Research article

Long-term impact of pharmacist intervention in patients with bipolar disorder: extended follow-up to the EMDADER-TAB study

Andrea Salazar-Ospina [a,b,*], Pedro Amariles [a], Jaime A. Hincapié-García [a], Sebastián González-Avendaño [a]

[a] Grupo Promoción y Prevención Farmacéutica, Facultad de Ciencias Farmacéuticas y Alimentarias, Universidad de Antioquia UdeA, Calle 70 No 52-21, Medellín, Colombia
[b] Grupo de Investigación en Tecnología en Regencia de Farmacia, Facultad de Ciencias Farmacéuticas y Alimentarias, Universidad de Antioquia, Calle 70 No 52-21, Medellín, Colombia

ARTICLE INFO

ABSTRACT

Background: Pharmaceutical care (PC) through the Dader method (DMet) vs. the usual care process (UCP) significantly reduced psychiatric hospitalizations and emergency service consultations during one year of follow-up of outpatients with bipolar I disorder (BD-I). To date, the effect of long-term PC on the use of health services by BD-I patients once pharmacist intervention has ended is unknown.

Objective: To determine whether the effect of PC measured by the decrease in psychiatric hospitalizations and emergency service consultations is maintained one year after pharmacist intervention ceases.

Methods: This was a retrospective analysis of patients who had previously participated in a randomized, controlled, prospective, single-center clinical trial to compare PC (intervention group) vs. UCP (control group) in BD-I patients. Data were collected from November 2012 to March 2014. The primary outcome was the use of health services measured by the number of psychiatric hospitalizations and emergency service consultations. Descriptive statistics, Student's t-test, Kaplan–Meier function, and Log-Rank test were used.

Results: The study included 92 patients: 43 in the intervention group and 49 in the control group. Eleven psychiatric hospitalizations occurred for the intervention group and 19 for the control group. One year after pharmacist intervention ceased, there were no significant differences between the groups in psychiatric hospitalizations (p = 0.261). There were 14 emergency service consultations for the intervention group, and 24 for the control group without significant differences (p = 0.212).

Conclusions: PC through the DMet has no long-term effects on psychiatric hospitalizations and emergency department consultations in patients with BD-I following discontinuation of pharmacist intervention; the effect dissipates when the intervention ceases. Future studies should focus efforts on identifying factors associated with PC that explain why the outcomes derived from this intervention are not maintained in the long term.

1. Introduction

Bipolar disorder (BD) is a chronic and disabling psychiatric illness with significant morbidity and mortality characterized by episodes of mania, hypomania, and major depression, alternating with periods of remission [1]. There is evidence that suggests that the role of the pharmacist as a member of the mental health team could contribute to the achievement of therapeutic goals for these patients, mainly with the use of effective and safe drugs and improve the patient's quality of life through PC [2, 3, 4].

The EMDADER-TAB [4] study was the first randomized controlled trial to evaluate the effect of pharmaceutical intervention using the DMet of PC in the achievement of therapeutic goals in patients with BD-I. This study was carried out in a psychiatric healthcare institution, San Juan de Dios Clinic, La Ceja, Antioquia, Colombia. The intervention group (IG) received usual care and pharmaceutical care for one year provided by a specially trained pharmacist using the DMet [5, 6, 7]. According to this approach, to identify, prevent, or promptly resolve problems related to the process and outcomes of pharmacotherapy, PC was in constant contact with the pharmacist through a weekly telephone call lasting from 20

---

to 30 min until the end of the study as part of the pharmaceutical care program. The purpose of these calls was to gather information related to patient treatment adherence and to evaluate whether pharmacotherapy was necessary, effective and safe, considering the process (DRPs) and outcome problems (NOMs), and the evaluation of pharmaceutical interventions. After collecting the patient information, the pharmacist completed the assessment form and worked with the clinical mental health team, patient, and family/caregiver. After interventions were completed, the pharmacist evaluated and verified the results. Interventions were performed as needed. The educational focus of the pharmaceutical intervention consisted of: education about the disease (causes, pharmacological and non-pharmacological treatment, nature), the recognition of signs and symptoms of the disease as well as, those caused by medications (effectiveness and safety); the adoption of habits and healthy lifestyles, the recognition of prodromal symptoms of BD-I and the priority of searching timely help, and finally, the importance of the patients' knowledge of their medication in improving its correct use and the medication adherence. The administrative management processes were related to information about: the procedures to access a medical appointment (medical authorizations), medicines (medications not covered by the health benefits plan of the country), laboratory test to monitor any parameter, inter-consultation with other medical specialties, request for unscheduled outpatient visits in the case of bipolar decompensation or referral to the emergency department when patient safety was at risk. The control group (CG) received UCP, which consisted of routine dispensing and verbal and written counseling regarding BD. The written material contained mental health and BD information, which focused on the importance of adherence to pharmacological and non-pharmacological interventions to achieve treatment goals.

The results of the EMDADER-TAB study showed that PC for outpatients with BD-I reduces hospitalizations and emergency service consultations from baseline through one year of follow-up compared with the UCP, where the risks of hospitalization and emergency service consultations were higher in 9.032 and 3.383 times, respectively. These findings could be explained because the PC can contribute to identify and to intervene possible factors that precipitate a relapse [4]. Additionally, the inclusion of PC based on DMet as a health technology accompanying UCP proved to be a cost-effective strategy in patients with BD-I in Colombia, reducing the frequency of the use of health services, and therefore offers significant savings, which is a fundamental aspect to consider in the implementation of this type of intervention during UCP [8].

However, it is not known to what extent this effect is sustained following discontinuation of the intervention because, to date, there are no studies that assess the long-term efficacy of this type of continuous intervention complementary to pharmacotherapy. The main purpose of this study was to determine whether one year of pharmacist intervention applied in the EMDADER-TAB study comparing PC vs. UCP has long-term effects on the use of healthcare services (hospitalizations and emergency department consultations) following discontinuation of the pharmacist intervention in patients with BD-I.

2. Materials and methods

2.1. Study design and setting

This study was a retrospective observational design based on the EMDADER-TAB trial described above. The detailed methods of this study were previously published elsewhere [9].

2.2. Inclusion criteria

We included male or female patients between 18 and 65 years of age, with a diagnosis of BD-I according to the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV), who participated in the EMDADER-TAB study and completed 12 months of follow-up.

2.3. Sampling

We obtained a sample for convenience, including all patients of the EMDADER-TAB, who met the inclusion criteria.

2.4. Data collection procedures

A trained pharmacist examined medical records of all patients who met the inclusion criteria, one year following the end of the EMDADER-TAB. Also, another pharmacist contacted all patients by telephone to complete the hospital records. All information was collected in a specific database designed by an external person using Microsoft Access (version 2007, Microsoft Corporation, Redmond, Washington). Patients' data were collected between November 2012 and March 2014.

2.5. Outcome assessment

The outcomes measured were: number and rate of psychiatric hospitalizations, number, and rate of emergency service consultations, and survival time for psychiatric hospitalizations and emergency service consultations.

2.6. Statistical analysis

Sociodemographic and clinical variables were summarized using descriptive statistics. Psychiatric hospitalizations and emergency service consultations during the study period were quantified. The average length of hospital stay, the hospitalization rate, and the emergency service consultations rate were calculated. We used the Kaplan-Meier survival function to provide the graphical representation of patients who have or have not experienced the outcome of interest during the 12-months following the end of the EMDADER-TAB study, and we performed a Log-Rank test to establish significant differences between the survival curves. Student's t-test was used to make comparisons between groups. Statistical analyses were performed using SPSS version 22.0 (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp). A p-value of <0.05 was considered statistically significant.

2.7. Ethical approval

The EMDADER-TAB (NCT01750255) protocol, and this study were approved by the Bioethics Committee of the SJDC (reference number 06/10), following good clinical practice guidelines and the Helsinki Declaration. All patients provided written informed consent, and their information remained confidential and anonymous. Likewise, approval was obtained from the Bioethics Committee of the SJDC (reference number 2707/15) for the development of this study.

3. Results

A total of 92 patients were included in the analysis (IG: 42; CG: 49). The demographic and clinical characteristics of patients are listed in Table 1. No statistically significant differences were found between the sociodemographic variables of the groups.

3.1. Psychiatric hospitalizations

At the end of the follow-up period, a total of 30 hospitalizations were registered, of which 11 occurred in the IG (0–3 months: 3; 3–6 months: 6; 6–9 months: 2; 9–12 months: 0), and 19 occurred in the CG (0–3 months:

Table 1. Demographic and clinical characteristics of patients.

Demographic and Clinical Variables	Total (N = 92)	CG (n = 49)	IG (n = 43)
Age, mean [SD]	46.6 [11.1]	47.4 [11.9]	45.6 [10.1]
Gender, n (%)			
Female	52 (56.5)	29 (59.2)	23 (53.5)
Education, n (%)			
Elementary school or less	32 (34.8)	16 (32.7)	16 (37.2)
High school	35 (38.0)	19 (38.8)	16 (37.2)
University education	25 (27.2)	14 (28.6)	11 (25.6)
Age of illness onset (yrs), mean [SD]	29.5 [10.5]	29.9 [11.8]	28.9 [8.9]
Duration of illness, n (%)			
1 - 5 years	9 (9.78)	4 (8.16)	5 (11.63)
6 - 10 years	25 (27.17)	15 (30.61)	10 (23.26)
>10 years	58 (63.04)	30 (61.22)	28 (65.12)

7; 3–6 months: 6; 6–9 months: 5; 9–12 months: 1). The global average length of hospital stay was 8.4 ± 0.4 days (CG: 9.5 ± 0.4 days; IG: 6.7 ± 2.6 days, p < 0.001). The overall psychiatric hospitalization rate in both groups was 32.6% (CG: 20.6%; IG: 12.0%), meaning 0.33 episodes per person-year. The 12-month mean psychiatric hospitalizations survival time was longer for patients who received PC (11.5 months [95% CI, 11.2–11.8 months] vs. 11.3 months [95% CI, 10.9–11.6 months]) than for patients who received UCP. Figure 1 (A) illustrates 1-year Kaplan–Meier survival curves for psychiatric hospitalizations after one year of follow-up of the EMDADER-TAB study, and there are no significant differences between both the groups (log-rank = 1.26, p = 0.261).

3.2. Emergency service consultations

After 12 months of follow-up, there were 24 emergency service consultations (ESC) for the CG (0–3 months: 8; 3–6 months: 7; 6–9 months: 7; 9–12 months: 2) versus 14 for the IG (0–3 months: 4; 3–6 months: 7; 6–9 months: 2; 9–12 months: 1). The overall emergency service consultations rate in both groups was 41.3% (CG: 26.1%; IG: 15.2%), meaning 0.41 episodes per person-year. The 12-month mean ESC survival time was longer for patients who received PC (11.4 months [95% CI, 11.1–11.7 months] vs. 11.2 months [95% CI, 10.8–11.5 months]) in patients who received UCP. Figure 1 (B) illustrates 1-year Kaplan–Meier

survival curves for emergency service consultations after one year of follow-up of the EMDADER-TAB study, and there are no significant differences between both groups (log-rank = 1.56, p = 0.212).

4. Discussion

The results from this retrospective study indicate that the effect of PC on psychiatric hospitalizations, and emergency service consultations is not maintained after one year of the end of the EMDADER-TAB study. These outcomes differ from the findings in the previous year during the pharmacist intervention, where PC had a statistically significant effect in reducing these outcomes during a 1-year follow-up period [4], which indicates that the long-term effects of PC on these outcomes are not maintained.

As far as we know, this research is the first detailed report documenting long-term clinical outcomes (hospitalizations and emergency service consultations) in patients with BD-I after discontinuation of pharmaceutical intervention. Unfortunately, there are no previous studies that analyze the long-term relationship between PC and the use of health services in patients with BD-I; however, this study contributes important data to the literature and could answer the concerns of other authors who propose to investigate whether positive effects of PC persists in patient populations after cessation of interventions [10].

Although there is no long-term evidence of the effects of PC in patients with mental disorders once it ends, evidence is available for other health conditions. For instance, a study has been described on patients with uncontrolled hypertension, in which PC through the DMet was compared with a sham intervention, finding significant differences after PC [11]. However, in other health problems, including heart failure conditions, evidence suggests that the beneficial effects of PC were dissipated when the intervention ceased [12].

At the level of pharmaceutical interventions, there is evidence that demonstrates that the sustained effect after this type of intervention, which does not necessarily correspond to PC, stops [13, 14], suggesting the need to continue pharmacist intervention to get better outcomes [15, 16]. One study found significantly more effective blood pressure control in the intervention group (management provided by physician-pharmacist) than in the control group (UCP) after 18 months following discontinuation of a 6-month physician-pharmacist intervention [13]. Another study focused on a multifaceted pharmacist intervention resulting in significant and sustained improvement in medication adherence for hypertension patients, but without a significant effect on persistence and clinical outcomes [14]. An intensive intervention
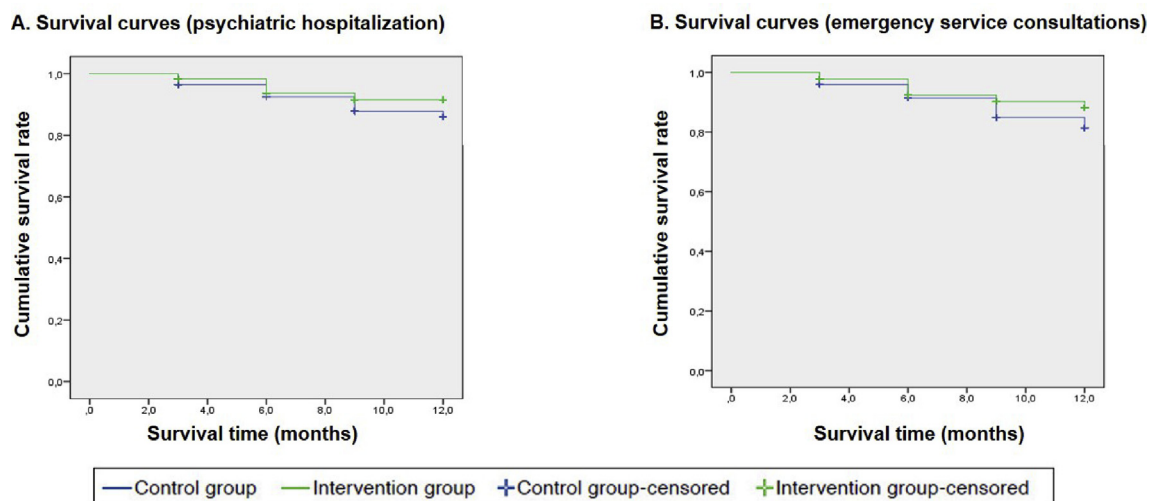

Figure 1. Kaplan–Meier survival curves one year following the 12-months of the EMDADER-TAB study for psychiatric hospitalization (A) and emergency service consultations (B).

achieved substantial blood pressure reduction and showed sustained effects for 24 months (12 months after the intervention ended). This latest study suggested that long-term maintenance strategies may be needed to maintain the effects of the intervention for several years, and there is a need to work to determine the content, intensity, and duration of reinforcement that are needed to maintain intervention benefits over a longer period [15].

At the level of interventions in the field of psychiatry, the decrease over time of the apparent benefits achieved with interventions adjuvant to the pharmacological treatment of patients with BD has been described in the literature. This evidence suggests that long-term maintenance for therapy sessions may be needed to improve BD outcomes [17], in addition to PC, that could be considered as coadjuvant treatment in the management of these patients, and implies that it should be carried out systematically, continuously, and be well-documented [18]. However, among coadjuvant treatments, six-month group psychoeducation was the first psychological intervention shown to have long-lasting prophylactic effects in individuals with BDs compared to control over the 5-year follow-up period (p = 0.002) [19,20].

One of the hypotheses that could explain the loss of effect after cessation of intervention is based on the continuity of PC service, which allows the pharmacist to be in permanent contact with the patient, and thereby identify symptoms of decompensation promptly. In this sense, the pharmacist can contribute to the risk management of the patient, seeking timely help, and decreasing the likelihood of hospitalization or emergency services consultations. Due the effect of the PC dissipating when the intervention ceases, in order to promote the continuity of this service and make it sustainable in the long term it is necessary to establish strategies based on prioritization of patients by risk, which would allow approaches to those patients with BDs most likely to benefit from a continuous intervention by the pharmacist. These outcomes are similar to those reported for psychosocial interventions, where it is still unclear which populations are most likely to benefit from which approach and what is the best time to implement it [21]. Another plausible hypothesis that could explain this phenomenon has been described as an educational intervention, where patients show improvements in the first six months of intervention due to the psychological effects of being monitored, and this often drops off thereafter [22]. In this sense, it is necessary to generate evidence to identify the factors related to the duration of the effect of PC over time.

These findings support the use of PC as a cost-effective [8], adjuvant, and preventive strategy to the UCP, allowing significant healthcare cost savings and reducing the risk of hospitalization and emergency service consultations in this group of patients [4]. Additionally, this study also extends the available knowledge regarding the continuous effect of the pharmacist as part of a multidisciplinary mental health team in achieving therapeutic goals, focused mainly on the monitoring of the effectiveness and safety of pharmacotherapy through assessment of patient outcomes, and also on both the process (e.g. degree of adherence) and the outcomes of pharmacotherapy (effectiveness and safety) [3]. There is a need to promote the training of pharmacists in this area of knowledge to improve treatment outcomes in bipolar populations and increase the coverage of mental health care.

5. Limitations

This study has several limitations that should be considered when interpreting the findings. The major limitations are related to its observational and retrospective nature. In fact, given the limited number of variables collected, a Cox proportional hazards regression model could not be made to control potential confounding effects and to confirm findings of the risk of psychiatric hospitalization or emergency service consultations between the two groups one year after completing the EMDADER-TAB study. Thus, further study controlling for several factors could be required. Although databases from the SJDC were used to identify the use of healthcare services, this approach can be subject to

information bias given that patients of both groups could attend the emergency services or be hospitalized in health institutions other than the SJDC; therefore, the rate of hospitalizations or emergency service consultations could be underestimated. However, it should be noted that the psychiatric hospitalization center of choice for these patients is the SJDC. Additionally, to decrease this information bias and to complete the records, this information was requested of the patient and their relatives and recorded in the database of hospitalizations and emergency service consultations, as reported by the patients or their relatives. Despite these limitations, we believe our study results add value to the literature and point to a key next step in the role of the pharmacist in the follow-up of these patients.

6. Conclusions

The findings of this study provide evidence that the effect observed of PC through the Dader method has no long-term effects on the use of healthcare services (hospitalizations and emergency department consultations) in patients with BD-I following discontinuation of the pharmacist intervention, meaning that the effect dissipates when the intervention ceases. Additionally, future studies should focus efforts on identifying factors associated with PC that explain why the outcomes derived from this intervention are not maintained in the long term. Further studies are required to identify bipolar patients who might benefit from or should be targeted with this intervention, as well as to assess other prospective long-term factors additional to PC that may alter these outcomes among individuals with bipolar disorder.

References

[1] American Psychiatric Association, Diagnostic and Statistical Manual of Mental Disorders, fifth ed., Washington D.C, 2013.

[2] J.S. Bell, A. Rosen, P. Aslani, P. Whitehead, T.F. Chen, Developing the role of pharmacists as members of community mental health teams: perspectives of pharmacists and mental health professionals, Res. Soc. Adm. Pharm.: RSAP 3 (2007) 392–409.

[3] M. Rubio-Valera, T.F. Chen, C.L. O'Reilly, New roles for pharmacists in community mental health care: a narrative review, Int. J. Environ. Res. Publ. Health 11 (2014) 10967–10990.

[4] A. Salazar-Ospina, P. Amariles, J.A. Hincapie-Garcia, S. Gonzalez-Avendano, D.M. Benjumea, M.J. Faus, L.F. Rodriguez, Effectiveness of the dader method for pharmaceutical care on patients with bipolar I disorder: results from the EMDADER-TAB study, J Manag. Care Spec. Pharm. 23 (2017) 74–84.

[5] G.D.I. EN Atención Farmacéutica de la Universidad de Granada, Método Dáder para el seguimiento farmacoterapéutico, Ars. Pharm 46 (2005) 4. http://revistaseug.ugr.es/index.php/ars/article/view/5098.

[6] Pharmaceutical Care Research Group, University of Granada (Spain), Pharmacotherapy follow-up: the Dader method (3rd revision: 2005), Pharm. Pract. 4 (2006) 44–53.

[7] D. Sabater Hernández, M.M. Silva Castro, M.J. Faus, Dader Method: Guidelines for Pharmacotherapy Follow-Up, third ed., Pharmaceutical Care Research Group, University of Granada, Granada (Spain), 2007. http://www.atencionfarmaceutica-ugr.es.

[8] M. Monsalve David, J.A. Hincapié García, A. Salazar Ospina, P. Amariles, Coste-efectividad del seguimiento farmacoterapéutico en pacientes con trastorno afectivo bipolar-I: ensayo clínico aleatorizado EMDADER-TAB, PharmacoEconomics Spanish Res. Articles 14 (2017) 31–38.

[9] A. Salazar-Ospina, P. Amariles, D.M. Benjumea, F. Gutierrez, M.J. Faus, L.F. Rodriguez, Effectiveness of the Dader Method for pharmaceutical care in patients with bipolar I disorder: EMDADER-TAB: study protocol for a randomized controlled trial, Trials 15 (2014) 174.

[10] Z.-U.-D. Babar, R. Kousar, G. Murtaza, S. Azhar, S.A. Khan, L. Curley, Randomized controlled trials covering pharmaceutical care and medicines management: a systematic review of literature, Res. Soc. Adm. Pharm.: RSAP 14 (2018) 521–539.

[11] M.S. de Castro, F.D. Fuchs, M.C. Santos, P. Maximiliano, M. Gus, L.B. Moreira, M.B.C. Ferreira, Pharmaceutical care program for patients with uncontrolled hypertension. Report of a double-blind clinical trial with ambulatory blood pressure monitoring, Am. J. Hypertens. 19 (2006) 528–533.

[12] M.D. Murray, J. Young, S. Hoke, W. Tu, M. Weiner, D. Morrow, K.T. Stroupe, J. Wu, D. Clark, F. Smith, I. Gradus-Pizlo, M. Weinberger, D.C. Brater, Pharmacist intervention to improve medication adherence in heart failure: a randomized trial, Ann. Intern. Med. 146 (2007) 714–725.

[13] D.M. Wentzlaff, B.L. Carter, G. Ardery, C.L. Franciscus, W.R. Doucette, E.A. Chrischilles, K.A. Rosenkrans, L.M. Buys, Sustained blood pressure control following discontinuation of a pharmacist intervention, J. Clin. Hypertens. 13 (2011) 431–437.

[14] U. Hedegaard, L.J. Kjeldsen, A. Pottegard, J.E. Henriksen, J. Lambrechtsen, J. Hangaard, J. Hallas, Improving medication adherence in patients with hypertension: a randomized trial, Am. J. Med. 128 (2015) 1351–1361.

[15] K.L. Margolis, S.E. Asche, A.R. Bergdall, S.P. Dehmer, S.E. Groen, H.M. Kadrmas, T.J. Kerby, K.J. Klotzle, M.V. Maciosek, R.D. Michels, P.J. O'Connor, R.A. Pritchard, J.L. Sekenski, J.M. Sperl-Hillen, N.K. Trower, Effect of home blood pressure telemonitoring and pharmacist management on blood pressure control: a cluster randomized clinical trial, J. Am. Med. Assoc. 310 (2013) 46–56.

[16] C. Yamada, J.A. Johnson, P. Robertson, G. Pearson, R.T. Tsuyuki, Long-term impact of a community pharmacist intervention on cholesterol levels in patients at high risk for cardiovascular events: extended follow-up of the second study of cardiovascular risk intervention by pharmacists (SCRIP-plus), Pharmacotherapy 25 (2005) 110–115.

[17] J. Scott, B. Etain, Which psychosocial interventions in bipolar depression? L'Encephale 37 (Suppl 3) (2011) S214–S217.

[18] U. of G. (Spain), Pharmaceutical care research group, pharmacotherapy follow-up: the dader method (3rd revision: 2005), Pharm. Pract. 4 (2006) 44–53.

[19] F. Colom, E. Vieta, J. Sanchez-Moreno, R. Palomino-Otiniano, M. Reinares, J.M. Goikolea, A. Benabarre, A. Martinez-Aran, Group psychoeducation for stabilised bipolar disorders: 5-year outcome of a randomised clinical trial, Br. J. Psychiatr.: J. Ment. Sci. 194 (2009) 260–265.

[20] D.J. Miklowitz, Group psychoeducation increases time to recurrence in stabilised bipolar disorders, Evid. Base Ment. Health 12 (2009) 110.

[21] M. Reinares, J. Sanchez-Moreno, K.N. Fountoulakis, Psychosocial interventions in bipolar disorder: what, for whom, and when, J. Affect. Disord. 156 (2014) 46–55.

[22] H. Cooper, K. Booth, S. Fear, G. Gill, Chronic disease patient education: lessons from meta-analyses, Patient Educ. Counsel. 44 (2001) 107–117.