Use of a serious game to strengthen medication adherence in euthymic patients with bipolar disorder following a psychoeducational programme: A randomized controlled trial

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Kathlyne Dupuis Maurin[1], Chloé Girod[1], M.D., Julia Lou Consolini[3], PhD, Raoul Belzeaux[3, 7], MD, PhD, Bruno Etain[4, 7], MD, PhD, Barbara Cochet[5], Marion Leboyer[5, 7], Catherine Genty[1,2], Lucie Gamon[6], Marie Christine Picot[6], MD, PhD, Philippe Courtet[1,2, 7] MD, Ph.D, and Emilie Olié[1,2, 7] MD, PhD.

[1] Department of Emergency Psychiatry and Post-Acute Care, CHRU Montpellier, France
[2] INSERM U1061, Neuropsychiatry: Epidemiological and Clinical Research, Montpellier, France.
[3]APHM, Department of psychiatry, INT-UMR7289, CNRS Aix Marseille University, Marseille, France
[4]Université de Paris, INSERM UMRS1144 and Assistance Publique des Hopitaux de Paris – Hôpital Fernand Widal, Paris, France
[5]Assistance Publique des Hôpitaux de Paris, CHU Henri Mondor-Albert Chenevier, Creteil, France
[6] Department of Medical Information CHRU Montpellier, France
[7] Fondamental Foundation, Créteil France

Corresponding author: Dr Emilie Olié, Department of psychiatric emergency and post-acute care, Lapeyronie Hospital 191 avenue Doyen Gaston Giraud 34295 Montpellier cedex 5 France

Tel.: +33 4 67 33 85 81 / Fax: +33 4 67 33 89 88

Email: e-olie@chu-montpellier.fr

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Kathlyne Dupuis Maurin: contributed substantially to data interpretation and drafted the manuscript.

Chloé Girod, Julia Lou Consolini, Raoul Belzeaux, Bruno Etain, Barbara Cochet, & Marion Leboyer: contributed to patients' recruitment, revised the manuscript critically for important intellectual content.

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AstraZeneca Pharmaceutics, in collaboration with Ubisoft, developed BIPOLIFE®, a serious game for patients with bipolar disorder. Astra Zeneca funded psychologists and clinical research associates. They did not intervene in the study design and data interpretation.

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Abstract (234 words)

Background: Although psychoeducation programmes are the gold-standard intervention in bipolar disorder (BD), more innovative tools are needed to broaden and consolidate their effects, especially on treatment adherence. Serious games could be an option.

Methods: We carried out a two-arm open randomized controlled trial to compare the add-on use of the serious game BIPOLIFE® for one month (n=20) vs. treatment as usual (TAU; n=21) following the completion of a psychoeducation programme in euthymic adults with BD. The primary outcome was the percentage of adherent patients (i.e., patients with a Medication Adherence Rating Scale, MARS, total score >7) at 4 months after the end of the psychoeducation programme. We also measured the changes in therapeutic adherence and beliefs on pharmacological treatments (Drug Attitude Inventory, DAI) between study inclusion and the 1-month (end of BIPOLIFE® use) and 4-month visits, healthcare use during the study period, and BIPOLIFE® acceptability.

Results: The percentage of adherent patients was lower in the BIPOLIFE® group than in the TAU group at inclusion (p=0.02). Conversely, the absolute variation of the MARS and DAI scores was higher in the BIPOLIFE® than in the TAU group at the 1-month visit (p=0.03 and p=0.002, respectively) but not at the 4-month visit (p=0.22 and p=0.07, respectively).

Limitations: Small sample size, and low frequency of connexion to BIPOLIFE® declared by the patients.

Conclusion: BIPOLIFE® may help patients with BD to increase their confidence in medications, if used regularly.

Keywords: Serious game, bipolar disorder; psychoeducation; BIPOLIFE®; medication adherence; psychosocial intervention

1 Introduction

More than 50% of patients with bipolar disorder (BP) do not take their medications as prescribed (Leclerc et al., 2013). Poor medication adherence is associated with a higher risk of mood recurrence, cognitive impairment, depressive residual symptoms, and suicidal acts, as well as increased use of mental healthcare and poorer quality of life (Altman et al., 2006, Gonzalez-Pinto et al., 2006, Gianfrancesco et al., 2008, Martinez-Aran et al., 2009, Belzeaux et al., 2013, Sparding et al., 2015). Psychoeducational programmes have been developed to improve medication adherence. Their short-term (i.e., just after programme completion) efficacy has been demonstrated (D'Souza et al., 2010, Javadpour et al., 2013), but their positive effects seem to decrease in the long term. For instance, Eker and Harkin (2012) reported that 13% of patients who completed a psychoeducational programme were non-adherent 6 weeks later. Colom et al. (2003) found higher lithium but not valproate and carbamazepine plasma levels in patients enrolled in a psychoeducation programme compared with controls (no programme) at the 2-year follow-up visit. Conversely, at the 5-year visit, treatment adherence (on the basis of the patients' clinical assessment, first-degree relatives' interviews, and plasmatic dosages of mood stabilizers) was not different between patients in the psychoeducation programme and controls (Colom et al., 2009). Therefore, additional innovative tools should be developed to consolidate the psychoeducation programme positive effect on medication adherence because most of these programmes do not include booster sessions for maintaining the effects.

One potential strategy could be serious games. These are "interactive computer applications, with or without a significant hardware component, that have a challenging goal, are fun to play with, incorporate some concept of scoring, and impart in the user a skill, knowledge or attitude which can be applied in the real world" (Bergeron, 2006). Some serious games have been developed for psychiatric patients. For example, SPARX is an interactive fantasy game designed to deliver cognitive behavioural therapy for depression. Its use efficiently reduced depressive symptoms at the 3-month follow-up in depressed adolescents compared with patients treated as usual (Merry et al., 2012). In BD, it has been shown that using new technologies to provide complementary mental care is feasible and acceptable. For instance, the use of a mobile application to monitor thymic status and early warning signs after a psychoeducation programme can improve depressive symptoms. Moreover, the compliance to this application is good (Depp et al., 2015). SIMPLE, a smartphone-based psychoeducation programme (Hidalgo-Mazzei et al., 2016), is another satisfactory and acceptable add-on instrument for BD self-management. Finally, MoodSwings 2.0, an internet-based self-

management programme that includes psychoeducation and cognitive behavioural therapy, efficiently improved depressive symptoms in patients with BD with a good acceptability (Gliddon et al., 2019).

Recently, AstraZeneca Pharmaceutics, in collaboration with Ubisoft, developed BIPOLIFE®, a serious game (or edutainment tool) for patients with BD. This interactive tool gives information about BD and its management, and the influence of routine daily behaviours on mood. BIPOLIFE® wants to highlight the importance of: 1/ adherence to medication, 2/ healthy lifestyle (regular sleep, physical activity, social contacts, and avoidance of alcohol and illicit substances), and 3/ visit to a psychiatrist in case of relapse.

We hypothesized that BIPOLIFE® could be used as an additional tool to strengthen the immediate benefits of a psychoeducational programme on therapeutic adherence. To this aim, we carried out a randomized controlled study to compare compliance rate up to 4 months after completion of psychoeducation in patients using or not BIPOLIFE®. Our secondary objectives were to assess modifications in beliefs/attitudes towards medications and BIPOLIFE® acceptability.

2 Methods

Study design

This study was a prospective, open, randomized controlled trial, registered at clinicaltrials.gov (Clinical Trial ID#NCT02936466). Eligible participants were randomly assigned with a 1:1 ratio to connect to BIPOLIFE® for 4 weeks as an add-on tool to their treatment, or to follow their treatment as usual (TAU). The randomization sequence was centralized and computed in blocks of four for each level of stratification by the study statistician in an order unknown by the investigators.

Population

Participants were recruited from the Departments of Psychiatry in three French Academic Hospitals (Montpellier, Marseille, and Créteil). Inclusion criteria were: older than 18 years of age; diagnosis of BD according to the DSM-IV TR; being euthymic, defined by a total Montgomery and Asberg Depression Rating Scale (MADRS) score <12, and Young Mania Rating Scale (YMRS) score <8 during the last 3 months; having completed a psychoeducation programme within the week preceding their inclusion; having attended more than half of the psychoeducation sessions; having access to internet; and being able to speak, read and understand French.

The psychoeducational program preceding the intervention was led by two trained caregivers (nurse, psychologist and / or psychiatrist) of the center. It was consisting of 12 weekly sessions of 90 min and included up to 12 patients (adapted from Colom and Vieta (2008)).

The primary outcome was the adherence rate, defined by a Medication Adherence Rating Scale (MARS) total score >7 (Thompson et al., 2000, Rosa et al., 2007) at the 4-month follow-up visit. Secondary outcomes were the variation of MARS adherence score, attitude toward psychiatric medications assessed using the Drug Attitude Inventory (DAI-10) (Hogan and Awad, 1992), and healthcare use between the inclusion and the 1- and 4-month follow-up visits. Moreover, the serious game acceptability and satisfaction were also investigated in the intervention group.

The study was conducted in accordance with the CONSORT ethical guidelines. All participants signed a written informed consent form. The study was approved by the Montpellier University Hospital (CPP Sud Mediterranée IV) ethics committee.

Treatment conditions and procedures

Serious game BIPOLIFE®

BIPOLIFE® is a gaming experience centred on an avatar who has BD and acts in a variety of everyday life situations. The objective is to learn how to regulate the avatar's mood and energy levels by making daily life choices. The player must balance mood and energy levels to reach a situation of euthymia.

First, patients choose a personalized avatar (gender, name, physical appearance). Then, during a tutorial, they discover the rooms of the house where the avatar lives and the possible interactions with the environment (Figure 1). The rooms represent the main domains of the patient's life. The living room stands for social life, the kitchen stands for personal health practices, the office stands for business/work, the bedroom stands for sleep, and the bathroom stands for hygiene/self-care. A clock helps to identify the time of actions during the day. During the tutorial, the avatar gradually shows more manic symptoms, leading to hospitalization. Patients receive information on the characteristics of the manic and depressive phases, and advice on how to manage them by watching the psychiatrist and the avatar. Then, the serious game starts.

Patients have to drive their avatar through daily actions: eating, sleeping, taking medications, having fun, learning about BD, calling the psychiatrist or friends, avoiding alcohol/illicit substances, and practicing sports. Patients receive feedbacks ("bonus" or "malus" points)

related to the consequences of their decisions on the avatar's mood and energy levels. The game is over when the patient manages to maintain the mood/energy balance for 3 consecutive virtual days. In addition to "bonus" or "malus" points, the computer provides messages to promote appropriate actions he/she could do. For example when the avatar is standing in the kitchen at a given period of the day, a message "you could have breakfast" may appear. In addition, the patient is invited to read short messages to learn about the consequences of given actions during the game. For example, the patient may have explanations about why practicing sport may be associated with bonus points during euthymia (i.e. to promote physical health) or malus points when the level of energy is high (i.e. symptom of mania).

Patients were asked to play how often and how long they wanted during the month following their inclusion. The frequency and mean duration of connection were rated by patients during the follow-up visits.

Treatment as usual (TAU)

TAU consisted of visits to the referral psychiatrist and the prescription of at least one mood stabilizer. The frequency of visits to the psychiatrist was not standardized; it was defined by the referral psychiatrist who was not systematically involved in the study. Patients could receive any additional pharmacological treatments or could follow any additional psychotherapeutic programs.

Assessments

Clinical assessments were carried out by trained psychologists or psychiatrists who remained blind to the group allocation. Participants were instructed not to communicate their group assignment. Three visits were planned: pre-intervention (inclusion) within the week following the completion of the psychoeducation programme, at 1 month after inclusion (at the end of the period of BIPOLIFE® use for the intervention group), and at 4 months after inclusion. Sociodemographic (sex, marital status, level of study, occupational status) and lifetime axis I diagnoses according to the DSM-IV using the MINI 5.00 (Sheehan et al., 1998) were recorded at inclusion. At inclusion and at each follow-up visit, clinicians assessed depressive and manic symptomatology using the MADRS (Montgomery and Asberg, 1979) and the YMRS questionnaires (Young et al., 1978), and global functioning using the Functioning Assessment Short Test (FAST) (Rosa et al., 2007). They also recorded the number of visits to a psychiatrist (scheduled/emergency/attended) and to the emergency department, and the

number of hospitalizations for psychiatric reasons since the last visit, based on the patient's declarations.

Patients assessed their medication adherence using the MARS (Thompson et al., 2000) and their beliefs on pharmacological treatments using the DAI-10 (Hogan and Awad, 1992). Patients in the intervention group were asked to rate their satisfaction about the BIPOLIFE® game at the 1-month follow-up visit.

2.1 Statistical analysis

Baseline characteristics were described for each group using means and standard deviations (SD) or median and inter-quartile ranges (IQR) for continuous variables, and frequencies and proportions for categorical variables.

The primary analysis was performed according to the intention to treat principle, and involved all patients for whom data on the primary outcome (MARS score) at inclusion and at the 1- and 4-month follow-up visits were available (full analysis set).

Categorical data (primary and secondary outcomes) were compared using the chi-square test. Continuous variables (total MARS, YMRS, FAST, DAI scores and their absolute variation between inclusion and follow-up visits) were compared between groups using the Student's *t*-test (in the case of normal distribution) or the Mann Whitney test. The bilateral significance threshold was set at 5%. The effect size was estimated with the Cohen's d. All analyses were performed with Statistical Analysis Software (SAS Institute, Cary, North Carolina).

3 Results

3.1 Participant flow

The participant flow is shown in Figure 2 : 43 patients signed the consent form; one patient had a manic relapse before randomization, and one patient withdrew the consent. Therefore, 41 patients were randomized at inclusion.

In the BIPOLIFE ® group (n=20), one participant was lost to follow-up during the first month, and one between the 1- and 4-month follow-up visits. Another participant had a depressive relapse during the study period. Fifteen patients (75%) connected to BIPOLIFE during the first month (and five continued to connect afterwards). Ten participants (50%) completed the BIPOLIFE® game during the first month (i.e., maintained the avatar's mood/energy balance for 3 virtual days).

In the control group (TAU; n=21), only one participant was lost to follow-up between the 1- and 4-month follow-up visits.

In total, data were available for 41 participants at inclusion (after the psychoeducation programme), for 40 patients (98%) at the 1-month visit (end of the intervention), and for 37 patients (90%) at the 4-month visit.

3.2 Baseline characteristics (Table 1)

At inclusion, sex, marital status, education level, occupational status, BP type, current psychiatric comorbidities, BP duration, and number of hospitalizations for mental health reasons were not significantly different between groups. Antidepressant intake was more frequent in BIPOLIFE® than in TAU group.

3.3. Mood and global functioning during the study period (Table 2)

All patients (but one) remained euthymic during the study period. Depressive (MADRS score) and manic symptomatology (YMRS score) and global functioning (FAST score) were comparable between groups. The patients were euthymic according to MADRS and YMRS scores, with a mildly to moderately impaired global functioning according to FAST score.

3.4. Adherence and attitudes towards treatment (Table 3)

At inclusion, the percentage of patients with MARS score >7 was higher in the TAU than in the BIPOLIFE® group (90% vs. 40%, p= 0.02). The difference was no longer significant at the 1-month (68% vs 81%; p=0.36) and 4-months visits (80% vs. 53%; p=0.07).

Moreover, the absolute variation of the MARS and DAI scores was higher in the BIPOLIFE® than in the TAU group at the 1-month visit (p=0.03 and p=0.002, respectively) but not at the 4-month visit (p=0.22 and p=0.07, respectively).

The number of consultations with a psychiatrist (scheduled or in emergency) during the study period was not significantly different between groups (data not shown).

These results remained unchanged when considering per protocol analyses, i.e. only patients having declared at least one connection to BIPOLIFE ® during the first month vs. TAU group (data not shown).

3.3 Acceptability and satisfaction with BIPOLIFE® (Table 4)

For the BIPOLIFE ® group (N=19), the median frequency of connexion to BIPOLIFE® was once per week (min-max : 0-5) for a median duration of 60 minutes (min-max : 0-180) par week. Four participants declared no connexion to BIPOLIFE®. When considering only patients declaring a connexion to BIPOLIFE ® during the first month (N=15), the median number of connexion was 1.5 times (min-max : 0.5 - 5) per week with a

mean weekly duration of 90 minutes (min-max : 20 - 180). Most participants said to be satisfied with BIPOLIFE®: 82% of participants found that the serious game content was informative and would be relevant to others, and 76% of participants thought that the information provided by the game was useful.

4. Discussion

Our study is the first to investigate the efficiency and acceptability of a serious game as an add-on psychoeducational tool in euthymic patients with BD. Our results suggest that the use of BIPOLIFE® after completing a psychoeducation programme improves medication adherence and attitudes towards medication at the 1-month, but not at the 4-month follow-up visit. Our results could be underestimated because three participants in the intervention group never connected to BIPOLIFE®. The serious game BIPOLIFE® may be an additional tool to propose to patients who have not reached adequate adherence after a conventional psychoeducational programme. While playing, the patient gradually learns to identify harmful actions that worsen mood and energy level, and also behaviours that promote mood balance. Our results on medication adherence are not explained by different access/use of psychiatric care between groups during the follow-up. Interestingly, the attitude towards medications, which is positively associated with medication adherence (Sharifi et al., 2009, Levin et al., 2016), was improved after the 1-month BIPOLIFE® intervention. Enhancing positive beliefs and attitudes towards treatment by playing BIPOLIFE® could contribute to strengthen medication adherence.

In our study, half of participants in the intervention group completed the BIPOLIFE® game (i.e. maintained the avatar's balance mood and energy for 3 consecutive virtual days). Lauder et al. (2015) found a similar rate of completion for online psychoeducation modules in patients with BD. This low completion may be explained by the age of our intervention group (46.58 ± 14.01 years) because older age decreases the odds of using internet (Bauer et al., 2016). It would be interesting to assess completion rate in younger patients with BD who are more at risk of poor compliance (Baldessarini et al., 2008, Proudfoot et al., 2012). For example, Merry et al. (2012) found good adherence rates to SPARX ®, a serious game for depressed adolescents: 60% of participants completed the game.

Patients declared that BIPOLIFE ® was a satisfactory instrument to provide and consolidate psychoeducational messages. We previously conducted a pilot study to assess acceptability and feasibility of BIPOLIFE ® in euthymic BD patients with encouraging results (Quintilla, 2013). Among 63 consecutive bipolar patients, only 11% could not be

enrolled in the study because of computer's defection or absence of access to internet. Moreover, all of patients reported to well understand information delivered by BIPOLIFE®. The game may improve adherence through psychoeducational messages but also through the observation of the consequences of actions of avatar on mood and energy. Some patients reported that if helped them to realize how quality of lifestyle and treatment adherence are important to manage bipolar disorder. Other patients reported that it was important to test actions on avatar in order to observe what the consequences were. By contrast, patients criticized the limited number of possible actions leading the game be repetitive. Finally, some patients pointed out that BIPOLIFE ® did not seem appropriate to be a psychoeducational tool for relatives.

Previous studies showed that patients consider useful the availability of psycho-education programs for BD on internet (Simon et al., 2011, Proudfoot et al., 2012, Todd et al., 2014, Barnes et al., 2015, Gliddon et al., 2019). It could be interesting to develop a BIPOLIFE® version for tablets and smartphones because they are more frequently used than computers for serious games in mental health (Lau et al., 2016). Moreover, the application format may help to increase BIPOLIFE® use over time. For instance, SIMPLE, a smartphone-based psychoeducational programme for BD, was still used by 74% of participants after 3 months (Hidalgo-Mazzei et al., 2016).

This study has some limitations. First, the sample size was small and may lack power to demonstrate an effect at 4 months. Second, BIPOLIFE® use was only declarative and not measured based on connexion data (e.g., frequency, duration). Participants declared to play BIPOLIFE ® on average once a week, with a connexion lasting for one hour, during the month following their inclusion. Patients declared to drastically reduce their rate of connexion during the follow up (5 patients connected to BIPOLIFE ® after the first month).It would be of great interest to define the minimal frequency or duration of connexion to have an improvement and to define a targeted population benefiting from such interventions.

Third, the limited and repetitive daily actions of the avatar may impair the motivation to regularly play to BIPOLIFE ®. To add other actions such as working, or having social contacts would make the game more playful and enhance patient's engagement (Shah et al., 2018).

Fourth, medication adherence was only evaluated according to a self-report measure, which may overestimates medication adherence compared to objective measures (Jonsdottir et al., 2010). WHO recommends to combine both subjective and objective measures (i.e. plasma levels or pill counts) (Sabate, 2003). Fifth, our results are not fully generalizable because the

study was only proposed to patients having completed more than 50% of the psychoeducation sessions.

Nevertheless, our results may encourage developing the use of add-on serious games to strengthen or maintain the effects of psychoeducation programmes.

Highlights

- Additional tools may help to maintain medication adherence after psychoeducational programmes
- BIPOLIFE® a serious game centred on an avatar teaches how to regulate mood and energy in everyday life
- BIPOLIFE® improves attitudes towards medications during the first month after a psychoeducation programme

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Table 1

Comparability of demographic and clinical variables between the two groups at inclusion

	BIPOLIFE ® (n=20)	TAU (n=21)
	n (%)	n (%)
Female	12 (60)	14 (66.7)
Age (years), mean (SD)	46.58 (14.01)	41.44 (7.62)
Study level >12 years	15 (75)	14 (66.7)
Marital Status		
Married	11 (55)	10 (47.6)
Single	5 (25)	7 (33.3)
Separated/divorced	4 (20)	4 (19.1)
Employed	13 (65)	14 (66.7)
Bipolar disorder *type*		
Subtype I	9 (45)	13 (61.9)
Subtype II	9 (45)	7 (33.3)
Not otherwise specified	2 (10)	1 (4.8)
Duration of disorder (years), mean (SD)	22.05 (13.88)	18.18 (11.69)
Current psychiatric comorbidity		
Anxiety disorder	6 (30)	9 (43)
Alcohol or substance abuse/dependence	1 (5)	1 (4.8)
Eating disorder	1 (5)	2 (10)
Mood state and functioning		
MADRS (score), mean (SD)	2.90 (1.74)	3.24 (2.57)
YMRS (score), mean(SD)	0.90 (1.52)	1.1 (1.97)
FAST (score), mean (SD)	19.1 (7.66)	22.29 (10.46)

MADRS : *Montgomery and Asberg Depression Rating Scale ; YMRS : Young Mania Rating Scale; FAST : Functioning Assessment Short Test*

Table 2

Mood state and Functioning during the study

	Post intervention (1 month)			Follow up (4 months)		
	Bipolife®	TAU		Bipolife®	TAU	
	mean (SD)	*mean (SD)*	*p value**	*mean (SD)*	*mean (SD)*	*p value**
MADRS	4.42 (4.18)	5.71 (8.21)	0.87	5.18 (7.33)	6.05 (5.25)	0.24
YMRS	2.00 (3)	1.33 (2.22)	0.63	1 (1.46)	2.4 (5.05)	0.91
FAST	19.26 (7.87)	20.43 (9.89)	0.77	16.41 (9.8)	20.9 (8.94)	0.15

**between group comparisons at each visit*

MADRS : Montgomery and Asberg Depression Rating Scale ; YMRS : Young Mania Rating Scale; FAST : Functioning Assessment Short Test

Table 2

Mood state and Functioning during the study

	Post intervention (1 month)			Follow up (4 months)		
	Bipolife®	TAU		Bipolife®	TAU	
	mean (SD)	*mean (SD)*	*p value**	*mean (SD)*	*mean (SD)*	*p value**
MADRS	4.42 (4.18)	5.71 (8.21)	0.87	5.18 (7.33)	6.05 (5.25)	0.24
YMRS	2.00 (3)	1.33 (2.22)	0.63	1 (1.46)	2.4 (5.05)	0.91
FAST	19.26 (7.87)	20.43 (9.89)	0.77	16.41 (9.8)	20.9 (8.94)	0.15

**between group comparisons at each visit*

MADRS : Montgomery and Asberg Depression Rating Scale ; YMRS : Young Mania Rating Scale; FAST : Functioning Assessment Short Test

Table 3

Adherence and attitudes towards treatment

	Pre-intervention (inclusion)			Post-intervention (1 month)			Post-intervention (4 months)		
	BIPOLIFE ®	TAU		BIPOLIFE ®	TAU		BIPOLIFE ®	TAU	
	mean (SD)	mean (SD)	p value *	mean (SD)	mean (SD)	p value *	mean (SD)	mean (SD)	p value *
Adherent patients (MARS total score >7),	11 (60%)	19 (90%	**0.02**	13 (68%)	17 (80%	0.36	9 (53%)	16 (80%)	0.07

n (%)			)			)				
DAI	total score	5.00 (4.70)	7.05 (2.65)	0.08	7.37 (3.59)	7.14 (2.33)	0.32	6.47 (3.43)	7.50 (2.59)	0.41
	absolute variation				2.42 (3.81)	0.10 (2.41)	**0.00 2**	1.88 (3.04)	0.60 (3.05)	0.07
MARS	total score	7.42 (2.12)	8.52 (1.03)	0.11	8.05 (1.96)	8.52 (0.98)	0.76	7.41 (2.27)	8.30 (0.98)	0.24
	absolute variation				0.72 (0.83)	0.00 (1.05)	**0.03**	0.31 (1.14)	-0.15 (1.09)	0.22

**p value: difference between groups at each visit*
DAI: Drug Attitude Inventory; MARS: Medication Adherence Rating Scale; TAU: Treatment As Usual

Table 4
Patients' opinion about BIPOLIFE® at the 4-month visit (N=17)

Use frequency	Always	Often	Rarely	Never
	n (%)	n (%)	(%)	n (%)
Informative content	9 (52.94)	5 (29.41)	-	3 (17.65)
Usefulness of content	9 (52.94)	4 (23.53)	1 (5.88)	3 (17.65)
Relevance to others	8 (47.06)	6 (35.29)	1 (5.88)	2 (11.76)

Figure 1: Image showing a screen shot of the *BIPOLIFE*® serious game

Figure 2: Flowchart