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To cite this version:

Raoul Belzeaux, Laurent Boyer, Pascale Mazzola-Pomietto, Pierre Michel, Nadia Correard, et al.. Adherence to medication is associated with non-planning impulsivity in euthymic bipolar disorder patients. Journal of Affective Disorders, 2015, 184, pp.60–66. 10.1016/j.jad.2015.05.041 . hal-01985796

HAL Id: hal-01985796

https://hal.science/hal-01985796v1

Submitted on 18 Jan 2019

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Adherence to medication is associated with non-planning impulsivity in euthymic bipolar disorder patients

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Keywords:
Substance Use Disorders
Impulsivity
Anxiety disorders
Mood disorders

a b s t r a c t

Background: Adherence to medication is a major issue in bipolar disorder.
defined as a lack of future orientation, has been demonstrated to be the main impulsivity domain altered during euthymia in bipolar disorder patients. It was associated with comorbidities.
Methods: To investigate relationship between adherence to medication and non-planning impulsivity, we included 260 euthymic bipolar patients. Adherence to medication was evaluated by Medication Adherence Rating Scale and non-planning impulsivity by Barrat Impulsiveness Scale. Univariate analyses and linear regression were used. We conducted also a path analysis to examine whether non-planning impulsivity had direct or indirect effect on adherence, mediated by comorbidities.
Results: Adherence to medication was correlated with non-planning impulsivity, even after controlling for potential confounding factors in linear regression analysis (Beta standardized coefficient¼ 0.156; p¼ 0.015). Path analysis demonstrated only a direct effect of non-planning impulsivity on adherence to medication, and none indirect effect via substance use disorders and anxiety disorders.
Limitations: Our study is limited by its cross-sectional design and adherence to medication was assessed only by self-questionnaire.

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1. Introduction

Poor adherence to medication is one of the main challenges in Bipolar Disorder (BD) treatment. About 12–64% of BD patients are considered as poor or nonadherent whatever the phase of the illness, including symptomatic remission (Leclerc et al., 2013). Poor adherence to medication is viewed as one of the main factor of poor treatment response (Goodwin and Jamison, 2007). It is associated with a wide range of consequences including relapses, recurrences and an increased risk of suicide (Goodwin and Jamison, 2007; Hong et al., 2011).

As a consequence, understanding why patients are not adherent to medication is a crucial issue. Interestingly, adherence to medication would imply complex decision-making processes and imbalance between short- and long-term advantages and consequences of pill-taking. The inability of an individual to weigh up the long-term as opposed to the immediate results of his action could be defined as non-planning impulsivity or "lack of future orientation". Accordingly, a recent meta-analysis indicated that non-planning impulsivity was increased in remitted bipolar patients in comparison to healthy controls (Saddichha and Schuetz, 2014). In addition, non-planning impulsivity has been also correlated with decision making processes, evaluated by the Iowa Gambling Task, in euthymic bipolar patients (Christodoulou et al., 2006) as well as in alcohol-dependent subjects (Tomassini et al., 2012). As a consequence, we hypothesize that higher non-planning impulsivity may have a strong negative effect on adherence to medication in euthymic bipolar patients.

However, it is not clear how non-planning impulsivity could influence adherence to medication. The inability of an individual to weigh up the long-term as opposed to the immediate results of his action may be an important factor of non-adherence to medication. Moreover, both SUD (Etain et al., 2013) and anxiety disorders (Del Carlo et al., 2012) have been associated with higher non-planning impulsivity in euthymic bipolar patients, while these psychiatric comorbidities were also found to strongly influence adherence to medication (Bauer et al., 2005; Leclerc et al., 2013; Lingam and Scott, 2002). These observations suggest that non-planning impulsivity may influence adherence to medication both directly and indirectly by increasing the risk of SUD and anxiety disorders.

So the aim of this study was to investigate the relationship between non-planning impulsivity and adherence to medication in euthymic BD patients, while considering key socio-demographic and clinical confounding factors. Moreover, we aimed to determine whether the relationship between higher impulsivity and lower adherence is mediated by comorbidities (i.e. SUD and anxiety disorders) or if impulsivity and adherence interact directly.

2. Patients and methods

2.1. Study design and population

We conducted a cross-sectional multicenter study involving the nine French expert centers created under the aegis of the Fonda-Mental Foundation. The data were extracted from the Fondamental Advanced Centers of Expertise in Bipolar Disorders (FACE-BD) database (Henry et al., 2011). We only included the data from subjects who were at the time of the interview: outpatients, between 18 and 75 years old, diagnosed according DSM-IV criteria (APA, 1994), suffering from either a bipolar disorder type I, type II or Not Otherwise Specified (NOS), in symptomatic remission according to the ISBD task force recommendations (Tohen et al., 2009).

The procedure was approved by the ethical review board (CPP-Ile de France IX, January 18, 2010) and by the committee in charge of the safety of computerized databases (CNIL) (DR-2011-069).

2.2. Data collection

A large standardized clinical evaluation with structured clinical interview for DSM-IV (SCID) (First et al., 1996) was used to determine the diagnosis of BD and characterize the history of disorder (i.e. age of onset, number of past mood episodes, past psychotic symptoms during previous mood episodes, past mixed episodes), comorbid psychiatric conditions (i.e. lifetime anxiety disorders, no, past or current SUD) and sociodemographic factors (age, educational level and marital status).

Standardized evaluations were used to assess symptomatology and functioning. Manic symptoms were assessed with Young Mania Rating Scale (YMRS) (Young et al., 1978), depressive symptoms with Montgomery Åsberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979). Functioning was evaluated with Global Assessment of Functioning (GAF). In accordance with the strongest definition of symptomatic remission as proposed by ISBD task force (Tohen et al., 2009), scores on the MADRS and YMRS had to be inferior to 8. Focusing specifically our analyses on strictly euthymic patients allow controlling the influence of depressive symptoms on adherence to medication (Belzeaux et al., 2013) as well as on the level of impulsivity (Stanford et al., 2009).

Side effects of treatment were evaluated with Patient Rated Inventory of Side Effects (PRISE) (Belzeaux et al., 2013; Bryan et al., 2010; Rush and Asberg, 1999). PRISE is a self-report questionnaire consisting of a 31-item checklist of side effects that allows evaluating both frequency and severity of side effects experienced by the patients over the last 7 days. Side effects are classified by symptom domain (gastrointestinal, heart, skin, nervous system, eyes/ears, genital/urinary, sleep, sexual functioning, and others, including weight gain). Each domain has multiple symptoms that can be endorsed. For each domain, the patient rates whether or not the symptoms are absent (¼0), tolerable (¼ 1) or distressing (¼ 2).A total score defines a global side effect level by taking into account both the frequency and the severity of all side effects.

Adherence to medication was measured as a continuous variable by the Medication Adherence Rating Scale (MARS) as previously used in BD by a number of authors (Belzeaux et al., 2013; Rosa et al., 2007; Thompson et al., 2000). The MARS is a self-report consisting of 10-yes/no items and with reverse items. A MARS total score is obtained by summing score of each item. This total score has been shown to correlate with likelihood of medication adherence and a total MARS score Z8 has been found to be associated with a high likelihood of medication adherence (Rosa et al., 2007; Thompson et al., 2000).

Non-planning impulsivity was evaluated by one of the three subscores reflecting three factors of the Barrat Impulsiveness Scale (BIS) version 10 (Patton et al., 1995; Stanford et al., 2009). The BIS is the most widely used self-report measure of impulsivity in the literature. The version 10 was used in current study as it is the last

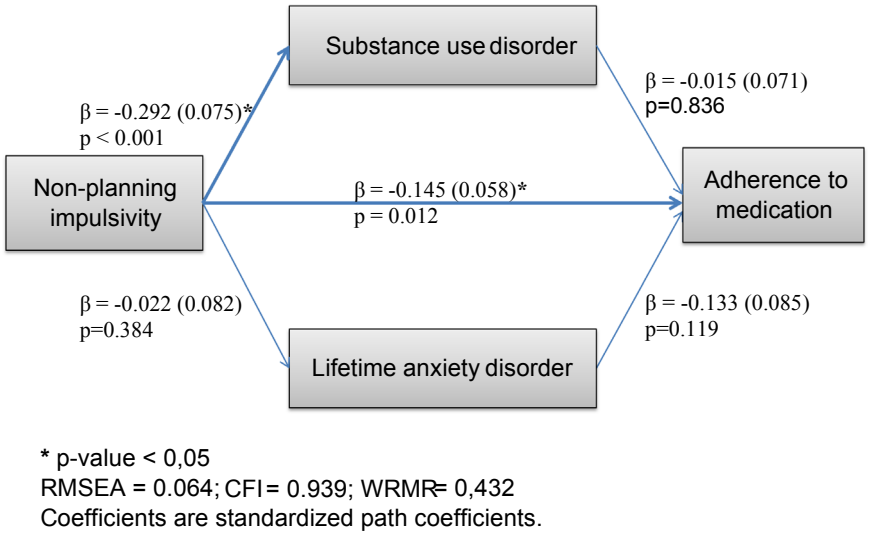

Fig. 1. Direct and indirect effect of the non-planning impulsivity on adherence to medication based on path analysis. * p-Valueo0.05, RMSEA¼0.064; CFI¼0.939; WRMR¼0.432, coefficients are standardized path coefficients.

version validated in French language (Bayle et al., 2000) and used in French speaking BD patients (Etain et al., 2013). BIS-10 is a 34-item self-report questionnaire that measures impulsiveness as a stable characteristic. Each item is rated on a 4-point scale ranging from 1 (rarely/never) to 4 (almost always/always).

2.3. Hypothesis and analyses plan

The main objective of the study was to investigate the relationship between non-planning impulsivity and adherence to medication in remitted euthymic bipolar patients. We first conducted a correlation analysis between MARS total score and the non-planning impulsivity subscores of the BIS-10. Moreover, we explored in univariate analyses other factors associated with adherence.

Then, in order to evaluate whether the correlation between MARS total score and BIS-10 non-planning impulsivity sub-score remained significant when potential confounding factors were taken into account, we performed a linear regression using simultaneous model with several confounding clinical factors that were identified by univariate analyses and examining data from previous studies as covariables.

Finally, we conducted path analysis using maximum likelihood estimation with MPlus. We examined whether the non-planning impulsivity had direct and indirect effects on adherence i.e. if there was a mediated effect of two major comorbidities of BD known to be associated with impulsivity and adherence, namely SUD and anxiety disorders.

2.4. Data analyses

Data were expressed as proportions or means and standard deviations. To determine whether univariate normality exists, we followed the recommendation of Weston and Gore (2006) and examined skewness and kurtosis for each quantitative variable (Weston and Gore, 2006).

As a consequence, the univariate analyses that were used to investigate the associations between MARS score, BIS non-planning impulsivity sub-score and other continuous variables were performed by using nonparametric Spearman's correlations tests. In addition, the analyses testing the effect of gender, familial status, education level, bipolar type and other categorical variables on MARS, were performed by using Mann–Whitney or Kruskal–Wallis tests as appropriate. Kruskal–Wallis post-hoc analyses were performed when necessary (as described by Marta Garcia Granero, http://gjyp.nl/marta/).

Linear regression was used to control for potential confounding factors. Confounding factors were selected based on the results of univariate analyses with thresholds p-value r0.2 and data of prior studies. We used as co-factors the following variables: age, illness duration, anxiety disorders, SUD, psychotic features and PRISE total score. We excluded number of previous episodes as it was strongly correlated with illness duration (Spearman's correlation coefficient ¼0.427; po10 ^{5}). Non-normally distributed variables whom distribution deviated from normality (i.e. MARS total score, PRISE total score) were transformed by the mean of a square-root data transformation method as advised by Tabachnick and Fidell (2014) and Howell (2013).

Finally, we conducted a path analysis using weighted least squares estimation with MPlus of the relationships between non-planning impulsivity, substance use disorder, lifetime anxiety disorder and adherence to medication. We constructed hypothetical relationships among the following variables (i.e., non-planning impulsivity, substance use disorder, lifetime anxiety and adherence to medication) by examining previously published research and results of univariate analyses. We hypothesized that non-planning impulsivity influences adherence, both directly and indirectly via SUD and lifetime anxiety disorders (Fig. 1).

Path analysis is an extension of multiple regression analysis and is a type of structural equation modeling. It assesses the strengths of correlational relationships to clarify potential causal relationships. Coefficients are standardized path coefficients. Path analysis allows one to decompose the sources of a correlation between independent variables (i.e., non-planning impulsivity, substance use disorder, lifetime anxiety disorders) and a dependent variable (i.e., adherence) into direct and indirect effects (Joffe and Mindell, 2006).

Bootstrapping techniques were applied to calculate the 95% CI around the estimates of the direct and indirect effects using 10,000 bootstrap samples.

Model fit was evaluated using the Chi-square test of model fit, the root mean square error of approximation (RMSEA) r0.06, the Comparative Fit Index (CFI) Z0.95, and the weighted root mean square residual (WRMR) o1 (Gamborg et al., 2011).

All statistical tests were two-sided. Significance was defined as pr0.05. Statistical analyses were performed using SPSS Statistics

Table 1
Sociodemographic and clinical characteristics of 260 euthymic bipolar patients.

	n (%) or mean (SD)
Socio-demographic characteristics	
Age (years)	41.5 (712.7)
Gender (female)	151 (58.1%)
Marital status (single)	91 (35%)
Education level (high school diploma or higher)	201 (77.3%)
Bipolar disorder type	
Bipolar disorder type I	148 (56.9%)
Bipolar disorder type II	85 (32.7%)
Bipolar disorder type NOS	27 (10.4%)
Comorbidity	
Lifetime anxiety disorders	83 (31.9%)
Substance use disorder (SUD)	66 (24.4%)
SUD	55 (21.2%)
SUD	11 (4.2%)
Symptomatology and functioning	
Depressive symptoms (MADRS [a])	2.8 (72.4)
Manic symptoms (YMRS [b])	1.2 (71.8)
Functioning (GAF [c])	73.9 (715.9)
Impulsivity: BIS [d]-10	
BIS-10 nonplanning	25.5 (74.6)
Illness course	
Illness duration (years)	15.9 (710.7)
Total number of mood episodes	8 (75.2)
At least one mood episode with psychotic features	116 (44.6%)
At least one mixed episode	34 (13.1%)
Side effects level (PRISE [e])	9 (77.3)
Adherence to medication (MARS [f])	7.6 (71.9)

[a] Montgomery Åsberg Depression Rating Scale.
[b] Young Mania Rating Scale.
[c] Global Assessment of Functioning.
[d] Barrat Impulsivity Scale.
[e] Patient Rated Inventory of Side Effects.
[f] Medication Adherence Rating Scale.

for Windows, Version 20. Chicago: SPSS Inc.and MPLUS (Muthén and Muthén, 1998–2011).

3. Results

3.1. Population description

Two hundred and sixty BD patients in symptomatic remission were included in the study. Socio-demographic and clinical characteristics of the sample are summarized in Table 1. Among these patients, 56.9% had bipolar I disorder and 32.7% had bipolar II disorder. Mean total scores for MADRS and YMRS were 2.8 (72.4) and 1.2 (71.8) respectively. Mean score for GAF was 73.9 (715.9).

In our sample, the mean and median MARS total scores were 7.6 (7 1.9) and 8 (inter-quartile range at 2), respectively. These data indicate sub-optimal adherence behaviors in the whole cohort.

3.2. Factors associated with adherence to medication

In the univariate analyses, we found a significant negative correlation between MARS and BIS non-planning sub-score as indicated by Spearman's correlation coefficient¼ 0.136 (p¼ 0.029) (Table 2). Only a significant correlation between MARS total score and duration of the illness was observed (Spearman's coefficient correlati on¼0.160, p¼ 0.011).No significant linear associations between the level of adherence and sociodemographic variables, clinical variables or PRISE total score were found. A detailed presentation of the data is provided in Table 2.

Table 2
Sociodemographic and clinical correlates of medication adherence assessed by MARS (total score) in 260 euthymic bipolar patients.

	MARS[a] total Mean (SD) or Speaman's correlation coefficient	p-Value (Mann–Withney test, Kruskal–Wallis test or Spearman test)
Age	0.10	p¼0.117
Gender		
Female	7.5 (2.1)	p¼0.342
Male	7.8 (1.7)	
Familial status		
Single	7.3 (2.2)	p¼0.546
Married	7.6 (1.9)	
Separed	8.0. (1.4)	
Educational level		
Less than high school diploma	7.6 (2.3)	p¼0.312
High school or higher diploma	7.5 (1.9)	
Bipolar disorder (BD) Type		
BD I	7.6 (2.1)	p¼0.558
BD II	7.6 (1.8)	
BD NOS	7.4 (1.7)	
At least one mood episode with psychotic features		
Yes	7.3 (2.2)	p¼0.107
No	7.9 (1.5)	
At least one past mixed episode		
Yes	7.5 (1.9)	p¼0.227
No	7.8 (2.0)	
Total number of episodes	0.15	p¼0.154
Illness duration	0.16	p¼0.011
Substance use disorder		
Current	6.6 (2.4)	p¼0.177
Past	7.8 (1.8)	
None	7.6 (1.8)	
Lifetime anxiety disorders		
Yes	7.9 (1.7)	p¼0.154
No	7.5 (2.0)	
PRISE[b] Total score	0.11	p¼0.116
BIS-10[c] nonplanning impulsivity sub-score	0.14	p¼0.029

[a] Medication Adherence Rating Scale.
[b] Patient Inventory of Side Effects.
[c] Barrat Implusivity Scale-10.

Based on the results of these univariate analyses, we conducted a linear regression analysis as described in methods section. We found a significant association between MARS total score and BIS-10 non-planning impulsivity sub-scale (Beta standardized coefficient ¼0.156; p¼0.015), while other factors did not shown significant association (Table 3).

3.3. Path analyses

Path analysis of the relationships between non-planning impulsivity, substance use disorder, lifetime anxiety disorder and adherence to medication is presented in Fig. 1.

The tested model showed good fit based on the RMSEA¼0.064, the CFI¼0.939 and the WRMR¼ 0.432.

The path analysis revealed two significant but moderate associations, i.e., the direct effect of non-planning impulsivity on adherence to medication (β¼ 0.145, p¼0.012) and the effect of

Table 3
Factors associated with adherence to medication according to linear regression models using MARS [a] total score, BIS-10[b] nonplanning impulsivity sub-scale score, age, illness duration, anxiety disorder, substance use disorder, psychotic features and PRISE[c] total score as co-factors.

	MARS[a] Total score[d]	
	β[e]	p-Value
BIS-10[b] nonplanning impulsivity sub-scale score	0.156	0.015
Age	0.050	0.540
Illness duration	0.148	0.061
Lifetime anxiety disorders	0.083	0.178
Substance use disorder	0.026	0.690
Psychotic features	0.101	0.109
PRISE[c] total score [e]	0.068	0.284

[a] Medication Adherence Rating Scale.
[b] Barrat Impulsiveness Scale-10.
[c] Patient Inventory of Side Effects.
[d] Square Root transformation.
[e] β Standardized coefficient.

non-planning impulsivity on substance use disorder (β¼ 0.292, po0.001).

Contrary to our hypotheses, there was no significant indirect effect of non-planning impulsivity on adherence to medication via mediated factors such as substance use disorder or lifetime anxiety disorder (all p-values 4 0.05).

4. Discussion

Improving knowledge on factors associated with low adherence to medication is crucial because lower adherence is associated with overall worse prognosis of bipolar disorders. However, non-adherence tends to be under-estimated by psychiatrists and could be hard to predict in clinical practice (De las Cuevas et al., 2013; Lingam and Scott, 2002).

To the best of our knowledge, our study is the first study assessing specifically the hypothesis of a relationship between non-planning impulsivity and low medication adherence in euthymic remitted BD patients. Focusing on patients with symptomatic remission, we evidenced a negative correlation between BIS-10 non-planning impulsivity sub-score and MARS total score. This association remained significant even after controlling for potential confounding factors in a linear regression analysis. Moreover, using path analyses, we demonstrate that the effect of non-planning impulsivity on adherence to medication is not mediated by SUD or anxiety disorders comorbidities but is likely to act directly on adherence.

Our results are consistent with a few previous studies suggesting that non-planning impulsivity influences adherence to medication or treatment dropout. In particular, non-planning impulsivity has been demonstrated to be associated with higher treatment dropout and smoking relapse in smokers (Lopez-Torrecillas et al., 2014). However, in an earlier study carried out in a relative small cohort of patients suffering from different severe psychiatric disorders including BD patients, no significant difference in non-planning impulsivity subscore between patients with or without poor medication adherence was reported (Liraud and Verdoux, 2001). In a larger and recent study, performed in depressed BD type II patients, higher BIS total scores as well as all three domains subscores were demonstrated in non-adherent as compared to adherent patients(Fornaro et al., 2013) but it could not be exclude that mood symptoms influence also impulsivity (Stanford et al., 2009).

Moreover, our results, based on path analysis, suggest that comorbidities, such as SUD, are not causal or intermediate factors on adherence behavior, contrary to the common hypothesis that, in bipolar disorders, SUD may specifically and importantly predispose to lower adherence to medication.

Although our study has a number of strengths (i.e. a large and well characterized sample of bipolar patients in symptomatic remission that includes patients with and without SUD, several level of analyses including path analyses), it also has some limitations. It remains unclear how our findings could be extended to general practice as our sample was recruited from tertiary centers and we focused on patients with symptomatic remission with a good level of functioning, as demonstrated by GAF mean value¼73.9 (715.9). In addition, adherence to medication was assessed only by self-questionnaire. Although the accuracy of such a method that reflects subjective experience of patients is well documented (Rosa et al., 2007; Thompson et al., 2000), it has been demonstrated that patients' self-report scores tend to overestimate adherence to medication in comparison to serum concentrations (Jonsdottir et al., 2010).

Moreover, based on several previous works, we decided to test specifically the relationship between non-planning impulsivity and adherence to medication. While impulsivity is well known to be a multi-dimensional construct, understanding the relative contribution of each subscale is considered critical (Stanford et al., 2009). Several studies suggested that the different sub-domains of impulsivity may be associated with different biological substrates in genetic (Khadka et al., 2014) as well as electrophysiological studies (Kam et al., 2012). Non-planning impulsivity sub-score was specifically associated with some laboratory measures of impulsivity or cognitive executive functions (Stanford et al., 2009; Swann et al., 2002). Moreover, a comparison of the three sub-domains of impulsivity, using BIS, showed the greatest difference between euthymic remitted bipolar patients and healthy controls in non-planning impulsivity compared to the motor and cognitive impulsivity (Saddichha and Schuetz, 2014) suggesting that non-planning impulsivity is the main impulsivity domain altered during euthymia. Nonetheless, further studies are needed to better characterize the potential importance of other sub-scores of impulsivity in medication adherence behavior.

Finally, our study is limited by its cross-sectional design. Thus, we cannot conclude about the cause-effect relationship between high non-planning impulsivity and low adherence.

The results of our study may have several implications for treatment. First of all, they may support the opinion expressed by some authors (Saddichha and Schuetz, 2014) that non-planning impulsivity needs to be taken into account when planning for treatment, as it leads to poor problem solving and low resilience, and to a lack of sense of future. As regards drug treatment, we found only one randomized controlled trial dealing with impulsivity in bipolar disorders, which showed an improvement of non-planning impulsivity with lithium (Hollander et al., 2005), although there is some evidence for efficacy of other mood stabilizers, antipsychotics and antidepressants on impulsive behavior (Ingenhoven et al., 2010; Singh and Zarate, 2006). Our finding may explain why there are contradictory data regarding better adherence with lithium as compared to other mood stabilizers in bipolar patients (Sajatovic et al., 2007). If indeed lithium does better on non-planning impulsivity, differences in non-planning impulsivity scores among patients included in different studies may be responsible for such findings. Whatsoever, our finding may support the choice of lithium as a first-line treatment in bipolar patients with high scores on non-planning impulsivity, in order to improve adherence to medication.

As far as psychotherapeutic interventions, those that have been shown to be effective on adherence include interpersonal group therapy, cognitive-behavioral therapy, group session for partners of persons with BD, and patient and family psycho-education

(Sajatovic et al., 2004). However, as highlighted by Moeller et al., one of the most consistently effective treatments currently available for substance dependence involves increasing, through the use of monetary or other types of incentives, short-term rewards for abstinence from substance use. By increasing short-term rewards for abstinence, contingency management therapy targets the lack of non-planning for the future (i.e. impulsivity) that is common in SUD (Moeller et al., 2001). Our findings suggest that this type of intervention could successfully be used to address adherence issues in BD patients, at least in those with high non-planning impulsivity levels. Interestingly, a recent study (Priebe et al., 2013) reported on the effectiveness of financial incentives to improve adherence to maintenance treatment in bipolar patients.

Finally, cognitive rehabilitation, which was found to display some efficacy to improve executive functioning in bipolar patients (Deckersbach et al., 2010), might enhance adherence in those with non-planning impulsivity. Further studies are warranted to demonstrate the effectiveness of lithium and selected psychotherapeutic interventions in impulsive bipolar patients, as suggested by our findings.

In conclusion, our study suggests an association between high non-planning impulsivity and low adherence to medication. We demonstrated also that the effect of non-planning impulsivity on adherence to medication is not mediated by the presence of SUD or anxiety disorders.

This result may help to a better understanding of the determinants of non-adherence behaviors. The association between impulsivity and adherence to medication may lead to systematically evaluate impulsivity for example with standardized questionnaire such as BIS in clinical practice to better predict risk of non-adherence and, thus, contribute to promote personalized treatment strategy.

Funding sources

Authors are members of the FondaMental Foundation as such this work was supported (in part) by the Investissement d'Avenir program managed by the ANR under reference ANR-11- IDEX-0004-02.

Conflict of interest

The authors declare no conflicts of interest.

Acknowledgments

The authors of this report would like to thank patients with bipolar disorders who agreed to participate in this study and the clinicians, psychologists and nurses who are working in FACE-BD group.

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