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Effect of specialised versus generalised outpatient treatment for bipolar disorder: the CAG Bipolar trial - study protocol for a randomised controlled trial

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ABSTRACT

Introduction Despite current available treatment patients with bipolar disorder often experience relapses and decreased overall functioning. Furthermore, patients with bipolar disorder are often not treated medically or psychologically according to guidelines and recommendations. A Clinical Academic Group is a new treatment initiative bringing together clinical services, research, education and training to offer care and treatment that is based on reliable evidence backed up by research. The present Clinical Academic Group for bipolar disorder (the CAG Bipolar) randomised controlled trial (RCT) aims for the first time to investigate whether specialised outpatient treatment in CAG Bipolar versus generalised community-based treatment improves patient outcomes and clinician's satisfaction with care in patients with bipolar disorder.

Methods and analysis The CAG Bipolar trial is a pragmatic randomised controlled parallel-group trial undertaken in the Capital Region of Denmark covering a catchment area of 1.85 million people. Patients with bipolar disorder are invited to participate as part of their outpatient treatment in the Mental Health Services. The included patients will be randomised to (1) specialised outpatient treatment in the CAG Bipolar (intervention group) or (2) generalised community-based outpatient treatment (control group). The trial started 13 January 2020 and has currently included more than 600 patients. The outcomes are (1) psychiatric hospitalisations and cumulated number and duration of psychiatric hospitalisations (primary), and (2) self-rated depressive symptoms, self-rated manic symptoms, quality of life, perceived stress, satisfaction with care, use of medication and the clinicians' satisfaction with their care (secondary). A total of 1000 patients with bipolar disorder will be included.

Ethics and dissemination The CAG Bipolar RCT is funded by the Capital Region of Denmark and ethical approval has been obtained from the Regional Ethical Committee in The Capital Region of Denmark (H-19067248). Results will be published in peer-reviewed academic journals, presented at scientific meetings and disseminated to patient organisations and media outlets.

Trial registration number NCT04229875.

Strengths and limitations of this study

► The Clinical Academic Group for bipolar disorder (CAG Bipolar) randomised controlled trial (RCT) is the first to investigate effects of large-scale specialisation in bipolar disorder.

► The CAG Bipolar RCT use a pragmatic design with no exclusion criteria.

► The results of the trial will be generalisable to patients who are receiving outpatient treatment in mental services with a diagnosis of bipolar disorder.

► The primary outcome (psychiatric hospitalisation) and the secondary outcome on use of medication will be available for all included patients (100%) from nationwide Danish registers.

► In the CAG Bipolar RCT we will not be able to identify effects of individual components of the intervention.

INTRODUCTION

Bipolar disorder is a common often disabling psychiatric disorder with a prevalence of 1%–2%, a high risk of recurrence of manic and depressive episodes,[1] a lifelong elevated risk of suicide and a decreased life expectancy of 8–12 years compared with the general population.[2 3]

Bipolar disorder is conceptualised as a progressive disorder with increasing risk of recurrence for every new affective episode and with decreasing cognitive and psychosocial function during the course of illness.[4] The majority of patients have contacts to the

secondary healthcare services during the course of illness often resulting in hospitalisation.[1]

Despite current available treatment, patients with bipolar disorder suffer from affective symptoms approximately half of their lifetime alternating between depressive episodes and manic episodes three times per year on average, while 10% suffer from permanent symptoms.[5] Between 30% and 60% of patients with bipolar disorder have impaired overall functioning even during remitted states causing interrupted educational courses and long-term sick leaves.[6 7] In clinical practice, the present treatment offers do not stop the progression of the illness in a large proportion of the patients with a tendency toward increasing number of mood episodes and hospitalisations.[1 8] Internationally (as well as in Denmark) patients with bipolar disorder are not treated medically or psychologically according to guidelines and recommendations,[9] as further addressed below.

Pharmacological treatment
Pharmacological treatment of bipolar disorder is complex and in Denmark and internationally, approximately 80% of patients with bipolar disorder get combination treatment including lithium, anticonvulsants and/or atypical antipsychotics.[10] Lithium is the main mood stabilising treatment for bipolar disorder due to the strong and increasing evidence,[11–15] but the use of lithium has decreased during the last decade in Denmark[10] and internationally.[16–18] The use of antidepressants is constantly high in clinical practice in Denmark[10] and internationally,[16 17] also not aligning with recommendations from national[19] and many international guidelines.[20–22]

An important reason for the decreased use of lithium is the fear of developing kidney disease but recent findings show that use of lithium in accordance with modern clinical recommendations[19] does not increase the risk of end-stage chronic kidney disease.[23 24] Other challenges relating to metabolic syndrome as a consequence of use of atypical antipsychotics is frequently overlooked[25 26] such as insufficient consideration of side effects in the risk–benefit assessment of the different therapeutic strategies and insufficient monitoring for side effects increasing the risk of cardiovascular disorders and diabetes.[27 28]

Thus, improved high-level and updated medical skills and standards are needed among medical doctors as well as other clinicians to provide optimal pharmacological treatment of bipolar disorder.

Psychological and behavioural treatment
Psychotherapeutic treatment for patients with bipolar disorder is also complex, as therapists must have a profound insight into the psychopathology, course and dynamic of bipolar disorder as well as insight into the pharmacological treatment. A major reason for relapse and rehospitalisation is decreased adherence to maintenance treatment.[29 30] A large proportion of patients does not, at least in periods, acknowledge or have insight into suffering from bipolar disorder, and it is an important

and demanding longtime work to achieve concordance between clinicians, patients and relatives on diagnosis and treatment. On the other hand, there is strong evidence that group-based psychoeducation improves treatment adherence and decreases illness recurrences and number and duration of hospitalisations and reduces stigma.[31 32] Nevertheless, group-based psychoeducation is not systematically provided to patients with bipolar disorder internationally[33 34] nor in the Capital Region of Denmark according to recent data.[35]

Challenges in the current treatment organisation of bipolar disorder
Like in most developed countries outpatient treatment in Denmark is organised around local community psychiatric centres treating patients with severe mental illness including schizophrenia, bipolar disorder and depressive disorder as well as personality disorders, severe anxiety disorders, etc, in a large numbers of outpatient ambulatories. This implies a number of challenges including (1) low number of patients with bipolar disorder per clinician resulting in decreased clinical experience during all states of the disorder, (2) varying standards of diagnosing and medical and psychosocial treatment across psychiatric centres and individual ambulatories, (3) difficulties with recruiting patients for starting group-based psychoeducation on a regular basis, (4) limited research in bipolar disorder and (5) delayed translation of research findings into clinical practice.

Although psychiatric treatment generally has shifted from inpatient treatment to outpatient treatment during recent decades, patients with bipolar disorder are still frequently hospitalised to psychiatric wards in standard care, ranging from approximately 6%[36] to 32% per year.[37] In the Mental Health Services, Capital Region of Denmark, 2100 patients with a main diagnosis of bipolar disorder were treated as outpatients and 636 were hospitalised during a 1-year period corresponding to a 30% hospitalisation rate (data from November 2017 to November 2018) and with a substantial and unfounded variation in the average duration of hospitalisation spanning from 33 days per hospitalisation in one centre to 48 days in another. Thus, costs of psychiatric hospitalisation is still a major burden and in Denmark comprising two-third parts of all direct costs.[38]

A delineated experience with specialised treatment for newly diagnosed bipolar disorder
We have previously shown in a large pragmatic randomised controlled trial covering the entire Mental Health Services, Capital Region of Denmark (the Early Intervention Affective Disorders trial), that specialised combined optimised pharmacological treatment and group-based psychoeducation improved patient outcomes substantially.[39] Early intervention in a specialised mood disorder clinic, the Copenhagen Affective Disorder Clinic, decreased the risk of re-hospitalisation with 41%, improved adherence to medication and increased satisfaction with care compared

with standard care.[39] Furthermore, the total direct net costs for treatment in the mood disorder clinic were €3194 less per patient than for standard care taking into account sparred hospitalisations, corresponding to 11% of the costs for standard care.[39] Based on this research, the Mental Health Services in the Capital Region of Denmark decided to make the 2-year treatment programme in the Copenhagen Affective Disorder Clinic a permanent treatment offer to all patients with newly diagnosed bipolar disorder in the region. Further, inspired by these findings, other specialised bipolar mood disorder clinics have been established internationally during recent years, for example, the Optima Clinic in Maudsley, London.[40] Nevertheless, it is not clear or evident in any way that specialised treatment is more efficacious than generalist psychiatric treatment for patients with more progressed bipolar disorder, that is, for patients who have been ill during many years with ongoing mood episodes and frequent comorbidity.[41]

The Mental Health Services in the Capital Region of Denmark covers a catchment area of 1.85 million people. The Copenhagen Affective Disorder Clinic has during the last 8 years annually provided treatment for approximately 200 patients with newly diagnosed/first episode bipolar disorder from the entire Mental Health Services, Capital Region of Denmark. The referring criteria for the clinic are specified as a first ever diagnosis of a single manic episode or bipolar disorder given less than 2 years ago. Nevertheless, the majority of patients with bipolar disorder get long-term treatment outside the specialised mood disorder clinic in other psychiatric centres in the Capital Region or periodically in primary care by general practitioners or private psychiatrists, as these patients suffer from progressed bipolar disorder that needs cross disciplinary treatment and further they have had a diagnosis of a single manic episode or bipolar disorder for more than 2 years.

A new organisation for all patients with bipolar disorder: the Clinical Academic Group for bipolar disorder

Inspired by experiences from the specialised Copenhagen Affective Disorder Clinic, described above, and the King's College/Institute of Psychiatry, London, the Mental Health Services, Capital Region of Denmark, has decided to implement a new organisation of the treatment services for all patients with bipolar disorder in the Capital Region, a so-called the Clinical Academic Group for bipolar disorder (the CAG Bipolar). CAGs bring together clinical services, research, education and training to offer care and treatment that is based on reliable evidence backed up by research (https://www.kcl.ac.uk/ioppn/depts/ps/about/cags/index.aspx). A major aim of the CAGs is to aid effective and rapid use of the latest research to improve the care and treatment provided. CAGs also provide high quality teaching for clinical staff and scientists. King's College London and King's Health Partners currently comprises 22 different CAG's including cancer, cardiovascular disease and CAG's

within mental health (https://www.kingshealthpartners.org/clinical-excellence).

The CAG Bipolar in the Mental Health Services, Capital Region of Denmark

The CAG Bipolar started in January 2020 and will include more than 1000 patients with progressed bipolar disorder, that is, after the early stages (a diagnosis of a single manic episode or bipolar disorder for more than 2 years), from five psychiatric centres (Psychiatric Center Copenhagen, North Zealand, Amager, Glostrup and Ballerup). The CAG Bipolar model is to centralise bipolar treatment into one localised CAG bipolar clinic for each of the five psychiatric centres (treating the vast majority of bipolar patients) instead of one localised treatment facility for the entire region, thus balancing centralisation of treatment and geographical distance for patients to outpatient clinics.

Currently more than 600 patients have been included.

A window of opportunity

Effects of organisational changes in health services are rarely investigated scientifically. The CAG Bipolar is the first CAG established by the Mental Health Services, Capital Region of Denmark, and will provide valuable experience of implementation of CAG's for bipolar disorder elsewhere and of future CAG's in other psychiatric disease areas.

It has never been investigated whether specialised treatment in a CAG improves patients outcomes compared with standard care for any disorder, psychiatric or physical. Consequently, it is an open and unaddressed question whether treatment for progressed bipolar disorder should be carried out by specialised or generalised psychiatric teams. As the organisational changes in relation to CAG Bipolar started in January 2020 there is currently an outstanding possibility to investigate the effects of a CAG in a randomised controlled trial (RCT) comparing specialised treatment in localised CAG Bipolar clinics versus generalised dispersed community-based standard treatment.

Hypotheses

In patients with bipolar disorder, specialised treatment in the CAG Bipolar versus generalised community-based treatment improves patient outcomes and clinician's satisfaction with care.

Objectives and hypotheses

To investigate in a randomised controlled parallel-group trial whether specialised treatment in the CAG Bipolar versus standard treatment decreases the risk of hospitalisation and the cumulated duration of hospitalisation. Further, to investigate whether specialised treatment in CAG Bipolar decreases depressive symptoms, manic symptoms and perceived stress and increases quality of life, patients' satisfaction with care. Lastly, to investigate whether specialised treatment increases adherence to international and national guidelines of

medical treatment (with increased use of three main maintenance mood stabilisers for bipolar disorder: lithium, lamotrigine or quetiapine, and decreased use of antidepressants) and increases clinicians' satisfaction with their care.

METHODS

The present trial protocol is reported according to the CONsolidated Standards Of Reporting Trials (CONSORT) statement and Standard Protocol Items: Recommendations for Interventional Trials.[42–44]

The trial protocol describes a randomised controlled parallel-group trial, the CAG Bipolar RCT, investigating the effect of specialised outpatient treatment in adult patients with bipolar disorder.

Trial design and study organisation

The CAG Bipolar RCT is designed as a pragmatic randomised controlled parallel-group trial with an unbalanced allocation ratio of 7:3 of adult patients with bipolar disorder and with stratification according to psychiatric centre from where the patients receive treatment. A total of 70% of outpatients with bipolar disorder will be randomised to treatment in the CAG Bipolar (intervention group) and 30% to standard treatment (treatment as usual) (control group) during a 1-year trial period. The CAG Bipolar patients will be centralised into one localised CAG Bipolar clinic per psychiatric centre increasing the number of bipolar patients for each clinician.

The flow diagram of the CAG Bipolar RCT is presented in figure 1. The trial is conducted at Psychiatric Center Copenhagen, North Zealand, Amager, Glostrup and
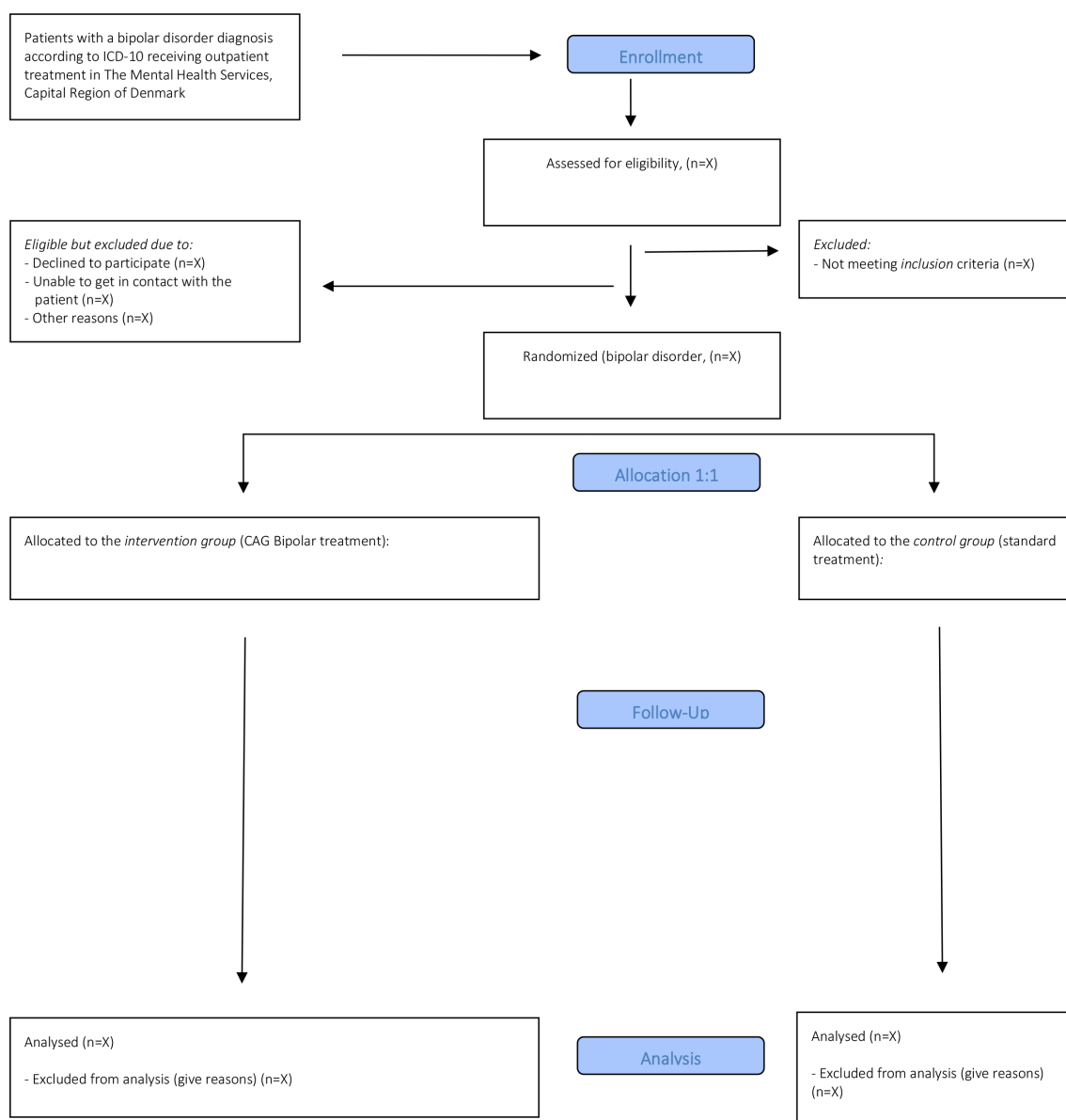
Figure 1 Flow diagram—the CAG Bipolar randomised controlled trial. CAG Bipolar, Clinical Academic Group for bipolar disorder; ICD-10, International Classification of Diseases, V.10.

Table 1 Outcome assessments during the CAG Bipolar randomised controlled trial

	Background information	Questionnaires	Registry data
Baseline	x	X	X
Randomisation to: 1. Specialised CAG Bipolar treatment (the intervention group). 2. Standard treatment (treatment-as-usual) (the control group).			
6 months follow-up		X	X
12 months follow-up		X	X
Questionnaires: Self-rated depressive symptoms according to Major Depressive Inventory; self-rated manic symptoms according to Altman Self Rating scale for Mania; quality of life according to WHO Quality of Life-BREF; perceived stress according to Cohen's Perceived stress scale; satisfaction with care according to Verona Satisfaction Scale-Affective Disorder.			
Registry data: Continuous collection of information on the number and duration of psychiatric hospitalisation, and use of medication during follow-up.			

CAG Bipolar, Clinical Academic Group for bipolar disorder.

Ballerup, in the Capital Region of Denmark. No changes in study design or methods have been made after trial commencement.

Participants and settings

Inclusion criteria: all patients aged 18 years or older with a bipolar disorder diagnosis according to the International Classification of Diseases, V.10 who are referred to outpatient treatment in the Mental Health Services, Capital Region of Denmark, from January 2020.

Exclusion criteria: (1) patients with a newly diagnosed/first episode bipolar disorder (a diagnosis of a single manic episode or bipolar disorder for less than 2 years) and (2) patients with moderate-to-severe dementia.

Study procedure

All potential participants are invited to participate in the CAG Bipolar RCT by the staff. All potential participants who accept to participate in the CAG Bipolar RCT are screened by trained clinicians to make sure they fulfil the criteria for participation, and are then included in the CAG Bipolar RCT. Following inclusion, the included patients are randomised separately according to psychiatric centre to either the intervention group or the control group within the centre for a 12 months trial period.

An overview of the data collection during the trial is presented in table 1. Information regarding the primary outcome, psychiatric hospitalisation and duration of admissions and the use of medication, will be obtained after completion of the RCT by linkage of the unique personal identification number (Civil Person Registration number), which is assigned to all 5.8 million persons living in Denmark[45] with the Danish Psychiatric Central Register[46] and the Medicinal Product Statistics,[47] respectively.

The intervention group

As part of the CAG Bipolar intervention, clinical expertise in bipolar disorder will be provided to all approximately 70–80 clinicians in CAG Bipolar teams by seven overall means:

1. Patients will be treated in a localised CAG Bipolar clinic within each of the five psychiatric centres increasing the number of patients with bipolar disorder for each clinician hereby increasing the expertise for each clinician.

2. All clinicians will get certified in diagnosing and treating bipolar disorder (bipolar certification) by joining an initial 4-day educational course on diagnosing and medical and group-based supportive psychoeducation. This will be followed by ongoing courses and supervision in order to secure continuous high standard treatment in accordance with guidelines. Courses will be provided by the CAG leaders in cooperation with the specialised staff in the Copenhagen Affective Disorder Clinic.[39]

3. Treatment will include a group-based psychoeducation programme that has been shown to reduce illness recurrences, hospitalisations and stigma and to increase treatment adherence.[31] The psychoeducation programme has been revised to be more supportive, focusing on how to improve quality of life while still suffering from bipolar disorder. Clinicians in the five CAG Bipolar clinics will be trained and supervised in group-based supportive psychoeducation.

4. Coordinated targets to improve quality of life of patients by increasing concordance between clinicians, patients and relatives on well-defined treatment goals.

5. Continued ongoing supervision of the CAG Bipolar teams in relation to specific patient cases with focus on diagnosing and medical treatment undertaken by the specialised clinical team from the Copenhagen Affective Disorder Clinic.

6. Up to 3-month bidirectional exchange of two clinical staff members between the Copenhagen Affective Disorder Clinic and each CAG Bipolar clinic to increase learning.

7. Recovery mentors (current or prior patients) who will be systematically involved supporting patients.

The control group

Patients allocated to the control group continue with their standard treatment for 1 year at which time, they will be included in CAG Bipolar as part of the implementation of CAG Bipolar.

Treatment in the control group is generalised as clinicians here treat patients with all kinds of severe mental illness and decentral/local in a large numbers of community-based psychiatric ambulatories in contrast to treatment in the intervention group that is specialised as clinicians here treat patients with bipolar disorder, only or mainly, centralised in CAG Bipolar teams in each of the five mentioned psychiatric centres.

Common treatment modalities in the intervention group and the control group

Treatment in the intervention group and the control group is based on Flexible Assertive Community Treatment (F-ACT).[48 49] In F-ACT, teams are multidisciplinary, including a psychiatrist, case managers, a psychologist, a peer specialist (recovery mentor) and a supported employment specialist. The teams offer two levels of care: individual case management for most patients, and full ACT when there is a need for shared caseload and assertive outreach. To combine care for these two groups, the F-ACT team employs a flexible switching system. Thus, patients requiring full ACT are on a daily basis placed on a board due to various reasons like temporary worsening of symptoms, treatment avoidance, admission to a psychiatric hospital, etc.[48] For patients requiring less intensive care, the same team provides individual case management with multidisciplinary treatment and support.

Assessments of outcome measures

The primary outcome measure (hospitalisation) and the secondary outcome measure of medication use are based on public registry-based data blinded for intervention. All other outcomes are assessed without blinding to the intervention. The patients are, regardless of randomisation group, enrolled for a 12 months trial period and invited to fill out questionnaires three times during follow-up—at baseline, after 6 months and after 12 months (table 1). Data collection of basic sociodemographic, clinical data and outcome measures (besides the primary) including questionnaires will be handled electronically via the REDCap database in accordance with the standard procedure in the Capital Region of Denmark.

Outcomes
Primary outcomes
Risk of psychiatric hospitalisation and cumulated duration of psychiatric hospitalisation according to data from the population-based Danish Psychiatric Central Research Register.[46] This outcome measure benefits from (1) having a high face validity as admission to hospital reflects serious relapse of the illness[50] being critical for patients, relatives and clinicians, (2) being consistently recorded for all patients with no loss to follow-up (100% retention) and (3) can be assessed blinded for the intervention status.

Secondary outcomes
► Patient-based questionnaires collected at baseline, after 6 months and 12 months using the following questionnaires: self-rated depressive according to the Major Depressive Inventory[51]; self-rated manic symptoms according to the Altman Self-rating Scale for Mania[52]; quality of life according to WHO Quality of Life-BREF[53]; perceived stress according to Cohen's Perceived stress scale[54] as well as satisfaction with care according to scores on the Verona Satisfaction Scale-Affective Disorder.[55]
► Adherence to the Danish national guidelines of medical treatment of bipolar disorder according to use of three main maintenance mood stabilisers for bipolar disorder: lithium, lamotrigine or quetiapine, and use of antidepressants[19] and assessed via population-based registers[47]
► Proportion of patients starting in group-based psychoeducation.
► Clinicians' satisfaction according to responses to six standardised questions with their work at start and end of the RCT collected as one general measure for each clinician.

No changes in outcome measures have been made after trial commencement.

Statistical power and sample size calculation

All prevalent and newly referred approximately 2000 outpatients with a bipolar disorder diagnosis will be invited to participate in the present CAG Bipolar RCT during the planned 3-year study period. The RCT will run until at least 1000 patients have been included. It is estimated that more than two-thirds will accept participation in the trial as the alternative will be to wait for 1 year and at that time to be included in CAG Bipolar as part of the implementation of CAG Bipolar.

A total of 70% of outpatients with bipolar disorder will be randomised to treatment in the CAG Bipolar clinic within each of the five psychiatric centres and 30% to continue their usual outpatient standard treatment during the 1 year intervention period in the centre.

According to data from the Mental Health Services, Capital Region of Denmark (2017), at least 20% of outpatients in standard care will be hospitalised for a mean of 26 days (SD: 15 days) during the 1 year intervention period. We conservatively expect to be able to reduce the proportion of hospitalisations among patients with at least 5% per year (from 20% per year to 15% per year) and the average duration of hospitalisation days per year with at least 10% (from 43 days to 39 days, SD: 25) in CAG Bipolar versus standard treatment. With a power of 80% and a type 1 error risk of 0.05, we need to randomise 161 and 644 patients, respectively for the two primary measures, to the trial (http://powerandsamplesize.com). Drop out of the RCT during the 1 year study period is estimated to be 30%. Thus, 1000 patients need to be included to detect a statistically significant difference in duration of hospitalisation. Interim analyses are not feasible as the primary outcome measure is based on data from the Danish Psychiatric Central Research Register with a time

lack of 1 year (data are not available until 1 year after the actual incident).

Randomisation
Sequence generation
The company randomise.net is used for the randomisation (http://randomize.net). The randomisation is conducted using an online procedure with stratification according to psychiatric centre. Each centre is able to log on a web page using a secure code and will conduct the randomisation on site. Patients included in the trial are randomised with an unbalanced allocation ratio of 70:30 to (1) the CAG Bipolar (the intervention group) or to (2) standard treatment (the control group) (table 1). Block sizes of 10 are used to help preserve unpredictability.[56 57] The study will use a stratified design, where patients are stratified according to the psychiatric centres where patients are discharged from. The statistical analyses will be adjusted for the stratification variable, as well as age and sex as possible prognostic variables. Further, in analyses on continuous variables, potential differences in baseline score on the outcome in question will be included as a potential confounder.

Blinding
Owing to the type of intervention in the CAG Bipolar RCT, the patient, the patients' healthcare provider and the CAG researchers are aware of the allocated randomisation group. However, data on psychiatric hospitalisation and use of medication can be assessed blinded for the intervention status by the researchers. The researchers responsible for data entry, data analyses, interpretation of analyses and writing of papers are kept blinded to allocation during handling of data.

Statistical methods
Data from all randomised patients are collected until dropout or the end of the trial period. Analysis will be carried out with an intention-to-treat approach. Concerning the primary outcomes, multiple regression models will be conducted investigating differences in the proportion of psychiatric hospitalisations and the cumulated duration of all psychiatric hospitalisations during the 1 year trial period. Models will be conducted unadjusted and adjusted for age, sex, psychiatric centre (stratification variable) and number of previous psychiatric admissions at baseline. These covariates are chosen based on previous evidence that they can affect the rate of hospitalisation in patients with bipolar disorder.[1 58 59] Analysis of secondary outcomes will be done employing a linear mixed effects model with random intercept for each participant and a fixed effect of visit number (6 months and 12 months). Differences in outcomes between the intervention group and the control group will be analysed, first in an unadjusted model (except for differences in baseline values of the outcome variable in analyses on continuous variables) and then in models adjusted for the stratification variable (psychiatric centre), and also for age and sex as

possible prognostic variables. If there are no statistically significant main effects of age and sex, these variables will be excluded from the final analyses. Potential interactions between randomisation group and visit number on any specific outcome variable in the analyses will be investigated and reported accordingly. Participants and non-participants will be compared using register-based variables to evaluate whether participants in the trial are representative of patients with bipolar disorder in the Mental Health Services, Capital Region of Denmark, in general.

Long-term outcome measures
As part of the CAG Bipolar RCT, we will also investigate long-term register-based outcome measures at 3, 5 and 10 years follow-up by linking to Danish population-based registers using the unique personal identification number, which is assigned to all persons living in Denmark. The long-term register-based outcome measures will include: (1) long-term risk of psychiatric hospitalisation and the cumulated duration of hospitalisation according to data from the Danish Psychiatric Central Research Register,[46] (2) prescribed psychotropic medication according to data from Medicinal Product Statistics,[47] (3) demographic measures of education, income, employment status, cohabitation and marital status from Statistics Denmark,[45] (4) physical comorbidity according to data from the Danish National Patient Register[60] and (5) rate of suicide and death due to natural causes based on data on death and causes of death from the Danish Medical Register on Vital Statistics.[47] Analyses will be conducted using survival analyses taking time from inclusion in the CAG Bipolar RCT (T_0) into consideration hereby taking account of potential delayed referral to the CAG Bipolar RCT.

For all statistical analyses, the statistical threshold for significance is $p \leq 0.05$ (two-tailed). Data will be managed by LVK, NBK, PB-K and MF-J and entered using REDCap. All analyses will be done using SPSS V.22.0 (IBM) and Stata V.13 (StataCorp LP).

Patient and public involvement
There was no patient involvement in the design or conduct of the RCT or in the recruitment to the study. Patients have been involved in the development of CAG Bipolar and in the bipolar certification programme providing teaching courses.

Funding
The CAG Bipolar RCT is funded by the Capital Region of Denmark (A6508).

Ethics and dissemination
Ethical permission for the CAG Bipolar RCT has been obtained from the Regional Ethics Committee in The Capital Region of Denmark and the data agency, Capital Region of Copenhagen (H-19067248). The law on handling of personal data will be respected. The patients' healthcare journals will be read to confirm information

regarding the patients' clinical history. The trial was registered at ClinicalTrials.gov on 11 January 2020. All positive, neutral and negative findings of the trial will be published according to the CONSORT guidelines.[42–44] All potential participants are invited to receive information about the CAG Bipolar RCT on an individual basis where the information is given in a quiet and undisturbed room. All information is presented in both written and verbal form and participants can bring a friend or relative to the introduction conversation. Participants are informed that participation is voluntary, and that consent can be withdrawn at any time during the trial without this having any consequences for future treatment possibilities. All included patients sign a consent form and get a copy of this and their rights as a participant in a clinical trial. Participants do not receive other economic compensation for participating in the CAG Bipolar RCT.

Results will be published in peer-reviewed academic journals, presented at scientific meetings and disseminated to patient organisations and media outlets.

DISCUSSION

The CAG Bipolar RCT is the first RCTs investigating effects of specialised versus generalised treatment for patients with bipolar disorder in an entire treatment organisation (the Capital Region of Denmark). Furthermore, the CAG Bipolar RCT is the first RCT within bipolar disorder including outcome measures from all areas of the healthcare system comprising (1) data on health services (psychiatric hospitalisation), (2) patient-reported outcome measures on patient illness and well-being, (3) data on adherence to the guidelines of medical treatment of bipolar disorder and (4) data on clinicians' satisfaction with their care. The CAG Bipolar RCT includes a robust clinically meaningful register-based primary outcome measure that will be assessable for all study participants and during long-term follow-up.

As it is unknown and never has been investigated whether specialised and centralised treatment for patients with progressed bipolar disorder is better than generalised and decentralised treatment it is highly important to compare effectiveness of the two interventions in a RCT. Even if no difference is found on the primary outcome measures, effects in relation to the secondary outcome measures are important. The CAG Bipolar trial is designed with sufficient statistical power to investigate differences in relation to secondary outcome measures. Further, due to the size of the trial it will be possible in subanalyses to elucidate associations between specific components of the treatment including different pharmacological treatments and participation or not in group-based supportive psychoeducation and trial outcome measures.

CAG Bipolar is specifically targeting patients in the later stages of bipolar disorder, patients with progressed bipolar disorder. A great many of such patients present with multiple episodes, cognitive dysfunction, alcohol and drug abuse and treatment resistance, and may not be easy to help.[41] The CAG Bipolar initiative is based on the assumption and broad hypothesis that specialised treatment delivered by a trained team of clinicians targeting bipolar disorder, only, and including early detection of mood episodes, group-based supportive psychoeducation and a specific focus on increasing the use of lithium, lamotrigine and quetiapine and decreasing the use of antidepressants may improve patient outcomes and well-being in this frail group of patients.

Few studies have focused on patients with progressed bipolar disorder.[41] Alternative models such as the collaborative care model in primary care settings integrating care managers and consultant psychiatrists, with primary care physician oversight, has been shown to increase guideline-concordant antimanic treatment in a severely ill population of patients with bipolar disorder.[61–63]

Advantages

Within the next years, we expect to clarify effects of specialised treatment in bipolar disorder to the benefits of patients, relatives, clinicians and society in general. The learning potential of the trial is high due to the novelty, originality and methodological rigour of the CAG Bipolar RCT. The CAG Bipolar RCT is the first to investigate effects of large-scale specialisation in bipolar disorder.

The CAG Bipolar RCT use a pragmatic design with no exclusion criteria, that is, real-world patients with comorbid alcohol or substance abuse or personality disorders, etc, are included, and the results of the trial will be generalisable to patients who are receiving outpatient treatment in mental services with a diagnosis of bipolar disorder and have great clinical relevance. Further, it is a major advantage that information on the primary outcome (psychiatric hospitalisation) and on the secondary outcome, use of medication, will be available for all included patients (100%), regardless of whether they drop out of the trial or not, as data on date of psychiatric hospitalisation and duration of psychiatric hospitalisations routinely are reported nationwide to the Danish Psychiatric Central Register[46] and prescriptions of medication to the Medicinal Product Statistics.[47] In Denmark, all hospitalisations are in public domain and recorded in the Danish Psychiatric Central Register. Also, the information on psychiatric hospitalisations, duration of psychiatric hospitalisations and use of medication are collected without the risk of unblinding of the researcher and not based on the patients' subjective evaluations. Finally, long-term register-based outcome measures will be available at 3, 5 and 10 years follow-up by linking to Danish population-based registers.

Limitations

The CAG Bipolar RCT is designed to investigate the effectiveness of the entire specialised treatment in relation to patients referred to mental health services with progressed bipolar disorder. Thus, we will not be able to distinguish the effects of the individual components of the intervention.

As the CAG Bipolar study is designed as a large-scale pragmatic and naturalistic study aiming to include 1000 patients, the diagnosis of bipolar disorder is made by specialists in psychiatry as part of their daily clinical work and standardised diagnostic instruments are not systematically used. However, all clinicians working at CAG Bipolar have been through a specialised certification teaching course on diagnosing and treatment of bipolar disorder conducted by the authors of the present study.

In large scale pragmatic trials, contamination of the clinicians in the standard care group is a challenge due to possible exchange of knowledge from clinicians in the intervention group. To reduce contamination, clinicians in the intervention group has from start of the trial and ongoing been informed to keep information exchange with clinicians in the control group to a minimum.

The secondary outcome measures include self-rated depressive and manic symptoms, quality of life, perceived stress and satisfaction with care as assessed with standardised questionnaires. Since the patients are aware of their allocation status these outcome measures are therefore unblinded.

Generalisation

The results of this RCT on specialised treatment in the CAG Bipolar versus generalised community-based treatment can be generalised to patients with progressed bipolar disorder in general (not newly diagnosed patients with bipolar disorder), that is, real-world patients with any kind of comorbidity.

Perspectives

Findings from the present trial will directly be implemented in the CAG Bipolar in the Mental Health Services, Capital Region of Denmark, potentially in a revised version according to study findings. Furthermore, findings will have influence on specialisation and centralisation initiatives with regard to other psychiatric disorders in the Capital Region of Denmark as well as specialisation within the rest of Denmark (the four other regions) and internationally. More than 600 patients have been included in the ongoing CAG Bipolar RCT, and thus the trial is fully feasible. Finally, findings could have influence on organisation of outpatient treatment of patients with bipolar disorder internationally.

Trial status

The trial is ongoing. Recruitment began on 13 January 2020.

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REFERENCES

1 Kessing LV, Hansen MG, Andersen PK. Course of illness in depressive and bipolar disorders. naturalistic study, 1994-1999. *Br J Psychiatry* 2004;185:372–7.
2 Kessing LV, Vradi E, Andersen PK. Life expectancy in bipolar disorder. *Bipolar Disord* 2015;17:543–8.
3 Kessing LV, Vradi E, McIntyre RS, *et al*. Causes of decreased life expectancy over the life span in bipolar disorder. *J Affect Disord* 2015;180:142–7.
4 Kessing LV, Andersen PK. Evidence for clinical progression of unipolar and bipolar disorders. *Acta Psychiatr Scand* 2017;135:51–64.
5 Judd LL, Akiskal HS, Schettler PJ, *et al*. The long-term natural history of the weekly symptomatic status of bipolar I disorder. *Arch Gen Psychiatry* 2002;59:530–7.
6 Coryell W, Scheftner W, Keller M, *et al*. The enduring psychosocial consequences of mania and depression. *Am J Psychiatry* 1993;150:720–7.
7 MacQueen GM, Young LT, Joffe RT. A review of psychosocial outcome in patients with bipolar disorder. *Acta Psychiatr Scand* 2001;103:163–70.
8 Kessing LV, Hansen MG, Andersen PK, *et al*. The predictive effect of episodes on the risk of recurrence in depressive and bipolar disorders - a life-long perspective. *Acta Psychiatr Scand* 2004;109:339–44.
9 McIntyre R, Berk M, Brietzke E. Bipolar disorder: clinical challenges, new research findings, and treatment opportunities. *Lancet Psychiatry* 2020;396.
10 Kessing LV, Vradi E, Andersen PK. Nationwide and population-based prescription patterns in bipolar disorder. *Bipolar Disord* 2016;18:174–82.
11 , Geddes JR, Goodwin GM, *et al*, BALANCE investigators and collaborators. Lithium plus valproate combination therapy versus monotherapy for relapse prevention in bipolar I disorder (balance): a randomised open-label trial. *Lancet* 2010;375:385–95.
12 Severus E, Taylor MJ, Sauer C, *et al*. Lithium for prevention of mood episodes in bipolar disorders: systematic review and meta-analysis. *Int J Bipolar Disord* 2014;2:15.

13 Kessing LV, Bauer M, Nolen WA. Effectiveness of maintenance therapy of lithium vs other mood stabilizers in monotherapy and in combinations: a systematic review of evidence from observational studies. *Bipolar Disord* 2018;2010.1111/bdi.12623. [Epub ahead of print: 14 Feb 2018].

14 Miura T, Noma H, Furukawa TA, *et al*. Comparative efficacy and tolerability of pharmacological treatments in the maintenance treatment of bipolar disorder: a systematic review and network meta-analysis. *Lancet Psychiatry* 2014;1:351–9.

15 Kessing LV. Lithium as the drug of choice for maintenance treatment in bipolar disorder. *Acta Psychiatr Scand* 2019;140:91–3.

16 Karanti A, Kardell M, Lundberg U, *et al*. Changes in mood stabilizer prescription patterns in bipolar disorder. *J Affect Disord* 2016;195:50–6.

17 Lyall LM, Penades N, Smith DJ. Changes in prescribing for bipolar disorder between 2009 and 2016: national-level data linkage study in Scotland. *Br J Psychiatry* 2019;215:415–21.

18 Lin Y, Mojtabai R, Goes FS, *et al*. Trends in prescriptions of lithium and other medications for patients with bipolar disorder in office-based practices in the United States: 1996-2015. *J Affect Disord* 2020;276:883–9.

19 (rads) RfAaDS. Baggrundsnotat for medicinsk behandling AF bipolar lidelse, 2015. Available: http://www.rads.dk/media/1904/bipolar-depression-bgn-september-2015.pdf

20 Grunze H, Vieta E, Goodwin GM, *et al*. The world federation of societies of biological psychiatry (WFSBP) guidelines for the biological treatment of bipolar disorders: update 2012 on the long-term treatment of bipolar disorder. *World J Biol Psychiatry* 2013;14:154–219.

21 Grunze H, Vieta E, Goodwin GM, *et al*. The world federation of societies of biological psychiatry (WFSBP) guidelines for the biological treatment of bipolar disorders: update 2009 on the treatment of acute mania. *World J Biol Psychiatry* 2009;10:85–116.

22 Grunze H, Vieta E, Goodwin GM, *et al*. The world Federation of societies of biological psychiatry (WFSBP) guidelines for the biological treatment of bipolar disorders: update 2010 on the treatment of acute bipolar depression. *World J Biol Psychiatry* 2010;11:81–109.

23 Kessing LV, Gerds TA, Feldt-Rasmussen B, *et al*. Use of lithium and anticonvulsants and the rate of chronic kidney disease: a nationwide population-based study. *JAMA Psychiatry* 2015;72:1182–91. doi:10.1001/jamapsychiatry.2015.1834

24 Nielsen RE, Kessing LV, Nolen WA, *et al*. Lithium and renal impairment: a review on a still hot topic. *Pharmacopsychiatry* 2018;51:200–5.

25 McIntyre RS, Danilewitz M, Liauw SS, *et al*. Bipolar disorder and metabolic syndrome: an international perspective. *J Affect Disord* 2010;126:366–87.

26 Vinberg M, Madsen M, Breum L, *et al*. Metabolic syndrome in a cohort of affectively ill patients, a naturalistic study. *Nord J Psychiatry* 2012;66:142–5.

27 Coello K, Kjærstad HL, Stanislaus S, *et al*. Thirty-year cardiovascular risk score in patients with newly diagnosed bipolar disorder and their unaffected first-degree relatives. *Aust N Z J Psychiatry* 2019;53:651–62.

28 Kessing LV, Ziersen SC, Andersen PK, *et al*. A nation-wide population-based longitudinal study mapping physical diseases in patients with bipolar disorder and their siblings. *J Affect Disord* 2021;282:18–25.

29 Vestergaard P, Schou M. Prospective studies on a lithium cohort. 1. general features. *Acta Psychiatr Scand* 1988;78:421–6.

30 Kessing LV, Søndergård L, Kvist K, *et al*. Adherence to lithium in naturalistic settings: results from a nationwide pharmacoepidemiological study. *Bipolar Disord* 2007;9:730–6.

31 Soo SA, Zhang ZW, Khong Sarah Jia'En, Khong SJ, *et al*. Randomized controlled trials of psychoeducation modalities in the management of bipolar disorder: a systematic review. *J Clin Psychiatry* 2018;79.

32 Miklowitz DJ, Efthimiou O, Furukawa TA, *et al*. Adjunctive psychotherapy for bipolar disorder: a systematic review and component network meta-analysis. *JAMA Psychiatry* 2021;78:141–50.

33 Renes JW, Regeer EJ, Hoogendoorn AW, *et al*. A nationwide study on concordance with multimodal treatment guidelines in bipolar disorder. *Int J Bipolar Disord* 2018;6:22.

34 Renes JW, Maciejewski DF, Regeer EJ, *et al*. Guideline concordance and outcome in long-term naturalistic treatment of bipolar disorder - a one-year longitudinal study using latent change models. *J Affect Disord* 2021;283:395–401.

35 Region Hovedstadens Psykiatri. *Outcome book RHP-KAG bipolar lidelse*, 2020.

36 Joas E, Karanti A, Song J, *et al*. Pharmacological treatment and risk of psychiatric hospital admission in bipolar disorder. *Br J Psychiatry* 2017;210:197–202.

37 O'Hagan M, Cornelius V, Young AH, *et al*. Predictors of rehospitalization in a naturalistic cohort of patients with bipolar affective disorder. *Int Clin Psychopharmacol* 2017;32:115–20.

38 AuRuo P. Indsatsen for mennesker med psykiske lidelser – kapacitet, sammenhæng OG struktur. Bilagsrapport 1. *Afrapportering fra Arbejdsgruppe under Regeringens udvalg om Psykiatri* 2013.

39 Kessing LV, Hansen HV, Hvenegaard A, *et al*. Treatment in a specialised out-patient mood disorder clinic V. standard out-patient treatment in the early course of bipolar disorder: randomised clinical trial. *Br J Psychiatry* 2013;202:212–9.

40 Macritchie K, Mantingh T, Hidalgo-Mazzei D, *et al*. A new inner-city specialist programme reduces readmission rates in frequently admitted patients with bipolar disorder. *BJPsych Bull* 2019;43:58–60.

41 Post RM. How to prevent the malignant progression of bipolar disorder. *Braz J Psychiatry* 2020;42:552–7.

42 Moher D, Hopewell S, Schulz KF, *et al*. Consort 2010 explanation and elaboration: updated guidelines for reporting parallel group randomised trials. *J Clin Epidemiol* 2010;63:e1–37.

43 Boutron I, Moher D, Altman DG, *et al*. Extending the consort statement to randomized trials of nonpharmacologic treatment: explanation and elaboration. *Ann Intern Med* 2008;148:295–309.

44 Chan A-W, Tetzlaff JM, Altman DG, *et al*. Spirit 2013: new guidance for content of clinical trial protocols. *Lancet* 2013;381:91–2.

45 Statistics Denmark, 2017. Available: https://www.dst.dk/en

46 Munk-Jørgensen P, Mortensen PB. The Danish psychiatric central register. *Dan Med Bull* 1997;44:82–4.

47 Juel K, Helweg-Larsen K. The Danish registers of causes of death. *Dan Med Bull* 1999;46:354–7.

48 Nugter MA, Engelsbel F, Bähler M, *et al*. Outcomes of flexible assertive community treatment (fact) implementation: a prospective real life study. *Community Ment Health J* 2016;52:898–907.

49 Svensson B, Hansson L, Markström U, *et al*. What matters when implementing flexible assertive community treatment in a Swedish healthcare context: a two-year implementation study. *Int J Ment Health* 2017;46:284–98.

50 Burns T. End of the road for treatment-as-usual studies? *Br J Psychiatry* 2009;195:5–6.

51 Bech P, Rasmussen NA, Olsen LR, *et al*. The sensitivity and specificity of the major depression inventory, using the present state examination as the index of diagnostic validity. *J Affect Disord* 2001;66:159–64.

52 Altman EG, Hedeker D, Peterson JL, *et al*. The Altman self-rating mania scale. *Biol Psychiatry* 1997;42:948–55.

53 THE WHOQOL GROUP. Development of the world health organization WHOQOL-BREF quality of life assessment. The WHOQOL group. *Psychol Med* 1998;28:551–8.

54 Cohen S, Kamarck T, Mermelstein R. A global measure of perceived stress. *J Health Soc Behav* 1983;24:385–96.

55 Kessing LV, Hansen HV, Ruggeri M, *et al*. Satisfaction with treatment among patients with depressive and bipolar disorders. *Soc Psychiatry Psychiatr Epidemiol* 2006;41:148–55.

56 Schulz KF, Grimes DA. Allocation concealment in randomised trials: defending against deciphering. *Lancet* 2002;359:614–8.

57 Schulz KF, Grimes DA. Unequal group sizes in randomised trials: guarding against guessing. *Lancet* 2002;359:966–70.

58 Kessing LV. Recurrence in affective disorder. II. effect of age and gender. *Br J Psychiatry* 1998;172:29–34.

59 Kessing LV. Course and cognitive outcome in major affective disorder. *Dan Med J* 2015;62:B5160.

60 Andersen TF, Madsen M, Jørgensen J, *et al*. The Danish national hospital register. a valuable source of data for modern health sciences. *Dan Med Bull* 1999;46:263–8.

61 Bauer MS, McBride L, Williford WO, *et al*. Collaborative care for bipolar disorder: part I. intervention and implementation in a randomized effectiveness trial. *Psychiatr Serv* 2006;57:927–36.

62 Bauer MS, McBride L, Williford WO, *et al*. Collaborative care for bipolar disorder: part II. impact on clinical outcome, function, and costs. *Psychiatric Services* 2006;57:937–45.

63 Bauer MS, Biswas K, Kilbourne AM. Enhancing multiyear guideline concordance for bipolar disorder through collaborative care. *Am J Psychiatry* 2009;166:1244–50.