Collaborative care for patients with bipolar disorder: Randomised controlled trial.

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Abstract

Background A substantial number of patients with bipolar disorder show a suboptimal response to treatment.

Aims To study the effectiveness of a Collaborative Care program on symptomatology and medication adherence in patients with bipolar disorder, compared to care as usual.

Method A two-armed cluster randomised clinical trial was carried out in 16 outpatient mental health clinics in the Netherlands, in which 138 patients were randomized. Patient outcome measures include time spent symptomatic, severity of symptoms, and medication adherence. Outcomes were measured at baseline, six months and twelve months. Collaborative Care is a multicomponent intervention, provided by a multidisciplinary team, with the following elements: contracting; psychoeducation; problem solving treatment; systematic relapse prevention; and monitoring of outcomes. Mental health nurses function as care-managers in this program.

Results Collaborative Care had a significant and clinically relevant effect on number of months with depressive symptoms, both at 6 months ($z=-2.6$, $p=.01$, $d=0.5$) and at 12 months ($z=-3.1$, $p=.002$, $d=0.7$), as well as on severity of depressive symptoms at 12 months ($z=-2.9$, $p=.004$, $d=0.4$). There was no effect on manic symptoms, nor on treatment adherence.

Conclusions When compared with care as usual, collaborative care substantially reduced the time bipolar patients suffered from depressive symptoms. Also depressive symptom severity decreased significantly. As persistent depressive symptoms are difficult to treat and contribute to both disability and impaired quality of life in bipolar patients, collaborative care may be an important treatment modality for bipolar patients.
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Background

Long term naturalistic follow-up studies among patients with bipolar disorder (BD) have shown that on average these people experience symptoms for approximately half of the time, despite treatment (1;2). Even during so-called euthymic periods, i.e. when patients do not fulfill the formal criteria of a mood episode), many have subsyndromal symptoms that increase the risk of relapse and negatively influence their functioning and quality of life (3-6). Collaborative Care was developed and tested in primary care in order to enhance treatment effectiveness in patients with depression (7). Some previous studies have tested the effectiveness of collaborative care in bipolar disorder (8-11). Although these studies have shown promising results, the majority demonstrated an effect on manic only, not on depressive symptoms. Given the deleterious effect of persistent depressive symptoms, we focused our collaborative care intervention in particular on the management of depressive symptoms by adding problem-solving treatment, and tested in a randomised controlled trial whether collaborative care may be an effective intervention programme (12).

Method

A pragmatic, two-armed, cluster randomised controlled trial (RCT) was conducted in out-patient mental health clinics in The Netherlands. The collaborative care programme was compared to treatment as usual (TAU). CC was carried out by specially trained collaborative care teams, in which mental health nurses functioned as care managers. In The Netherlands there are relatively few barriers to treatment in specialised mental healthcare, and the standard of care is generally high. However, we assumed considerable practice variation between teams. Therefore, we assessed the quality and level of care delivered by the teams that were eligible for participation before the start of the trial, to avoid including teams that were already providing the core elements of collaborative care. Baseline measurements were obtained at inclusion, and follow-up measurements at 6 months and 12 months. The primary outcome measures were time spent with symptoms of mania or depression, and the severity of such symptoms, and the secondary outcome measure was medication adherence. The trial was registered with The Netherlands Trial Registry (NTR2600).

Randomisation

Clustered randomisation was performed at the level of the outpatient teams. Teams that treated at least 20 patients with bipolar disorder were invited to participate. The teams were matched on the number of nurses who were willing to participate in the study, in order to obtain approximately the same number of respondents in both research conditions. The two teams within every matched pair were randomly assigned to either the experimental or the control condition, by use of an internet random generator, performed blind by the second author (B.M.). There was no matching on other
characteristics since, despite of the practice variation we found, the overall level and quality of care appeared to be comparable among teams. Next, in each team a nurse or psychiatrist compiled a list of patients who met the inclusion criteria. Since executing a new intervention leads to an increased workload for the nurses in the experimental condition, the maximum number of patients to be included was set at ten per nurse. If more than ten patients per participating nurse met the inclusion criteria, these patients were listed in random order and approached by the psychiatrist or nurse for participation starting at the top of this list. Once the provisional agreement of the patient was obtained, the researcher contacted the patient to give detailed oral information about the study. If patients agreed to participate, additional written information was provided, including an informed consent form. The study protocol was approved by the medical ethical committee of the VU University Medical Center.

**Participants**

We included patients aged 18 - 65 years with a diagnosis of bipolar disordertype 1 or 2 or not otherwise specified (NOS) according to DSM-IV-TR (13). Diagnoses were derived from the medical records and subsequently confirmed by the treating psychiatrist, using the Dutch version of the Questionnaire for Bipolar Illness (QBP-NL) (14). Since collaborative care is a relatively intensive intervention, it is not appropriate for patients experiencing a severe manic or depressive episode. The intervention program is also less appropriate for patients who are stable enough to function well with only low-intensity treatment. Based on these considerations we applied the following exclusion criteria:

(a) Severe or very severe depression or mania, with a score of 6 or 7 on the Clinical Global Impression–Bipolar Disorder scale (CGI-BP) (15);
(b) a stable course of illness in the past year, allowing low intensity of treatment with a maximum of four consultations with the psychiatrist or nurse per year;
(c) insufficient command of the Dutch language;
(d) inability or unwillingness to give informed consent.

**Masking**

Given the nature of the intervention, masking of participants and professionals for the assigned treatment condition was not possible. Given the cluster randomisation patients were aware of the condition their treatment team was assigned to when their informed consent was asked. It was not possible to ensure masking of the research assistants who interviewed patients. In order to prevent bias, information about the course of illness was obtained by patient self-report via an interview using the strict format of the retrospective National Institute of Mental Health Life Chart (16).
Chapter 2. Collaborative care for patients with bipolar disorder: Randomised controlled trial.

**Intervention**

The rationale of collaborative care is that patients with chronic and intermittent disorders benefit from treatments in which the collaboration between patient and professionals is structured systematically and in which the self-management skills of the patient are enhanced (17). Within the CC framework different treatment can be offered. Our programme consisted of:

(a) The formation of a collaborative care team, including at least the patient, the nurse and the psychiatrist, where all decisions concerning treatment and care were made. If the patient consented, a family member or friend was invited to join the team. The team members met at 3 months, 6 months and 12 months. Coordination of care was provided by the mental health nurse in the role of care manager.

(b) Contracting, aiming at achieving agreement within the collaborative care team on the most important problems and treatment activities. A treatment plan was made, formulated as a contract, in which goals and treatment activities were recorded.

(c) Working with the treatment plan was based on systematic care needs assessment, making use of the Camberwell Assessment of Needs (CAN) (18). The execution and outcomes of the treatment plan were systematically monitored and evaluated by the collaborative care team.

(d) Psycho education (19;20), provided to patients and caregivers together in six sessions of 2 h each.

(e) Problem-solving treatment (PST) (21;22). PST is a brief (six-sessions) therapy, based on the principles of cognitive-behavioral therapy, applied according to a strict protocol and aimed at improving practical skills to solve everyday problems. The rationale of PST is that by increasing problem-solving skills, patients’ understanding of the relationship between everyday problems and mood increases, resulting in the experience of regaining control over their own life.

(f) Mood charting by means of the prospective Life Chart Method (16).

(g) Recognition of early warning signs of relapse, followed by predefined interventions as defined in a relapse prevention plan (23;24).

(h) Pharmacotherapy and somatic care, continued as appropriate. In addition, in the collaborative care team continuous monitoring of effects took place, with specific attention to medication adherence.
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**Procedures**

A manual-based training program was developed by the investigators with the assistance of an expert panel, consisting of five expert nurses, a psychiatrist, a patient and a family member. Nurses in the experimental condition received this 3-day training program, with 2 weeks in between each training day. The training aimed at enhancing knowledge about the interventions to be delivered, as well as skills training to perform the interventions adequately. Since PST was a new intervention for all nurses, a total of 6 h training in this skill was offered by an experienced, specialised PST trainer. During the entire training in collaborative care the importance of programme fidelity was emphasised, as well as dilemmas that might occur between strict programme fidelity and flexible patient-tailored care. Fifteen nurses were trained in collaborative care. Four psychiatrists participated in part of the training, receiving an overview of the rationale and the various elements of the collaborative care intervention, as well as information about the study procedures. The trained teams in the experimental condition performed collaborative care throughout 1 year. The nurses were primarily responsible for the coordination and continuity of treatment. Supervision of PST was given by the trainer. The primary investigator (N.V.) coached the nurses for the whole duration of the study. These supervisory contacts were offered both individually by telephone and in group sessions in the treatment facility of the teams. A mean number of coaching contacts of 15.4 (range 11-20) was provided. Nurses in the TAU condition received no training, coaching, or supervision.

**Measures**

Measurements were performed at baseline (T0) and after 6 months (T6) and 12 months (T12). At baseline, demographic data, illness history, diagnosis, illness characteristics and current treatment were recorded by both patient and the treating psychiatrist using the patient and clinician versions of the QBP-NL (14). Course of the illness and recurrence of mood episodes were assessed with the Retrospective Life Chart Method (LCM) during a telephone interview by a research assistant (16). Patients were asked to rate retrospectively their average mood, in each consecutive month, over the past 6 months, scores are based on the severity of mood symptoms and the associated degree of functional impairment. At T0, the 6 months preceding study entry were assessed. The LCM consists of a scale for manic symptoms (+1 to +3), and a scale for depressive symptoms (-1 to -3). The score of 0 indicates a euthymic state. Scores of +/- 2, and +/- 3 refer to syndromal episodes, whereas scores of +/- 1 refer to subthreshold symptoms, with only mild functional impairment. Severity of depressive symptoms during the last week was measured with the 16-item self-report version of the Quick Inventory for Depressive Symptomatology (QIDS) (25). Symptoms of mania during the past week were assessed with the Altman Self-Rating Mania Scale (ASRM) (26). Medication adherence
was assessed with the ten-item Drugs Attitude Inventory (DAI-10) (27); all ten items have a dichotomous outcome: adherent yes/no.

Nurses in the experimental group completed a fidelity checklist during the study, in order to register the collaborative care elements actually delivered. To avoid contamination bias, nurses in the control condition were not asked to fill in this checklist. Care consumption was measured in both groups with the Trimbos/iMTA questionnaire for Costs associated with Psychiatric Illness (TiC-P), to register elements of treatment actually delivered in both groups (28).

Statistical analysis
Our primary outcomes were the duration of symptoms (measured longitudinally with the retrospective LCM), and the severity of symptoms at follow-up (measured at three time points with the QIDS and the ASRM). Independent $t$-tests for continuous variables, and $\chi^2$ statistics for categorical variables were carried out to compare the two groups on baseline characteristics. These analyses were also performed to compare participants withdrawing from and completing the trial on baseline characteristics, in the total sample. First, means and standard deviations were calculated for the primary outcome variables, (months spent with depression or mania, and severity of symptoms) on the three measurements. Next, data were analyzed according to the intention to treat (ITT) principle. Differences in outcome between collaborative care and TAU were evaluated by means of linear mixed-model analysis for fixed and random effects. This method is statistically rigorous, allows for longitudinal testing of continuous data and is able to handle missing observations due to patients leaving the study. Our analyses were performed with a random intercept, and with condition and time as fixed effects.

A group x time-interaction term was entered into the model to test for differences in treatment effects over time. Next, effect sizes were calculated, based on the estimated differences between T0 and T6, and between T0 and T12, between groups, based on pooled pretest standard deviations (29). The analyses were extended using multilevel analyses that take the nesting of measurements into account. We also took into account to what extent patients were exposed to the intervention, by conducting a per protocol analysis. Finally, we repeated all analyses described above for the secondary outcome medication adherence.

Power calculation
The a priori power calculation concerned the comparison of outcomes from the experimental and control condition at T12, compared to T0. By the time we planned this study, we were not able to detect studies sufficiently comparable to ours to estimate the expected effect size. Therefore, we used an effect size of Cohen’s $d=0.5$, because this is considered to be a clinically relevant effect. With
an \( \alpha = 0.05 \) (two-tailed), and a power \((1-\beta)\) of 0.80, the required sample size was 63 patients per arm of the trial. In case of cluster randomization the rule of thumb is to add 25\% to this amount, bringing the total to \(2 \times 79\). Taking into account an expected drop out of 30\%, a sample of 103 patients in each group was needed.

**Results**

A total of 138 participants were included (Fig. 1). Initially, informed consent was obtained from 71 participants in the intervention group, and from 82 participants in the control group. However, due to organizational circumstances unrelated to the study, two teams with in total 15 patients withdrew from the experimental arm of the study, leaving 56 patients in the collaborative care arm and 82 in the control arm. After the baseline measurement 13 patients in the collaborative care condition stopped the allocated treatment, of whom 2 continued to participate in the study, leaving 11 patients not assessed at T12. Four patients in the control condition stopped allocated treatment, of whom 2 continued participation in the study. In total 21 participants were lost to follow-up (controls \(n=10\); CC \(n=11\)). Of the 45 patients in the collaborative care group at T12, 43 received the allocated intervention, and of the 72 patients who completed T12 in the TAU-group 70 received the allocated intervention. When the baseline characteristics of patients who left the study were compared with those who continued, these groups differed significantly only with respect to family history of bipolar disorder. Logistic regression was conducted to determine whether illness characteristics in patients randomised to collaborative care predicted withdrawal from the care programme. Only longer duration of mania symptoms in the 6 months preceding baseline predicted stopping with collaborative care.

Since the outcomes of multilevel analyses and analyses that ignore nesting were not significantly different, we present the analyses ignoring nesting. Moreover, as no significant differences were found between the results of ITT v. per protocol analyses, we report ITT only. In the final analyses, sample sizes may differ per questionnaire, due to the fact that not all measurements were entirely completed by the remaining participants. At T12, measurements of 117 patients (85\%) were included in the analyses (intervention: 80\%; control: 88\%, \(p=.3\)).

Sample characteristics are summarized in table 1. The mean duration of illness of the patients included was 21 years. At baseline, a few significant differences existed between the experimental and control conditions. Participants randomised to collaborative care reported a higher number of months with depressive symptoms during the 6 months prior to baseline than patients in the control group (mean 3.2 months, s.d.=2.1 v. mean 2.3 months, s.d.=2.2; \(p=0.02\)). Patients in the experimental condition had a greater severity of depressive symptoms than the control group in the week preceding baseline (mean QIDS score 10.5, s.d.=5.5, v. 8.1, s.d.=5.1; \(p=0.01\)).
Figure 1. Flow of participants through the trial
### Table 1. Sample characteristics

<table>
<thead>
<tr>
<th></th>
<th>Control condition N=82</th>
<th>Collaborative care N=56</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Socio demographic characteristics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, mean (sd)</td>
<td>44.7 (11.3)</td>
<td>46.8 (9.8)</td>
<td>0.3</td>
</tr>
<tr>
<td>Gender female, n (%)</td>
<td>49 (60)</td>
<td>39 (70)</td>
<td>0.1</td>
</tr>
<tr>
<td>Partner, yes, n (%)</td>
<td>45 (55)</td>
<td>36 (67)</td>
<td>0.2</td>
</tr>
<tr>
<td>Total years of education, mean (sd)</td>
<td>16.9 (3.3)</td>
<td>14.2 (3.5)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td><strong>Clinical characteristics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diagnosis, n (%)</td>
<td></td>
<td></td>
<td>0.1</td>
</tr>
<tr>
<td>Bipolar disorder I</td>
<td>49 (61)</td>
<td>39 (70)</td>
<td></td>
</tr>
<tr>
<td>Bipolar disorder II</td>
<td>28 (35)</td>
<td>11 (20)</td>
<td></td>
</tr>
<tr>
<td>Bipolar disorder NOS</td>
<td>4 (5)</td>
<td>2 (4)</td>
<td></td>
</tr>
<tr>
<td>More than 20</td>
<td>19 (26)</td>
<td>14 (32)</td>
<td></td>
</tr>
<tr>
<td>Age of onset, mean (sd)</td>
<td>23.9 (10.0)</td>
<td>23.5 (11.6)</td>
<td>0.8</td>
</tr>
<tr>
<td>Duration of illness, mean (sd)</td>
<td>20.5 (11.0)</td>
<td>23.0 (12.8)</td>
<td>0.2</td>
</tr>
<tr>
<td>Family history, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td>48 (59)</td>
<td>31 (55)</td>
<td>0.7</td>
</tr>
<tr>
<td>Bipolar disorder</td>
<td>21 (26)</td>
<td>21 (38)</td>
<td>0.2</td>
</tr>
<tr>
<td>Suicide or suicide attempts</td>
<td>12 (15)</td>
<td>10 (18)</td>
<td>0.6</td>
</tr>
<tr>
<td>Alcohol use disorder</td>
<td>26 (32)</td>
<td>17 (30)</td>
<td>1.0</td>
</tr>
<tr>
<td><strong>Recent course of illness, at baseline</strong></td>
<td></td>
<td></td>
<td>0.8</td>
</tr>
<tr>
<td>Most recent episode in last year, n(%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(hypo-) manic</td>
<td>21 (27)</td>
<td>11 (22)</td>
<td></td>
</tr>
<tr>
<td>Depressive</td>
<td>42 (54)</td>
<td>29 (58)</td>
<td></td>
</tr>
<tr>
<td>No episode</td>
<td>15 (19)</td>
<td>10 (20)</td>
<td></td>
</tr>
<tr>
<td>Nr of months with depressive symptoms in past 6 months, LCM, mean (sd)</td>
<td>2.3 (2.2)</td>
<td>3.2 (2.1)</td>
<td>0.02</td>
</tr>
<tr>
<td>Nr of months with manic symptoms in past six months, LCM, mean (sd)</td>
<td>1.0 (1.5)</td>
<td>1.0 (1.5)</td>
<td>1.0</td>
</tr>
<tr>
<td>Current severity of depression in past week, QIDS, mean(sd)</td>
<td>8.1 (5.1)</td>
<td>10.5 (5.5)</td>
<td>0.01</td>
</tr>
<tr>
<td>Current severity of mania in past week, ASRM, mean (sd)</td>
<td>1.8 (2.4)</td>
<td>2.3 (3.8)</td>
<td>0.4</td>
</tr>
</tbody>
</table>

**LCM:** Life Chart Method.
**QIDS:** Quick Inventory of Depressive Symptoms.
**ASRM:** Altman Selfrating Mania Scale.
*number of respondents differs slightly among measurements.*
Furthermore, patients randomised to collaborative care on average had a lower educational level than patients in the control condition (mean years of education 14.2, s.d.=3.5, vs. 16.9, s.d.=3.3; \( p<0.01 \)).

Concerning treatment characteristics at baseline, we found that several elements of collaborative care were already provided to a considerable number of patients in both conditions. Teams in both conditions worked with a Life Chart in almost half of the cases (intervention group 43%, control group 43%, \( \chi^2 \) (1df) = 0.005, \( p=.2 \)); relapse prevention plans were present in more than half of the cases (intervention 52%, controls 63%, \( \chi^2 \) (1df) = 1.6, \( p=.2 \)). In the 5 years prior to the trial, significantly more patients in the control condition than patients in the experimental condition had participated in a psychoeducation course (intervention group 37%, control group 64%, \( \chi^2 \) (1df) = 9.6, \( p=.003 \)). In two-thirds of cases one or more relatives were involved in treatment (CC 67%; controls 69%, \( \chi^2 \) (1df)=1.06, \( p=.9 \)). None of the teams had provided PST to their patients. The mean number of consultations with a nurse or psychiatrist in the 3 months preceding baseline did not differ between the two groups (intervention 5.8, s.d.=5.5, vs. controls 5.4, s.d.=6.3; \( p=.8 \)).

**Primary outcomes**

Table 2 shows observed means and standard deviations of number of months spent with manic or depressive symptoms, as well as severity of symptoms. Table 3 shows the results of mixed-models analyses. After 6 months patients in collaborative care demonstrated a larger reduction in the number of months with depressive symptoms than patients in the TAU group, with a medium effect size (\( z=-2.6, \ p=0.01, \ d=0.5 \)). After 12 months this reduction was even larger (\( z=-3.1, \ p=0.002, \ d=0.7 \)). Severity of depressive symptoms improved more after 12 months in patients who received CC, compared to patients treated as usual (\( z=-2.9, \ p=0.004, \ d=0.4 \)). There were no significant differences between the two conditions in time with manic symptoms or in change in severity of manic symptoms over 12 months.

We conducted sensitivity analyses, adjusting for all outcomes that differed at baseline, to investigate the impact of these baseline differences on the dependent variables (30;31). Both the effect of collaborative care at T12 on duration of depressive symptoms (\( z=-2.1, \ p=0.04, \ d=0.4 \)) and severity of depressive symptoms remained significant (\( z=2.2, \ p=0.03, \ d=0.3 \)). However the effect on duration of symptoms at T6 lost significance (\( z=-1.5, \ p=0.1, \ d=0.3 \)).
**Medication adherence**

No differences were found between treatment conditions in change in medication adherence between baseline and T6 ($z=0.3$ (238.3 df); $p=0.8$) nor between baseline and T12 ($z=0.2$ (237.8 df); $p=0.8$).

**Implementation of collaborative care**

After twelve months almost 80% of patients randomised to CC reported using a relapse prevention plan; 84% had been following a psychoeducation course; 55% used a Life Chart; 86% of relatives was involved in treatment; 72% had received one or more sessions of PST. The total number of contacts with mental health care providers did not differ between patients in the control group compared to patients who received collaborative care.

**Table 2. Observed mean scores (and standard deviations) of number of months spent with mania or depressive symptoms and severity of symptoms.**

<table>
<thead>
<tr>
<th></th>
<th>Control N=80*</th>
<th>CC N=56*</th>
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<tbody>
<tr>
<td></td>
<td>Mean (sd)</td>
<td>Mean (sd)</td>
</tr>
<tr>
<td>Number of months with manic symptoms, LCM</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Between 6 months before baseline and T0</td>
<td>1.0 (1.5)</td>
<td>1.0 (1.5)</td>
</tr>
<tr>
<td>Between T0 and T6</td>
<td>0.8 (1.5)</td>
<td>1.1 (1.8)</td>
</tr>
<tr>
<td>Between T6 and T12</td>
<td>0.5 (1.2)</td>
<td>0.4 (1.1)</td>
</tr>
<tr>
<td>Number of months depressive symptoms, LCM</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Between 6 months before baseline and T0</td>
<td>2.3 (2.2)</td>
<td>3.2 (2.1)</td>
</tr>
<tr>
<td>Between T0 and T6</td>
<td>2.2 (2.4)</td>
<td>2.0 (2.3)</td>
</tr>
<tr>
<td>Between T6 and T12</td>
<td>2.0 (2.3)</td>
<td>1.5 (2.1)</td>
</tr>
<tr>
<td>Severity of manic symptoms, ASRM</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T0</td>
<td>1.8 (2.4)</td>
<td>2.3 (3.8)</td>
</tr>
<tr>
<td>T6</td>
<td>2.2 (2.7)</td>
<td>2.0 (2.8)</td>
</tr>
<tr>
<td>T12</td>
<td>1.5 (2.3)</td>
<td>1.9 (2.4)</td>
</tr>
<tr>
<td>Severity of depressive symptoms, QIDS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T0</td>
<td>8.1 (5.1)</td>
<td>10.5 (5.5)</td>
</tr>
<tr>
<td>T6</td>
<td>8.3 (5.3)</td>
<td>9.8 (5.9)</td>
</tr>
<tr>
<td>T12</td>
<td>8.2 (6.0)</td>
<td>8.4 (5.3)</td>
</tr>
</tbody>
</table>

LCM: Life chart Method.  
ASRM: Altman Selfrating Mania Scale, score 1-5, manic symptoms in past week.  
QIDS: Quick Inventory of Depressive Symptoms, score 0-27, depressive symptoms in past week.  
T0: baseline assessment; T6: 6 months assessment; T12: 12 months assessment.  
*Number of respondents varies slightly among measurements.
Table 3. Test statistics and effect sizes of the condition by time interaction terms for number of months with symptoms and severity of symptoms, from mixed model regression analysis.

<table>
<thead>
<tr>
<th></th>
<th>z</th>
<th>p</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of months with manic symptoms</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cond*T6</td>
<td>0.8</td>
<td>.4</td>
<td>0.2</td>
</tr>
<tr>
<td>Cond*T12</td>
<td>-0.3</td>
<td>.8</td>
<td>0.1</td>
</tr>
<tr>
<td><strong>Number of months with depressive symptoms</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cond*T6</td>
<td>-2.6</td>
<td>.01</td>
<td>0.5</td>
</tr>
<tr>
<td>Cond*T12</td>
<td>-3.1</td>
<td>.002</td>
<td>0.7</td>
</tr>
<tr>
<td><strong>Severity manic symptoms</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cond*T6</td>
<td>-1.1</td>
<td>0.3</td>
<td>0.2</td>
</tr>
<tr>
<td>Cond*T12</td>
<td>-0.3</td>
<td>0.8</td>
<td>0.1</td>
</tr>
<tr>
<td><strong>Severity depressive symptoms</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cond*T6</td>
<td>-1.4</td>
<td>0.2</td>
<td>0.2</td>
</tr>
<tr>
<td>Cond*T12</td>
<td>-2.9</td>
<td>0.004</td>
<td>0.4</td>
</tr>
</tbody>
</table>

Number of months with symptoms: Measured with retrospective Life chart.

Z: test-statistic concerns the fixed effects regression parameters of the interaction conditionXtime in a mixed effects regression model.

T6=6 months assessment, T12=12 months assessment.

Severity of manic symptoms: Measured with the ASRM.

Severity of depressive symptoms: Measured with the QIDS.

P-value concerns the z-statistic.

Effect size: Between groups, using pooled pretest standard deviation.
Discussion
Although treatment for bipolar disorder is widely available in The Netherlands, many patients have persistent symptoms that have a considerable impact on their daily functioning and quality of life. Depressive symptoms are especially debilitating and naturalistic studies have shown that in general depression is the more difficult to treat condition of bipolar disorder (4;32). The majority of previous collaborative care studies have shown positive effects on manic symptoms, but no effects on depressive symptoms (8-11;33;34). For this reason we designed an intervention aimed not only at manic, but specifically at depressive symptoms by adding PST to the programme, which in previous studies has proven to be an effective treatment for (non-bipolar) depression. Patients randomised to collaborative care showed more improvement, both in terms of the proportion of time they reported depressive symptoms and in terms of depression severity at the 12-month follow-up. Collaborative care had no effect on symptoms of mania and no effect on medication adherence.

Collaborative care
Collaborative care has been tested in several treatment settings and in a diversity of patient populations (17). Most studies found collaborative care to be effective, albeit with small effect sizes (35;36). Most studies that investigated collaborative care in patients with bipolar disorder found improvements on manic, but not on depressive symptoms. In one study on the effects of collaborative care in bipolar patients with cardiovascular risks, post-hoc analysis in a subgroup of patients with elevated cardiovascular risks (34) showed a decrease in depressive symptoms. In contrast to most studies, we found a clear effect on depressive symptoms, with moderate effect sizes. Although it is not possible to assess which specific elements of collaborative care account for this effect, we presume PST to be important. No other collaborative care programme for bipolar disorder has included this treatment. High levels of heterogeneity exist between studies concerning the effect of PST on depressive symptoms; however, a recent meta-analysis suggested that PST is as effective as pharmacological therapy and as other psychosocial therapies in decreasing depressive symptoms (37). One might think that our finding of the effect of collaborative care on bipolar depression may be mainly due to PST and that, perhaps, PST could also be effective on bipolar depression when offered as a stand-alone intervention. Testing this would require a separate study, which may be worthwhile. We hypothesize however, that the effect of collaborative care is due to the combination of interventions in the program.

It is striking that no effect was found on symptoms of mania. This could be explained by the limited sample size. Research shows that these symptoms are less prevalent than depression, occurring on average 10% of the time (2); as a consequence the chance of finding these symptoms in a relatively small sample is limited. In our sample only a few patients experienced mania symptoms.
During the 12 months of the trial the mean number of months with symptoms of mania in the total sample was 1.4 (s.d. = 2.3), so patients spent on average approximately 10% of the time with mania. Only 15 patients reached the cut-off point indicating a high probability of manic or hypomanic condition on the ASRM scale (>6). Given these small numbers we presume that our study did not have enough power to find differences on time spent with mania symptoms, or the severity of manic symptoms.

**Sample size**

Treatment as usual in the Netherlands is assumed to be of relatively high quality, which probably decreased the chance of finding significant effects with our sample size. Adding PST, however, probably increased the strength of our collaborative care program, thus increasing the chance of finding significant effects. With our sample size, based on an effect size of Cohen’s $d=0.5$, we were able to detect significant differences between conditions, concerning the decrease of depressive symptoms after a year, with effect sizes ranging from 0.4 to 0.7 (see Table 3). Therefore, retrospectively, we still assume our *a priori* power analysis to be adequate for this study. The effect sizes we found are relatively high when compared with a recent review by Miller *et al.*, who found small effect sizes (.33) for collaborative care programs across mental health conditions (36).

**Treatment as Usual**

Given the level of usual care in The Netherlands, we expected that some elements of collaborative care would be provided in TAU in non-systematic ways. At baseline we assessed the presence of collaborative care elements in both treatment conditions. The level of care was relatively high in both groups. Given this high level of care at baseline, the room for improvement due to CC was limited. The fact that significant differences were nonetheless found is encouraging for further improvement of quality of care when interventions are planned and applied in a structured format. Our structured collaborative care programme with accompanying training may have contributed to a higher quality of (nursing) care, compared with probably less systematically performed TAU (38).

**Strengths and limitations**

The quality of this study is enhanced in several ways. First, we included the expertise of patients, informal caregivers, psychiatrists and nurses during the process of developing the collaborative care intervention. Second, implementation of the intervention was optimised by structured implementation of collaborative care in the experimental group, with 3 days of training, individual coaching for the nurses, and programme fidelity assessments. Implementation succeeded to a satisfactory degree; however, it should be noted that the number of patients working with the Life
Chart was low. Possible explanations for the latter finding are that patients experienced this long-lasting, daily home assignments as a burden, and also that nurses occasionally failed to stress the importance of the Life Chart and support the patient in completing it. This is in line with the report of Goossens et al. (38), who studied the activities nurses actually perform, and concluded that although nurses state the Life Chart to be important, their care for patients with bipolar disorder lacks a systematic approach. Third, the total number of contacts with the nurse and psychiatrist did not differ between the two treatment conditions, which makes the assumption plausible that extra costs for the execution of collaborative care would be limited. Finally, attrition of respondents was limited, since 85% of respondents completed the assessments.

The first limitation of our study is that baseline differences concerning illness characteristics were present between treatment conditions. This might be explained by our method of including participants. After having obtained consent to approach eligible patients, the investigator provided them with more details about the study. When informed about the collaborative care program, some patients declined participation, expecting that this program would be too intensive for them given their care needs. These are probably patients with less severe symptoms which would explain why the collaborative care group reported more depressive symptomatology at baseline. We showed, however, that after adjusting for these differences, the results remained. A second limitation was the fact that masking was not possible in the Life Chart interviews. However, the retrospective Life Chart is highly structured, and was administered on the basis of patient’s self-report, not the clinical judgment of the interviewer, which limits the possibility of bias. The third limitation was the withdrawal of two teams in the collaborative care condition, due to organizational circumstances unrelated to this study. Although there is no reason to assume that this has biased the results, it did reduce the statistical power of analyses.

We aimed to study the potential benefits of collaborative care for patients with bipolar disorder in actual clinical practice, which enables us to generalise our findings to real life, but also implied that full implementation of CC could not be achieved in every patient. Incomplete implementation may have led to underestimation of the effects of collaborative care. Moreover, collaborative care was tailored to the specific needs of the patient and his or her caregiver, resulting in not all elements of the program being delivered to all patients. Still, the overall implementation of the collaborative care program was successful to a satisfactory degree. In the collaborative care group at T12, there was a clear increase in the use of a relapse prevention plan, the use of a Life Chart, having followed psychoeducation and the involvement of relatives in treatment, compared with baseline. Problem-solving treatment showed the best degree of implementation, which supports the presumption that it was primarily accountable for the effect we found on depression.
Conclusions

This pragmatic trial is the first to evaluate the effectiveness of collaborative care for patients with bipolar disorder, including specific interventions aimed at improving depressive symptoms. During the study, patients randomised to collaborative care spent less time with depressive symptoms compared with patients in the control condition. Furthermore, a decline of severity of depressive symptoms was found in patients who received collaborative care. No difference was found in mania symptoms between groups, nor in medication adherence. Although it is not possible to determine which components of collaborative care were responsible for the results, we assume that PST has significantly contributed to these effects. Moreover, prompting mental health care professionals to deliver care in a more systematic way may have contributed to the effectiveness of this intervention.
Chapter 2. Collaborative care for patients with bipolar disorder: Randomised controlled trial.

Reference List


Chapter 2. Collaborative care for patients with bipolar disorder: Randomised controlled trial.


(36) Miller CJ, Grogan-Kaylor A, Perron BE, Kilbourne AM, Woltmann E, Bauer MS. Collaborative chronic care models for mental health conditions: cumulative meta-analysis and
