Clinical trial

Clin Ter 2020; 171 (2):e7-93. doi: 10.7417/CT.2020.2194

Enhancing adherence to antipsychotic treatment for bipolar disorders. Comparison of mobile app-based psychoeducation, group psychoeducation, and the combination of both: protocol of a three-arm single-blinded parallel-group multi-centre randomised trial

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Abstract

Group Psychoeducation (PE) is an effective strategy to enhance adherence to antipsychotic treatment in Bipolar Disorders (BD). However, it requires attendance to weekly sessions during a period of about 6 months. This may impede its application for those patients living far from mental health centres, resulting inequality in access to evidence-based care. Therefore, there is an increasing need to find new efficient strategies to deliver and extend PE programs to a wider population of BD patients. Mobile apps are a cost-effective way to deliver PE. In the Italian healthcare context, no evidence about the use of apps is available. The current paper presents the protocol about the development of a smartphone app to deliver PE for BD and the protocol for a trial assessing its effectiveness. In euthymic BD patients, the study will compare the adherence rates to antipsychotics between PE delivered through Bipolar mobile Application (Bip.App), group PE and a combination of both, will investigate demographic, socio-cultural and clinical predictors of lower adherence in the arms, and will investigate whether PE combined with Bip.App is associated with lower risk of recurrence of (hypo)manic and depressive episodes than group PE alone, and assess the feasibility and satisfaction for Bip.App. Participants will be recruited from mental health centres and included if they are 18-65 year-old, have primary BD in the euthymic phase, they have been prescribed a second-generation oral antipsychotic as a maintenance/prophylactic therapy for at least 1 year, they have not undergone a structured protocol of PE for BD, they have access to a smartphone and sufficient competence in using it. Participants will be excluded if they have neurological disease, mental retardation or learning disability, psychosis, limited fluency in Italian. Adherence will be assessed through count pills, blood levels, and self-reported adherence. A single-blinded parallel-group superiority multi-centre randomised controlled trial design will be used. ***Clin Ter 2020; 171 (2):e87-93. doi: 10.7417/CT.2020.2194***

Key words: *Bipolar disorder, psychoeducation, antipsychotics, self-management, euthymia, depression, mania*

Introduction

Adherence to antipsychotics in Bipolar Disorders: a challenging issue

Second-generation oral antipsychotics are effective and safe for long-term prophylactic and maintenance management of Bipolar Disorders (BD), and can be used as a monotherapy or an adjunct to mood stabilizers (1). However, non-adherence to antipsychotics in BD is a relevant phenomenon: mean rates of adherence to antipsychotic medication in BD are approximately 40% (2). Poor adherence includes discontinuation or intermittent assumption of medication. Such behaviour has a negative impact in terms of clinical and economic outcomes associated, increasing the risk of recurrence of episodes, hospitalization and chronicity (2). Factors associated with non-adherence include (a) demographics (male gender, young age, younger illness-onset, non-Caucasian ethnicity); (b) clinical factors (substance abuse and previous mania with psychosis, poor insight); (c) treatment-related factors (adverse effects and regimen complexity) (3).

Some assessment methods of adherence have been developed. According to guidelines (4), percentage of medication not taken is the preferred method of defining adherence, with 80% or more of medication taken endorsed as an appropriate cut-off for adherence in BD. The experts recommend that, if possible, clinicians use objective measures (e.g., pill counts, pharmacy records, and, when appropriate, serum levels) (4).

Psychoeducation: a strategy to enhance adherence

Psychoeducation (PE) has shown to be an effective strategy to enhance adherence in BD, including antipsychotics

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ISSN 1972-6007

(5) PE consists of providing information to the patient about his/her illness and its treatment, improving his/her awareness about symptoms, early warning signs of relapse, protective behaviours. Several PE manuals have been published.[6] PE is delivered during the euthymic phase, to ensure a better assimilation of the information provided, as a prophylactic treatment for relapse (6) Systematic reviews show that group PE is associated with lower relapse and better adherence rates than individual PE (7).

The new frontiers of BD management: using smartphones to deliver psychoeducation

Technology-based tools as an alternative or complementary way to deliver PE can be implemented as stand-alone interventions or as an adjunct to standard evidence-based treatments for BD (8). Researchers and clinicians are more and more interested in smartphones as a strategy, specifically for the development of mobile apps (9). Through the increasing embedded sensors and daily usage patterns, smartphones can collect a vast amount of information to identify behavioural symptoms patterns (9). Recently Hidalgo-Mazzei et al. developed the *SIMPLe* app (10). The researchers tested its feasibility on patients attending a mental health clinic: over 86% reported that the experience using the app was satisfactory (10).

Rationale of the study

Although PE is the first-line cost-effective strategy for the prevention of recurrence of BD episodes and also for the improvement of adherence to medication, group PE requires attendance to weekly sessions during a period of about 6 months. This may impede its application for those patients who live far from the specialist mental health centres, resulting in quite substantial inequality in access to evidence-based care. Therefore, there is an increasing need to find new efficient strategies to deliver and extend PE programs to a wider population of BD patients. Smartphone-delivered PE might be an alternative, cost-effective way to deliver information about the illness to the patient with the aim to empower him/her against recurrence of episodes, strengthening his/her adherence to antipsychotics. In addition, it might be hypothesized that the combination of group PE and smartphone-based PE offer a more powerful option to improve the patient's self-monitoring and self-management, which can increase adherence. While in some countries, there is an increase of pilot investigations testing the usefulness of apps as a way to deliver PE, in the Italian healthcare context there is a lack of new-technology-based tools to enhance standard evidence-based treatments for psychiatric illness.

Objectives

Phase I: development of Bip.App (Bipolar Disorders Mobile Application)

The first phase of the study will consist of the development of a mobile app for smartphones as a tool to deliver PE materials for BD. The app, which will be defined as Bip.App, will be developed by a team composed by an informatician with at least ten-year experience in the field of app construction, by a psychiatrist and a psychologist expert in BD and PE.

A User-Centred Design (UCD) method will be used to gather requirements and iteratively design the features of the app, therefore involving all team members in the iterative process. UCD methods are commonly used in contemporary design and, in particular, for consumer-oriented products. This process consists of different stages. Initially, end-users' needs, concerns, and aspirations must be identified. This is necessary for achieving the application goals. In a next stage, the project will need to consider the possible environments in which the application will be used. The environment variables include social and cultural aspects and the communication styles. The outcome will be useful for creating the design guidelines. The user-centred design is a cyclical process which will be implemented before, during and after the realisation of the app. According to the specific indications for software usability defined in the ISO/IEC 9126-1, (11) usability is "the capability of the software product to be understood, learned, used and attractive to the user, when used under specified conditions". Usability principles will drive the process, accordingly to its general definition (ISO 9241-11, 1997): "the extent to which a product can be used by specified users to achieve specified goals with effectiveness, efficiency and satisfaction in a specified context of use". This design phase will involve qualitative and quantitative data analysis and a life-cycle performance analysis will be conducted in conjunction with these activities.

Phase II: the protocol for the trial

In a group of euthymic individuals with a diagnosis of BD, the current study will aim:

1. to compare the adherence rates to antipsychotics between a group randomly assigned to PE delivered through a smartphone app ("*Bipolar mobile Application*": Bip. App), a group assigned to group PE and a group assigned to group PE combined with Bip.App. Adherence will be considered as the primary outcome.
2. to investigate socio-demographics as predictors of lower adherence in the different arms. Following the literature, (1) socio-demographic predictors will be considered (a) age, (b) gender, (c) marital status, (d) education level, (e) working status. Socio-cultural variables will include migrant status, religiosity.
3. to investigate clinical predictors of lower adherence rates in the different treatment arms. Following the evidence, (1) clinical variables will include (a) baseline severity of (hypo)manic symptoms, (b) depressive and anxiety symptoms, (c) positive and negative psychotic symptoms, (d) general functioning and quality of life, (e) level of illness insight, (f) comorbidity of personality disorders, (g) number of prescribed medications.
4. to assess the feasibility and satisfaction for Bip. App.

Methods

Participants' inclusion/exclusion criteria

Participants will be included if: (a) they are 18-65 years old; (b) they have a primary BD diagnosis according to the DSM-5; (12) (c) they are on the euthymic phase since at least

one month, as indicated by a score lower than 8 points on the Hamilton Depression Rating Scale (HDRS) (13) and a score on the Young Mania Rating Scale (YMRS) (14) lower than 6 points; (d) the duration of the euthymic phase is at least one month; (e) they have been prescribed a second-generation oral antipsychotic as a maintenance/prophylactic therapy for at least 1 year (the dosages will be those prescribed according to routine practice); (f) they have not undergone a structured protocol of PE for BD; (g) they have access to a compatible smartphone and sufficient competence in using it. Either Type I and Type II BD will be included; (h) they provide written informed consent to participate. Antipsychotics can be prescribed as a monotherapy, as augmentation or in combination with mood stabilizers or antidepressants. Participants will be excluded if they have: (a) neurological disease; (b) mental retardation or learning disability; (c) psychotic disorder; (d) limited fluency in Italian. Comorbid medical and psychiatric disorders, including personality disorders and any other Axis I conditions, will not be excluded. Exit criteria will be voluntary interruption of the participation and the re-occurrence of a (hypo)manic or depressive episode.

Recruitment strategies

Eligible participants will be identified and recruited through different strategies, including advertisements on the study website, sheets and e-mail messages sent to public and private mental health professionals. Participants will be referred by mental health professionals working in public or private settings or can self-refer to the clinic.

Baseline assessment and screening on BD

BD and any comorbid baseline Axis I disorder will be assessed through the Structured Clinical Interview for Axis I Disorders (SCID-I) (15). Comorbid personality disorders will be investigated through the Structured Clinical Interview for Personality Disorders (SCID-II) (16). The Clinical Global Impression (CGI) (17).

Adherence to antipsychotics

Adherence to antipsychotics will be assessed through objective (count pills and blood levels) and subjective measures (adherence self-reported by the patient). An overview of the measures is presented in Table 1.

Primary outcome: pills' count

Pills' count will be used as the primary outcome. Medication adherence will be evaluated using the medication possession ratio (MPR) for antipsychotics (18). The MPR will be used as the primary outcome, measured as a quantitative continuous variable. The MPR is defined as the ratio of the "Number of days' supply of medication that a patient has received" to the "Number of days' supply that he/she should have received". An MPR value equally to 1 or 100% indicates that the patient has received all medication needed to take antipsychotic medication as prescribed, whereas an MPR of 0.5% or 50% indicates that the patient has received medication sufficient to take only half of the prescribed dose. In cases where an individual is on two antipsychotics, a weighted average of the two MPRs will be calculated. According to Gilmer et al., (18) patients' degree of adherence will be assessed in three clinically relevant categories.

Blood levels

Blood samples will be routinely collected between 9 and 11 a.m. from all patients. When considering serum concentrations of antipsychotics, the concentration⁄dose ratio will be used, as it gives the best picture of drug intake (19). As suggested by Velligan and colleagues, (4) the patients will be grouped into three groups with regard to the concentration⁄dose ratio provided by the laboratory: 1) not detectable, 2) low levels, 3) within reference range or higher, as described previously (20).

Self-reported adherence to antipsychotics and informal caregiver-reported adherence

Adherence will be measured also through a self-monitoring diary, where the patient is asked to self-evaluate daily how many pills of the prescribed antipsychotic medications he/she has missed.

Secondary outcomes

The Young Mania Rating Scale (YMRS) (14) will be used to assess (hypo)manic symptoms. The Positive And Negative Syndrome Scales (PANSS) (21) will be used as a measure of psychotic symptoms. The Hamilton Depression Rating Scale (HAM-D) (13) will be used as a measure of severity of depressive symptoms. The Hamilton Anxiety Rating Scale (HAM-A) (22) will be used to measure anxiety symptoms. The Medical Outcomes Survey Short Form-36 (SF-36) (23) will be used as a measure of Health Status and quality of life. The Global Assessment of Functioning scale (GAF) (24) combines the evaluation of symptoms as well as relational, social and occupational functioning on a single axis. The UKU Side Effect Rating Scale (UKU-SERS-Pat) (25) will be used to measure the perception of side effects associated with antipsychotic medications.

Satisfaction for Bip.App and feasibility

Satisfaction for the mobile app will be evaluated through a questionnaire based on Hidalgo-Mazzei et al. (2016)

Table 1. Overview of measures of adherence to antipsychotics

Objective measures of adherence	**Assessment time-points**
Blood levels	Each month
Pills' count (MPR < 0.50 = non-adherence, 0.50 < MPR < 0.80 = partial adherence, MPR > 0.80 = full adherence)	Every 2 weeks
Subjective measures of adherence	
Self-monitoring diary completed daily by the patient	Every 2 weeks
Diary completed by an informal caregiver	Every 2 weeks

to assess their *SIMPLe* app. It covers Overall satisfaction, Utility according to the patient's condition and clinical state, Discretion and invasiveness on daily usage, Technical difficulties experienced. Feasibility will be measured through the System Usability Scale (SUS), (26) a scale covering aspects related to usability of the system, including Usability and Learnability.

Design and procedure

The trial will be conducted according to *The Standard Protocol Items: Recommendations for Interventional Trials* (SPIRIT 2013) (27). A single-blinded parallel-group superiority multi-centre randomised controlled trial design will be used. Participants on antipsychotic medications will be randomly assigned to group PE + Bip.App, Bip.App alone or group PE alone. The Flow Chart on progression over all the study is provided in Figure 1, according to CONSORT. Random sequence will be created by a computerized program. An independent researcher, not involved in the study, will assign participants to arms. Allocation will be conducted through a 1:1:1 blocking procedure. Random sequence will be concealed by an independent researcher, who will put random numbers into envelopes. Allocation concealment will be ensured, as the researcher will not release the randomization code until the patient has been recruited into the trial, which takes place after all baseline measures have been conducted. Assessment at baseline, post-treatment, and follow-up assessments will be conducted by blind independent assessors.

Each participant will be followed over one year. Both PE and the use of Bip.App will be delivered after allocation to the arm (Table 2). After treatment allocation, adherence

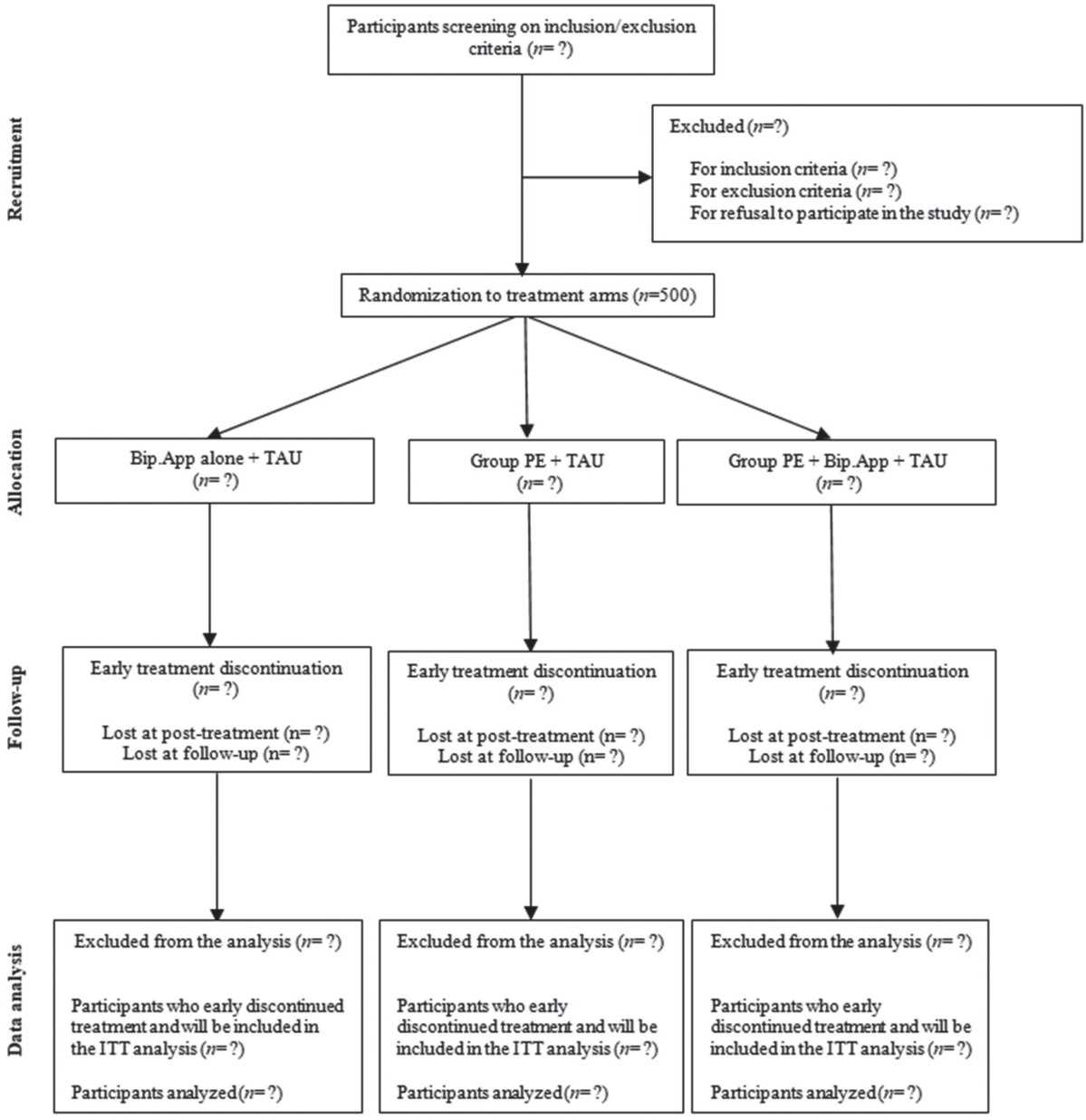

Fig. 1. CONSORT flowchart.

Table 2. Timeline

	Recruitment	Treatment	Post-treatment (4 months)	FU (8 months)	FU (1 year)
TIMEPOINT	t_0	t_1	t_2	t_3	t_4
RECRUITMENT					
Screening on inclusion/exclusion criteria	*X*				
Informed consent	*X*				
Random assignment to treatment arms	*X*				
ARMS					
Bip.App + TAU		X			
Group PE + TAU		X			
Bip.App + group PE + TAU		X			
ASSESSMENT					
SCID-I	*X*				*X*
SCID-II	*X*				*X*
CGI	X		*X*	*X*	*X*
SELF-REPORTED ADHERENCE	*X*	*X*	*X*	*X*	*X*
PILLS' COUNT	*X*	*X*	*X*	*X*	*X*
BLOOD LEVELS	*X*	*X*	*X*	*X*	*X*
YMRS	*X*		*X*	*X*	*X*
PANSS	*X*		*X*	*X*	*X*
HAM-D	*X*		X	X	*X*
HAM-A	*X*		*X*	*X*	*X*
SF-36	*X*		*X*	*X*	*X*
GAF	*X*		*X*	*X*	*X*
UKU-SERS-Pat	*X*		*X*	*X*	*X*
SUS			X		

measures (primary outcomes) will be assessed monthly/biweekly until follow-up after one year, while secondary outcomes will be assessed every four months.

The trial will be conducted in compliance with the Declaration of Helsinki. All the participants who will be screened for inclusion and all those who will be assigned to treatment arms will be provided a detailed description of the study's characteristics, of the aims, and the treatments offered.

Group PE and Bip.App

Group PE will be delivered by two clinical psychologists or psychiatrists. The PE protocol published in the manual of Colom and Vieta[6] will be applied. The group PE will be delivered in each of the centres. Group PE will be delivered for 21 weekly sessions of 90 minutes. The sessions will be delivered in a group setting of 8-12 patients with BD. Each session will aim at improving four key domains: illness awareness, adherence to medications, early identification prodromal warning signs and symptoms of recurrence, and life-style regularity. All the participants who will be assigned to group PE alone, will be offered the opportunity to use Bip.App after the conclusion of the trial. Training for the PE arms will consist of a 3-day intensive practical workshop delivered by a trainer expert in PE. The training will also include readings, discussion and role-play meeting. The same workshop will be delivered for all the professionals involved in all the centres. The contents included in the mobile app will be based on the materials of the protocol of Colom and Vieta (6).

Treatment as usual (TAU)

TAU will be delivered to all the patients and it will consist of routine psychiatric management delivered in each of the centres involved. TAU will be delivered by a psychiatrist. TAU will include the prescription of antipsychotic medications based on routine care, including mood stabilizers, antipsychotics, antidepressants and/or anxiolytics.

Data analysis plan

The estimated sample size will be 500 participants to be enrolled and randomly assigned to arms. An intention to treat approach will be used with The last observation carry-forward technique. Differences on the socio-demographic and clinical characteristics will be analysed through independent sample t-tests or chi squared statistics. Within- and between- effect sizes will be computed as unbiased Hedges' *g*. Differential effects of treatment arms on adherence rates will be assessed conducting time x group repeated measures ANOVAs. In order assess the effects of each treatment arm on secondary outcomes repeated measures ANCOVA (time x group interaction) will be applied adjusting for age, baseline mania/depressive/psychotic/severity. For all the analyses statistical significance will be set at a 0.01 *p*-value.

Discussion and conclusions

Although PE is the first-line intervention for the prevention of recurrence of BD episodes and for the improvement of adherence to medications, standard group PE courses require attendance to weekly sessions during a period of about 6 months, resulting in obstacles for those patients with difficulties accessing to evidence-based care. Therefore, there is an increasing need to find new efficient strategies to deliver and extend PE programs to a wider population of BD patients. While in some countries, there is a large amount of investigations that tested the usefulness of smartphone apps as a way to deliver PE, in the Italian healthcare context there is still a lack of new-technology-based tools to enhance standard evidence-based treatments for psychiatric illness.

Smartphone can be a familiar tool, easy to use, not linked to stigmatized representations of psychiatric therapy and therefore well accepted by patients as support for the therapeutic strategy. Smartphone-delivered PE could be an alternative, tailored, cost-effective way to deliver important information about the illness to the patient with the aim to empower him/her against recurrence of episodes, strengthening his/her adherence to antipsychotic medications. In addition, it could be hypothesized that the combination of standard group PE and smartphone-based PE can offer a more powerful option to improve the patient's self-monitoring and self-management processes, which can increase adherence to the prescribed treatment.

The clinical implications of the use of new strategies enhancing medication adherence may be that higher adherence to treatment can contribute to an improvement in different aspects related to BD, including remission and relapses. This might contribute to a reduction in healthcare costs related to repeated hospitalizations or treatments of the acute stages of the disorder. From an organizational perspective, improving patients' adherence to medication might contribute to reducing the workload of the health professionals involved in standard PE, and to optimising the commitment in relation to the specific needs of users involved in mental health services.

Finally, from a public health perspective, the maintenance of a symptom remission will also allow patients to be integrated into different life contexts (family, work, etc.) with an impact on quality of life (28-29). The present trial has also some methodological strengths including the randomised design according to CONSORT guidelines, the use of objective and subjective indicators of medication adherence, and the use of a multicentre recruitment.

A potential limitation of the trial will be the involvement of immigrant patients who might have difficulties reading/understanding the PE materials contained in the app; this point should be considered carefully as the immigrant population is a group at higher risk of developing psychotic spectrum symptoms (30). In addition, those patients who do not have access to a smartphone might be excluded from the study, thus determining a sample selection bias.

In conclusion, the current paper presented the proposal about the development of a new mobile app and the protocol of the first Italian trial on the use of a mobile app aimed to enhance adherence to antipsychotic medication in BD patients. The use of new technologies may have important public health implications that optimise the delivery of evidence-based treatments for populations of patients who are resistant to standard care or have poor access to it.

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