General Introduction
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1. Bipolar disorder

Bipolar disorder (BD) is a complex and severe mood disorder, characterized by at least one episode with (hypo-) manic symptoms, in most cases alternated with depressive episodes. Lifetime prevalence of BD is estimated at 1.4-2.8 % of the general population (1-4). The course of the disorder shows high heterogeneity among patients. Most patients experience euthymic periods between symptomatic episodes (table 1). A euthymic period is a relatively stable mood state, in which a patient does not meet the diagnostic criteria for a mood period. Many patients however suffer from sub threshold symptoms during these euthymic periods, despite adequate treatment, of which sub threshold depressive symptoms are most common (5). Age of onset differs between patients, with in most cases a first episode of the disorder between 15 and 30 years of age. Euthymic periods between mood episodes may last up to several years. In some patients euthymic periods are only very brief, and mood episodes occur rapidly (rapid cycling) (5). Severity of symptoms, as well length of episodes, show large variability between patients. On average patients experience more time with depressive symptoms than with manic symptoms (6). Psychiatric co-morbidities occur in about two-thirds of patients with BD, most frequently anxiety disorder, substance use disorders (7), and personality disorders (8). BD is associated with an increased mortality, by suicide, and by medical comorbidities, such as cardiovascular disease, diabetes, chronic obstructive pulmonary disease and unintentional injuries (4). Patients with BD have a shortened life expectancy of approximately 9.0 years when compared with the general population. Suicide risk is estimated at 10-fold among women and 8-fold among men with BD (4).

BD is associated with impaired functioning and quality of life in several domains of life, such as work, social relations and cognitive functioning (5;7;9-12). Only 40% of patients maintain their pre-morbid level of functioning. Functional impairment may persist during euthymic periods. Enhanced functioning has been reported in patients during hypomanic episodes. Close relatives and friends of
patients with BD experience a serious burden caused by the bipolar disorder and its consequences in daily life (13-15), and many of them suffer from medical or psychiatric problems themselves (16).

In the current classification systems, the following main types of bipolar disorder have been distinguished (17).

1. Bipolar I Disorder, in which the primary symptom presentation is manic, or rapid (daily) cycling episodes of mania and depression.
2. Bipolar II Disorder, in which the primary symptom presentation is recurrent depression accompanied by hypomanic episodes.
3. Bipolar Disorder Not Otherwise Specified, in which manic and/or depressive symptoms are significant but do not meet formal criteria for BP-I or BP-II
4. Cyclothymic Disorder, a chronic state of cycling between hypomanic and depressive episodes that do not meet the diagnostic criteria for bipolar disorder type I or II.
Table 1. Diagnostic criteria of mania, hypomania and depression (17)

<table>
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<tr>
<th>Manic episode:</th>
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<tr>
<td>A distinct period of abnormally and persistently elevated, expansive, or irritable mood, lasting</td>
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<td>at least 1 week (or any duration if hospitalization is necessary), and at least three of the</td>
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<td>following symptoms have persisted (4 if the mood is only irritable) and have been present to</td>
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<td>a significant degree:</td>
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<td>1. Increased self-esteem or grandiosity</td>
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<td>2. Decreased need for sleep (e.g., feels rested after only 3 hours of sleep)</td>
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<td>3. More talkative than usual or pressure to keep talking</td>
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<td>4. Flight of ideas or subjective experience that thoughts are racing</td>
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<td>5. Distractibility (i.e., attention too easily drawn to unimportant or irrelevant external stimuli)</td>
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<td>6. Increase in goal-directed activity (either socially, at work or school, or sexually) or</td>
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<td>psychomotor agitation</td>
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<td>7. Excessive involvement in pleasurable activities that have a high potential for painful</td>
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<td>consequences (e.g., engaging in unrestrained buying sprees, sexual indiscretions, or foolish</td>
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<td>business investments)</td>
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<th>Hypomania episode:</th>
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<td>A milder state of mania in which the symptoms are not severe enough to cause marked</td>
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<td>impairment in social or occupational functioning or need for hospitalization, but are sufficient</td>
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<td>to be observable by others.</td>
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<th>Major depressive episode:</th>
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<tr>
<td>Depressed mood and/or loss of interest or pleasure in life activities for at least 2 weeks and</td>
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<td>at least five of the following symptoms that cause clinically significant impairment in social,</td>
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<td>work, or other important areas of functioning almost every day:</td>
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<tr>
<td>1. Depressed mood most of the day.</td>
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<td>2. Diminished interest or pleasure in all or most activities.</td>
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<td>3. Significant unintentional weight loss or gain.</td>
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<td>4. Insomnia or sleeping too much.</td>
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<td>5. Agitation or psychomotor retardation noticed by others.</td>
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<td>6. Fatigue or loss of energy.</td>
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<td>7. Feelings of worthlessness or excessive guilt.</td>
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<tr>
<td>8. Diminished ability to think or concentrate, or indecisiveness.</td>
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2. Treatment of patients with bipolar disorder in The Netherlands

We assume that in The Netherlands treatment for patients with severe mental disorders, including bipolar disorder is of sufficient quality, however detailed data on care as usual for bipolar disorder are to be awaited (18). In The Netherlands, mental healthcare is easily accessible for patients, since most costs are paid for by healthcare insurance, and the system of mental health care is well developed in comparison to many other countries. Continuity of care is recognized by most professionals working in mental health organizations to be an important criterion of good care. The concept of continuity of care (19) contains various elements, such as longitudinality, individuality, comprehensiveness, flexible consistency, stability & relationship and accessibility. To achieve this, teams are well organized, multidisciplinary, thus providing a basis for systematic collaboration. Nurses are well educated, and the number of Advanced Nurse Practitioners (ANP) is increasing. Empowerment of patients is valued as an important and positive development, and recovery (defined in short as ‘re-finding a meaning in life’) is viewed increasingly as an ultimate goal of treatment. Despite this, patients with BD often experience persistent symptoms and severe impairment in functioning and quality of life (20). International guidelines recommend a combination of treatment options, including pharmacotherapy, psycho-education, supportive treatment and psychotherapy. Despite the wide dissemination of these guidelines, there is doubt concerning the actual implementation, which is recognized as suboptimal (18;21). The preceding leads to the central problem definition in this thesis: Despite the availability of guidelines and treatment, many patients with bipolar disorder experience persistent symptoms and impaired functioning and quality of life.

3. Mental health nursing

In The Netherlands, a significant part of mental health care is provided by mental health nurses. They offer care primarily aimed at supporting patients to cope with the illness, and with the consequences of the illness in daily life. In practice, many patients with bipolar disorder who are treated by mental health teams receive care from a nurse, next to pharmacological interventions monitored by a psychiatrist. This nursing intervention is often referred to as ‘structuralizing and supportive treatment’ and monitoring continuity of care is part of the nurse’s tasks. The quality of the working alliance between patient and nurse is an important element of continuity of care. A good working alliance is found to be positively related to various patient outcomes, such as time spent depressed (22), number of suicidal ideations and treatment adherence (23;24). Nurses are to a large extent free to decide what elements of care they provide to a patient, as are other mental health care providers. They still do not have many evidence-based interventions and appropriate tools at their disposal to guide their work, despite the fact that the body of knowledge on effective psychosocial interventions for patients with bipolar disorder is growing. An additional problem is that nurses tend not to use
available guidelines and intervention tools in their daily work (25-27). This may result in suboptimal quality of care (27).

To investigate to what extent teams throughout The Netherlands met criteria of collaborative care programs or provided self-management interventions, the principal investigator (NV) visited outpatient teams during the preparation phase of the trial described in this thesis. In a semi-structured interview with a nurse and a psychiatrist, a first impression was obtained of the elements of care provided to patients with BD, thus creating a picture of the level of care as usual. Team members were asked if the following elements of care were delivered to patients: use of a Life Chart, use of a Relapse Prevention Plan, having followed a Psycho education course, use of a treatment plan with personal goals of the patient, structured evaluations with the patient and a relative, having a relative invited to be structurally involved in the treatment, and Problem Solving Treatment (PST). As expected, teams appeared to differ to a large extent on these elements. All teams provided some, but not all, of these elements, in a not systematic way and not to all patients. PST was provided in none of the teams. Moreover, collaboration between various professionals was organized on an ad hoc basis, and patients or caregivers were seldom invited for treatment evaluations.

4. Bipolar disorder and benefits of treatment

In addition to these organizational factors that may negatively influence quality of treatment, characteristics of the disorder itself may be of influence on the effects of treatment. Patients in a depressive episode may withdraw from all activities and may not meet appointments with their care provider. Patients in a manic state often lack insight into the illness and may therefore be convinced not needing treatment. In general, non-adherence to treatment is a problem frequently occurring in patients with BD (28;29). Next to the need for psychiatric treatment, many patients with bipolar disorder are in need of somatic treatment (4). Even if patients adhere optimally to treatment, and care is organized to an optimal extent, many experience (sub-syndromal or syndromal) symptoms, or a decreased functioning and quality of life. Mechanisms explaining these phenomena are still lacking.

Effectiveness of various psychosocial interventions for patients with bipolar disorder have been described in two recent reviews (30;31). There is increasing evidence of the effectiveness of psycho-education interventions, as an adjunct to pharmacotherapy, and aiming at supporting the patient’s self-management of the disorder. Treatment focusing on improving acceptance of the disorder, and on enhancing awareness of early signs of relapse, appears to be effective. Other effective interventions are cognitive-behavioral therapy, interpersonal and social rhythm therapy, and family-focused treatment (30;31).
5. Chronic care and collaborative care programs

Some history

Almost two decades ago, in an attempt to enhance quality of care for chronic ill patients, Wagner (32) and Von Korff (33) pleaded for including the expertise of patients and their caregivers, since in chronic illness these are the primary experts (33). They reviewed effective programs for chronic illness, and described those features that appeared to account for the effects found on patient outcomes. They strongly advocated reforming healthcare programs to be able to promote patients’ self-care, with appropriate support from professional care. They developed a multi component intervention program, the Chronic Care Method (CCM), in which planned care is provided, based on guidelines. The CCM consisted of the following elements:

1. Practice redesign. This includes among others new definition of roles among team members.
   A care manager is designated who provides regular follow-up appointments to patients.

2. Patient education. Patients are supported in learning self-management skills.

3. Patients are offered psychosocial support, and patient participation is aimed at.
   Collaborative problem definition, collaborative goal-setting and planning of care, a continuum of self-management training, and active and sustained follow-up are important elements of care.

4. Expert system. Providers receive education that is needed to be able to provide high quality treatment. Decision support is given, e.g. in the form of a manual or protocol.

5. Information. Care providers receive information about 1st outcomes and quality of care, to be able to adapt treatment; 2nd moments that new steps in treatment are needed, as a reminder; 3rd content of treatment, in the form of consultation.

Although most chronic care or collaborative care programs are based on the Wagner model, the definitions differ, as do incorporated elements. However, agreement appears to exist on the Wagner elements to be the key features in these programs. Several collaborative care programs have been developed and implemented since, mainly in primary care, and mostly for depression (34) or somatic chronic disorders, such as diabetes (35;36). Still most CC programs for mental health disorders are implemented in primary care (37;38), and combine expertise of specialized (mental health) treatment with the care provided by the general practitioner. More recently, these programs have been extended to specialized mental health care, and so far with positive results, however, with small to medium effect sizes (39-41).

Collaborative care programs, the past decade

In the Netherlands, recently some CC-programs for patients with depression were implemented and studied for their effectiveness: in primary care, in occupational medical care settings, and in
hospitals in patients with somatic illnesses (42). Moreover, a CC-program was developed for patients with severe personality disorders, and tested in a multiple case-study in specialized mental health care in the Netherlands (43). These studies show promising results, and conclude CC adds to quality of care in chronic illness in several settings.

For patients with bipolar disorders, CC programs were firstly executed in specialized mental health care in the USA. Three research projects showed promising results with bipolar patients. Bauer et al.(44) implemented a CC model, the Life Goals Program, for patients with bipolar disorder and studied the effects in two randomized controlled trials. They found a significantly reduced number of weeks in manic episodes in the experimental group, but no effect was found on weeks depressed. Patients showed improved social functioning, quality of life, and treatment satisfaction. Total costs were similar in both groups. The Life Goals Program was extended by Kilbourne et al. (45-47), to address the many medical co-morbidities present in patients with bipolar disorder. Simon et al.(48) extended the Life Goals program with intensive outreaching nursing care. After two years, patients in the experimental group showed significant less severe manic symptoms, and these symptoms had a shorter duration, when compared to a control condition. No effect was found on depressive symptoms. Extra costs of this treatment were limited. In the Texas Medication Algorithm project, Suppes et al. (49) studied the effects of algorithms for pharmacotherapy for bipolar disorder, with added nursing care. Patients in the intervention group reported significant improvement of manic, but not depressive and psychotic symptoms.

More recently, as studies showed that the prevalence of medical co-morbidities in patients with BD is of major impact, collaborative care programs have been extended to the treatment for medical conditions next to psychiatric disorders (47;50;51). In one trial to study the effect of CC on bipolar patients with cardiovascular risks, no effects were found, although in a small subsample with high Body Mass Index and high blood pressure, a significant effect was found on both functioning and depressive symptoms (51). In another trial, patients in the CC group showed improvement on both blood pressure and manic symptoms (52). It is striking that all published studies reported improvement of manic but not depressive symptoms, except for the one small trial in which depressive symptoms improved in a subsample (51). The current study, described in this thesis, will be the first to implement CC for patients with bipolar disorder outside the USA. To specifically address depressive symptoms, we added Problem Solving Treatment (PST) to our CC-program, since PST has been found to improve depressive symptoms (53).

To summarize, CC is a structured and systematic program, providing evidence-based interventions, aiming at improving self-management skills. A number of studies showed positive results in patients with bipolar disorder. In CC, the collaboration between all professionals involved is enhanced, and the patient and his or her relatives are included in collaboration and are assigned with
an active role in treatment. The nurse has a central coordinating role in this program in her function as care-manager, as such providing the majority of the interventions to patient and relatives. Patient needs and outcomes are monitored over time, and treatment is adapted to these outcomes. In addition, we expect CC to offer good possibilities to strengthen the position of the nurse in the care process for patients with a bipolar disorder, both at the organizational and content levels.


Successful implementation of new interventions in healthcare remains a challenging task (54-56). Although multidisciplinary treatment guidelines are increasingly being developed, their implementation is still problematic. Once evidence is available for the efficacy of an intervention, it is of major importance to intensively guide the process of implementation. To enable adoption of a complex and composite intervention program in clinical practice, various interventions need to be performed by several parties. Replicating Effective Programs framework (REP) is a method that can be used to enhance implementation of such complex interventions (57). The framework was developed for interventions to get HIV/AIDS prevention programs implemented in practice. The framework specifies steps needed to maximize fidelity and allows opportunities for flexibility. REP consists of four phases: pre-conditions (e.g., identifying need, target population, and suitable intervention), pre-implementation (e.g., intervention packaging), implementation (e.g., package dissemination, training, technical assistance, and evaluation), and maintenance and evolution (e.g., preparing the intervention for sustainability). The key components of REP (intervention packaging, training, technical assistance, and fidelity assessment) are crucial to the effective implementation of effective interventions in health care. We chose to use REP for the implementation of our CC-program in the experimental condition of the RCT.

7. Studying interventions

Over the past 60 years, in scientific medical research, the ‘gold standard’ to test effectiveness of an intervention is a randomized controlled trial (RCT) (58). This is supposed to be the best method to obtain true, objective and generalizable findings. Explanatory trials measure efficacy of an intervention, which is the benefit that a treatment produces under ideal circumstances. In a pragmatic trial, complex interventions can be studied (58), in which the effectiveness of an intervention is measured, that is, the benefit of the treatment in routine clinical practice. In case of implementation and evaluation of a composite intervention program, it can not to be established which part of the intervention is accountable for the results. The central question to be answered is: Which treatment shows the best results in these particular clinical circumstances of the patients in the study?
Next to research questions about efficacy or effectiveness of interventions on the level of patient groups, many researchers are interested in experiences of individuals. Therefore, since the 1960’s qualitative research methods have been developed. Within these qualitative methods, a wide range of methodological measures was developed, to ensure quality of the study and the credibility of the outcomes. In the current thesis, results of both a pragmatic trial and qualitative studies will be reported, since we are interested in the effectiveness of the intervention as well as in experiences of patients and caregivers.

Outline of this thesis

Chapter 1 describes the study-protocol of the cluster-randomized controlled trial we conducted to study the effectiveness of CC for patients with bipolar disorder. The design of the intervention as well as the trial are described in detail, to enable readers to take note of the pre-defined measures and plans for analyses, once results of the trial are being published. Publishing protocols in advance allows for monitoring and enhancing quality in research.

Chapter 2 describes the main outcomes of the pragmatic trial, on severity of manic and depressive symptoms, as well as time spent with manic or depressive symptoms. This chapter provides an overview of the characteristics of the 138 patients who participated in the study, as well as the extent to which the intervention was implemented.

Chapter 3 contains the results of the trial on the two other main outcomes, i.e. psycho-social functioning and quality of life. We consider these outcomes to be essential for the thorough evaluation of our intervention program, in addition to the symptomatic recovery of the patient’s mood disorder.

Chapter 4 explores the relationship between functional recovery and remission of symptoms. It was hypothesized that, in patients with mood disorders, the time since last mood episode occurred is negatively associated with functional impairment, in other words functional recovery is lagging behind remission of symptoms. This was studied in 3 groups of patients: patients with major depressive disorder (MDD) who have experienced a single depressive episode, patients with MDD with multiple episodes, and patients with bipolar disorder, which is by definition a recurrent disorder. This study is based on analyses of data from the Netherlands Study on Depression and Anxiety (NESDA).
**Chapter 5** reports on patients’ experiences concerning helpful and obstructive elements of nursing care during a depressive episode. Patients participating in the experimental condition of the trial were interviewed, in line with the grounded theory method. This study resulted in a preliminary theory, that provides insight in the benefits of nursing interventions enhancing remission from a depressive episode, as experienced by patients.

**Chapter 6** describes experiences of spouses of patients with bipolar disorder. Spouses who were a member of the Dutch Society of Manic Depressives and Relatives (VMDB) were invited to participate. These spouses were interviewed about perceived burden, coping and needs for support. The grounded theory method was applied, and resulted in a grounded theory explaining the experiences of the spouses.

**Summary and general discussion.** This thesis ends with a summary of our main findings and general discussion on these findings.
Reference List


