaction coefficient indicates that the co-occurring condition is likely a moderator of treatment effect, as it is enhanced (or diminished) beyond would be expected from an additive effect of treatment and the moderator alone. In the presence of a significant moderator effect with the B-CCM (p<0.05), the direction of the interaction was determined by the sign of the beta coefficient.

3. Results

Of the 306, 290 had complete data on potential moderator characteristics. The mean age was 46 years (SD=10), 104 (34%) were diagnosed with a current SUD, 116 (38%) with current anxiety disorder, and 157 (52%) with psychosis. In addition, 144 (51%) had three or more medical comorbidities, and 52 (18%) were diagnosed with a CVD-related condition. Those missing and not missing medical comorbidity data did not differ in demographic or clinical characteristics, and comorbidity frequencies were similar across treatment arms.
Based on the mixed-effects regression models, treatment effects were comparable for those with and without current SUD or anxiety disorders, including weeks in affective episode, weeks manic, and mental and physical health-related quality of life (Table 1). However, psychosis was associated with an augmented B-CCM effect, with fewer weeks in affective episode (Beta = −1.07, \( p = 0.04 \)) and weeks manic episode (Beta = −0.85, \( p = 0.04 \)); note that negative betas reflect better outcome. This translates into approximately one fewer week in affective or manic episode in the B-CCM treatment compared to usual care.

However, having a CVD-related condition might have blunted the B-CCM effect on SF-36 physical health component score (Beta = −6.11, \( p = 0.04 \)), with a negative beta as a lower score reflecting worse outcome. That is, those in B-CCM with CVD risk had their physical health-related quality of life decline to a greater degree (i.e., ~6 points) than those without CVD risk in usual care.

4. Discussion

There has been little research examining moderators of treatment effects in psychiatry clinical trial outcomes. Paucity of such analysis is likely due in part to the 1) relative dearth until recently of effectiveness designs that attempt recruitment of samples with adequate representation of participants with co-occurring conditions, and 2) lack of RCTs that test interventions such as the CCM that are specifically designed a priori for patients with co-occurring conditions. Such analyses are important for determining whether the intervention is equally effective across different subpopulations, and in cases where treatment response is less optimal, for which subpopulations the intervention needs to be tailored. Such information is critical for planning future dissemination and adaptation of interventions.

We found that B-CCM appears to be equally effective for patients with and without co-occurring psychiatric and substance use disorders, and hence, the intervention thus appears to be applicable to a broad population of individuals with bipolar disorder. This contrasts, for example, with the experience of Scott et al. (2006) who, using a different methodology, found that CBT was less effective in patients with co-occurring conditions This may reflect the fact that the B-CCM intervention was designed to assist a lower functioning population who may be experiencing acute manic or depressive episodes, as opposed to CBT, which may not be completely effective for patients experiencing acute episodes given that such episodes may disrupt treatment engagement (Scott et al., 2006). Moreover, B-CCM does much more to integrate services, apply evidence-based pharmacotherapy, and manage patient needs beyond bipolar symptoms. The lack of strong moderator effects of B-CCM perhaps supports the ability of B-CCM to respond to a broad group of patients with bipolar disorder, in part by enabling more flexible care for those with co-occurring conditions than more pure psychological interventions.

It is intriguing to speculate regarding why the presence of psychosis or psychiatric comorbidity did not blunt the B-CCM effect, as appears to have been the case with cognitive-behavioral therapy (Nierenberg et al., 2006; Scott et al., 2006). While we cannot be certain in multi-component interventions which specific component(s)
were the most beneficial, the lack of difference in pharmacotherapy intensity (Bauer et al., 2006b) and the fact that the core elements of care reorganization and patient self-management skill enhancement appear to be common to virtually all successful collaborative care models for chronic medical illness (Badamgarav et al., 2003) suggest that such psychosocial components deserve further scrutiny. While it is difficult to imagine how psychoshow hypothesias per se was associated with augmented B-CCM effects, this may be a proxy for greater overall illness severity. It is not likely that regression to the mean was responsible for this finding, as similar effects were not seen in those with compared to those without psychosis treated in usual care. Such more severely ill patients may benefit from more intensive services more than those with less severe illness.

In contrast, the effect of the B-CCM on the secondary outcome variable of physical health-related quality of life may have been possibly blunted for patients with CVD comorbidities. In the original trial analyses there was no overall difference in this outcome measure (Bauer et al., 2006b), perhaps because the B-CCM was primarily designed to improve mental health-related outcomes. CVD is the most common condition associated with premature death in patients with mental disorders (Hennekens, 2007). Gaps in access, quality, and continuity of general medical care for patients with bipolar and other chronic mental disorders are prevalent (Horvitz-Lennon et al., 2006). Competing demands on B-CCM clinicians for attention to psychiatric needs may have “out-competed” attention to more medical concerns (Horvitz-Lennon et al., 2006). Regardless, our findings may suggest the need for the B-CCM to be tailored to address physical health care, particularly in those with CVD-related risk (Kilbourne et al., 2008).

4.1. Limitations

Several limitations to this study warrant consideration. First, we cannot be certain whether these results are due to chance (i.e., from multiple comparisons). In addition, this study was not originally designed to examine moderators. For example, given that the other medical illness moderator (3 or more illnesses) produced no significant effects, the possible blunting effect of B-CCM on physical health outcomes among patients with CVD needs to be interpreted with caution. Hence, our analysis might have been underpowered to detect significant differences in outcomes by subgroup, and our results might suggest a conservative estimate of the differential effects of moderators on B-CCM outcomes. Finally, the VA patient population, predominately male with military history, is not representative of the general U.S. patient population or populations served in community-based practices. Even so, the VA serves a disproportionate number of patients with high rates of relevant, active comorbidities which makes possible such study of treatment moderators.

5. Conclusions

In summary, the B-CCM is a promising intervention even for patients with co-occurring psychiatric and substance use disorders, likely due in part to the fact that it was specifically designed to accommodate such individuals, who represent the rule rather than the exception among individuals with bipolar disorder. Future efforts should focus on the broader dissemination of the B-CCM for bipolar disorder in community-based practices, where many patients with bipolar disorder suffer disproportionately from co-occurring conditions. At the same time, the possible blunted effect on physical health-related quality of life in those with CVD risk indicates a need to tailor treatment interventions to address co-occurring medical conditions among individuals with bipolar disorder, a process which is underway (Kilbourne et al., 2008). Moderator analyses can thus yield important information from psychiatry clinical trials data both to optimize dissemination and to enhance future intervention development.

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Conflicts of interest

The authors of this manuscript warrant that we have no actual or perceived conflicts of interest — financial or non-financial — in the procedures described in the enclosed manuscript.

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