Journal of Affective Disorders Reports 2 (2020) 100037

Contents lists available at ScienceDirect

Journal of Affective Disorders Reports

journal homepage: www.elsevier.com/locate/jadr

Research Paper

# Evaluation of the capacity to consent to treatment among patients with bipolar disorder: Comparison between the acute psychopathological episode and the stable mood phase

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ARTICLE INFO

*Keywords:*
Capacity to consent to treatment
Bipolar disorder
MacArthur Competence Assessment Tools
Manic episode
Euthymic mood state
Hospitalization

ABSTRACT

*Objective:* Treatment decision-making capacity (TDMC) is basic to therapeutic processes and can be measured with the MacArthur Competence Assessment Tool for Treatment (MacCAT-T). TDMC may fluctuate in bipolar disorder (BD). We used the MacCAT-T to compare BD inpatients with an acute manic or depressive episode with euthymic BD outpatients on their TDMC.

*Methods:* We used the MacCAT-T to cross-sectionally assessed from May 2018 through October 2019 the TDCM of adult BD patients with a Mini Mental State Examination score ≥18, a group of acutely ill hospitalized patients for a manic/hypomanic episode and another of euthymic outpatients during their regular visits at our outpatient clinic. Patients were assessed with other specific psychiatric rating scales. We also tested their TDCM to an alternative treatment.

*Results:* The inpatient group consisted of 53 patients and the outpatient of 47. Inpatients scored worse than outpatients on the MacCAT-T understanding, reasoning and expressing a choice subscale, but not on the appreciating scale. Outpatients were more capable in understanding the characteristics of an alternative advance treatment. MacCAT-T subscales correlated directly with mental state scores, and inversely with mania and psychopathology scores, while only the appreciating subscale correlated inversely with depression scores.

*Limitations:* The limitations include small sample size and cross-sectional design.

*Conclusions:* TDCM is higher in BD patients at their euthymic state, hence this is the right time to obtain consent from a BD patient in view of possibly depositing psychiatric advance directives.

## Introduction

Treatment decision-making capacity (TDMC) represents a prerequisite to provide valid consent to any medical act and to exercise the right to accept or refuse any proposed treatment (Appelbaum and Roth, 1982; Grisso and Appelbaum, 1998a). Recently the assessment of TDMC has become one of the most important legal and ethical issues in contemporary clinical practice within mental health, especially in the context of the emerging legislations all over Europe regarding competency and advance decision-making (Murray and Wortzel, 2019; Scholten et al., 2019; Tinland et al., 2019).

It has been shown that the capacity to consent to treatment is frequently adversely affected by the symptoms of a mental disorder (Rutledge et al., 2008), although about 70% of psychiatric patients still retain an adequate decisional capacity (Okai et al., 2007). Nonetheless many studies reported that psychiatric inpatients from different diagnostic groups have reduced levels of TDMC, (Grisso and Appelbaum, 1995; Cairns et al., 2005; Howe et al., 2005; Owen et al., 2008; Candia and Barba, 2011; Mandarelli et al., 2014; Bilanakis et al., 2017).

Although previous research has shown that manic and excitatory symptoms play a role in reducing patient's TDMC, only one study investigated capacity to give informed consent during acute mania in a

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https://doi.org/10.1016/j.jadr.2020.100037
Received 9 October 2020; Received in revised form 11 November 2020; Accepted 17 November 2020
Available online 20 November 2020

sample of patients suffering from bipolar disorder (BD) (Beckett and Chaplin 2006). Most existing studies focused on patients' capacity to give informed consent to clinical research among those diagnosed with BD (Misra and Ganzini, 2004; Misra et al., 2008a; 2008b; Klein et al., 2019). A study by Palmer et al. (2007) showed that people with BD had lower capacity than healthy controls and did not differ from patients with schizophrenia (Palmer et al., 2007). Another study correlated capacity to consent to clinical research with insight in BD and schizophrenia patients, finding a stronger effect size for the latter and a positive correlation in both samples (López-Jaramillo et al., 2016).

Altogether, data concerning capacity to give informed consent in BD patients are scattered and inconclusive, a circumstance that probably originates from the clinical complexity as well as the legal and ethical issues that often arise in BD patients (Richa et al., 2018). Mood fluctuation characterizes BD and the disorder is marked by the emergence of mood episodes amidst periods of wellness. Episodes may be either manic/hypomanic or depressive. This shifting to a non-euthymic phase in BD may be associated with changes in TDMC, by possibly decreasing as an episode worsens and returning to baseline with the remission of the phase (Gergel and Owen, 2015; Hindley et al., 2019).

To our knowledge, the possible impact of the episodic course of BD on patients' capacity to consent has not been investigated with structured standardized assessment tools. Given the fluctuating nature of BD, we aimed to investigate TDMC by using the MacArthur Competence Assessment Tool for Treatment (MacCAT-T) (Grisso et al., 1997; Grisso and Appelbaum, 1998b) in a group of patients with BD during different phases of the disorder. Specifically, we evaluated TDMC during acute episodes and during euthymia. We assumed that the former would be best represented in hospitalized BD patients for an acute episode, while the latter by euthymic BD outpatients. Patients followed at outpatient services could have greater capacity to provide consent to treatment than hospitalized patients with BD and we wanted to evaluate competency in relation to a future, possible, alternative treatment. Having such information has relevance, for identifying subpopulations at risk of decision-making inability, and for identifying the best time to acquire advance treatment decisions.

Thus, the primary aim of this study was to compare TDMC between two groups of BD patients in a different phase of their disorder. We hypothesized that patients diagnosed with BD during a phase of clinical recovery, treated at our outpatient clinic with maintenance treatment, would have higher TMDC compared with BD inpatients admitted in our psychiatric ward during an acute episode.

## Materials and methods

Patients were recruited according to DSM-5 (American Psychiatric Association, 2013) BD diagnosis, of which 87 with BD-I and 13 with BD-II, at the Department of Human Neuroscience and Mental Health of Umberto I University Hospital, Rome, Italy. Inpatients were hospitalized at the Psychiatric Intensive Care Unit for an acute psychopathological episode (manic, depressive or with mixed features) and were assessed during their episode, while outpatients were followed at our Depression and Mood Disorders Clinic of the same hospital and were evaluated during a phase of symptom compensation. The design was cross-sectional and parallel. Recruitment started on May 2018 and ended on October 2019; eligible patients were recruited consecutively.

Inclusion criteria were age between 18 and 70 years, primary school education or higher, being fluent in Italian, and Mini-Mental State Examination (MMSE) score ≥18. Exclusion criteria included neurocognitive disorders and intellectual disability. All patients were assessed with the following instruments:

### *Mini-Mental State Examination (MMSE)*

A 30-point test used to detect cognitive impairment, (Folstein et al., 1975), which takes about 5–10 min to administer.

### *Brief Psychiatric Rating Scale (BPRS)-24-item expanded version*

The BPRS has been developed during the early '60s to investigate general psychopathology (Overall and Gorham, 1962; Overall, 1974), the current 24-item version is among the most commonly used clinical tools to measure psychiatric symptoms severity (Lukoff et al., 1986; Ventura et al., 1993). The Italian version of the BPRS received validation and provides a manual with anchor scores (Roncone et al., 1999). The scale yielded four-factor solutions in factor analyses (Ventura et al., 2000; Thomas et al., 2004; Burlingame et al., 2006; Picardi et al., 2008). A recent specific BPRS factorial structure in involuntarily hospitalized psychiatric patients had been proposed (Tarsitani et al., 2019). There are no commonly accepted cutoffs, but some authors use BPRS-E 31 for mildly ill' 41 for moderately, 53 for markedly, and 70 for extremely ill (Leucht et al., 2005) and others consider a 20% drop of scores from baseline as a response criterion (Conley et al., 1998; Josiassen et al., 2005). Its internal consistency was found to be satisfactory, with Cronbach's alpha ranging from 0.69 to 0.74 in one multisite study (Ruggeri et al., 2005) to 0.79 for the entire scale and for each identified factor (0.68 for Thought Disturbance, 0.76 for Animation, 0.78 for Mood Disorder, and 0.73 for Apathy (Thomas et al., 2004).

### *Young Mania Rating Scale (YMRS)*

The Young Mania Rating Scale (YMRS) (Young et al., 1978) is the most frequently used clinician-rated scale to assess manic symptoms. It consists of 11 items and is based on the patient's subjective report of her/his clinical condition over the previous 48 hours. Additional information is based on clinician's impressions during the interview. Scores of ≤12 on the YMRS are used to define remission. A 93% sensitivity and 96% specificity were found at a 12.5 cutoff and internal consistency proved by a 0.72 Cronbach's alpha for the total scale (Mohammadi et al., 2018).

### *Montgomery–Åsberg Depression Rating Scale (MADRS)*

A derivative of the Comprehensive Psychopathological Rating Scale (Åsberg et al., 1978), it is a 10-item clinician-rating scale to rate depression and which is sensitive to change (Montgomery and Asberg, 1979). Scores of 0–6 indicate no symptoms/normal, 7–19 mild depression, 20–34 moderate, and >34 severe depression. Its sensitivity is 87%, its specificity 61%, the positive predictive value 74% and the negative predictive value 79% in making diagnosis of major depression at an 18 cutoff (Williams and Kobak, 2008).

Capacity to consent to treatment was assessed with the *MacArthur Competence Assessment Tool for Treatment (MacCAT-T)*, a semi-structured interview, widely used for TDMC assessment and validated for reliability in measuring capacity in patients with mental disorders by many scholars (Howe et al., 2005; Owen et al., 2008, 2009a, 2009b, 2009c; Mandarelli et al., 2012, 2014, 2017; 2018). This instrument was administrated and scored according to the MacCAT-T manual (Grisso and Appelbaum, 1998a, 1998b) by psychiatrists trained by the same senior expert during the research preparation stage. Treatment information disclosed to the patients during MacCAT-T sessions was based on the patient's psychopharmacological prescription, which had been previously decided by the treating staff and not necessarily coinciding with the research designers' opinions. Such information was collected before the interview by discussing with the treating staff and carefully analyzing case notes, records and prescriptions. The MacCAT-T investigates four domains: understanding, appreciating, reasoning and expressing a choice. Although it did not show convergence with the BPRS, its scores correlated inversely with BPRS scores (Grisso et al., 1997). With the understanding subscale we investigated each patient's understanding capacity regarding information disclosed to him/her about the clinical features of BD, his/her current psychopharmacological treatment,

**Table 1**
Socio-demographic and clinical characteristics of the two study groups.

| Measure | Total (*N*=100) | BD inpatients (*N*=53) | BD outpatients (*N*=47) | Test | *p* |
|---|---|---|---|---|---|
| Age, years, mean (SD) | 45.1 (13.8) | 42.8 (13.1) | 47.8 (14.2) | $t$=−1.83 | NS |
| Gender, Women, *n* (%) | | 29 (50%) | 29 (50%) | $\chi^2$=0.25 | NS |
| Men, *n* (%) | | 24 (57.1%) | 18 (42.9%) | | |
| Education, years, mean (SD) | 14.2 (3.4) | 14.7 (3.2) | 13.6 (3.5) | *t= 1.68* | NS |
| Marital status, Unmarried, *n* (%) | | 34 (60.7%) | 22 (39.3%) | $\chi^2$=2.37 | NS |
| Married, *n* (%) | | 19 (43.2%) | 25 (56.8%) | | |
| Previous psychiatric hospitalization, 0, *n* (%) | 51 (51.0%) | 20 (39.2%) | 31 (60.8%) | $\chi^2$=11.24 | <0.01 |
| 1-2, *n* (%) | 21 (21.0% | 11 (52.4%) | 10 (47.6%) | | |
| ≥3, *n* (%) | 28 (28.0%) | 22 (78.6%) | 6 (21.4%) | | |
| Previous IPH, 0, *n* (%) | 75 (75.0%) | 37 (49.3%) | 38 (50.7%) | $\chi^2$=4.12 | NS |
| 1-2, *n* (%) | 14 (14.0%) | 7 (50.0%) | 7 (50.0%) | | |
| ≥3, *n* (%) | 11 (11.0%) | 9 (81.8%) | 2 (18.2%) | | |
| Age at onset of BD, years, mean, (SD) | 27.5 (11.6) | 27.4 (10.5) | 27.6 (12.8) | $t$=−0.69 | NS |
| MMSE, mean (SD) | 28.1 (2.0) | 27.7 (2.1) | 29.06 (1.8) | $t$=−5.021 | <0.01 |
| BPRS, mean (SD) | 43.3 (13.1) | 51.22 (11.9) | 34.29 (7.1) | $t$=8.44 | <0.01 |
| MADRS, mean (SD) | 16.1 (10.2) | 19.07 (932) | 12.82 (10.1) | $t$=3.20 | NS |
| YMRS, mean (SD) | 11.9 (10.5) | 17 (11) | 6.12 (5.7) | $t$=6.04 | <0.001 |

*Note*. BD, bipolar disorder; BPRS, Brief Psychiatric Rating Scale; MADRS, Montgomery-Åsberg Depression Rating Scale; MMSE, Mini-Mental State Examination; IPH Involuntary Psychiatric Hospitalization; NS, not significant; YMRS, Young Mania Rating Scale.

and the associated risks and benefits. The subscale is scored on a Likert pseudo-continuous scale ranging 0–6. The appreciating subscale assesses the patient's level of agreement with the physician about his/her diagnosis (2 = agrees with all disclosed disease features, 1 = partially recognizes disease features, and 0 = does not recognize suffering from disease) and treatment (scoring similarly to appreciating diagnosis, from 0 to 2 points); points of the two subsections are added to obtain the subscale score, that ranges 0–4. The patient's ability to provide reasonable, logical, and coherent reasons for her/his treatment choices, including treatment refusal, is evaluated by the "reasoning" subscale, ranging 0–8. The reasoning subscale scoring includes eliciting patients' consequential and comparative thinking and analyzing its logical consistency, as well as patient's capacity to indicate possible treatment/no-treatment consequences on his/her everyday life. The "expressing a choice" subscale (ranging 0–2) measures patient's ability to express a clear and non-ambivalent treatment choice.

Since all patients were on polypharmacy, we focused the interview on the two drug classes deemed to be most important for long-term treatment, i.e. mood stabilizers and antipsychotics.

We focused the last part of the interview on the ability to make a valid choice between two proposed alternative treatments, including the current one, in case of a possible future, phase of decompensation. This ability was measured through the MacCAT-T Alternative Treatment (AT), which focused on *a)* understanding of AT characteristics (ranging 0–2= and *b)* understanding of AT benefits and risks (ranging 0–2). We moreover calculated a composite MacCAT-T AT score by summing the two.

In the present study the composite MacCAT-T AT score, which was calculated on the ability to understand a hypothetical new treatment, considered as an advance decision, should a new episode or decompensation occur, was proposed as a proxy of patients' capacity to consent to an advance treatment decision. The investigating clinician prospected to each patient an evidence-based alternative drug treatment, in line with the indications for BD, for a hypothetical scenario of future psychopathological decompensation formulated on the basis of the characteristics of previous episodes derived from patient's clinical record, or based on the characteristics of the current episode.

A total score for the MacCAT-T was not calculated as it is not recommended by the scale's originators (Grisso et al., 1997). We focused instead on the four subscale scores according to the interview standard procedure. This method agrees with the interview structure and with a multidimensional mental capacity approach, which suggests that poor performance in just one facet/subscale may imply incapacity even in the presence of a good performance in other domains.

Each patient received a detailed explanation of the study and provided written informed consent to participate. The study endorsed the Principles of Human Rights, as adopted by the World Medical Association at the 18th WMA General Assembly, Helsinki, Finland, June 1964 and subsequently amended by the 64th WMA General Assembly, Fortaleza, Brazil, October 2013. The research protocol has been reviewed and approved by the Ethics Committee of the Umberto I University Hospital, Rome, Italy prior to its initiation. All data were analyzed anonymously.

### 2.5. Statistical analysis

After testing for normality of data distribution through the Shapiro and Wilk (1965) test, differences between groups in continuous variables were analyzed by the independent sample *t* test. Chi-square test (with Yates' correction for continuity for 2 × 2 tables) or Fisher's exact test, as appropriate, was used for comparisons between categorical variables. Correlations were calculated by Pearson's correlation coefficient. The $\alpha$ value was set to .05; all tests were two-tailed. Data were analyzed using SPSS version 20.0.

## Results

The socio-demographic and clinical characteristics of 53 BD inpatients and 47 outpatients (49 BD-I, 4 BD-II; 38 BD-I, 9 BD-II respectively, chi-squared=2.965; $p$=0.085) are shown in Table 1. Independent sample t test disclosed that mean BPRS 4.0 and YMRS scores were significantly higher in hospitalized BD patients than in outpatients (BPRS $p$<0.01; YMRS $p$<0.001). No statistically significant differences were observed in mean MADRS scores. Mean MMSE scores were within the normal range for the sample overall. Outpatients scored significantly higher than inpatients on the MMSE (27.7±2.1 *vs*. 29.06±1.8; $p$<0.01) (Table 1).

We found significantly lower scores in MacCAT-T understanding, reasoning and expressing a choice in BD inpatients than outpatients, while no significant differences emerged in MacCAT-T appreciating (Table 2).

Pearson's correlation coefficient disclosed that cognitive functioning as measured by the MMSE was directly correlated with all the MacCAT-T subscale scores (Table 3). Conversely the measures we used to assess manic symptomatology (YMRS) and psychiatric symptoms severity (BPRS) negatively impacted on all the MacCAT-T facets investigating patients' capacity to consent to treatment (Table 3). Depressive symptoms as measured by the MADRS showed a significant inverse correlation just with the MacCAT-T appreciating subscale (Table 3).

**Table 2**
Individual capacity ratings on the MacArthur Competence Assessment Tool for Treatment (MacCAT-T).

| 1MacCAT-T | Total (*N*=100) | BD inpatients (*n*=53) | BD outpatients(*n*=47) | *p* |
|---|---|---|---|---|
| MacCAT-T Understanding, mean (SD) | 4.9 (1.0) | 4.51 (0.9) | 5.24 (0.9) | <0.001 |
| MacCAT-T Appreciation, mean (SD) | 3.1 (1.1) | 2.96 (1.2) | 3.36 (1.0) | NS |
| MacCAT-T Reasoning, mean (SD) | 4.4 (2.3) | 3.77 (2.3) | 5.21 (2.0) | <0.001 |
| MacCAT-T Expression of a choice, mean (SD) | 1.6 (0.6 | 1.43 (0.7) | 1.87 (0.4) | <0.005 |

*Note.* BD, bipolar disorder; NS= not significant; SD, standard deviation. *p* values by independent sample *t* test.

**Table 3**
Correlations between capacity ratings (MacCAT-T), cognitive functioning and psychopathological features.

| Clinical rating scales | MacCAT-T Understanding | MacCAT-T Appreciating | MacCAT-T Reasoning | MacCAT-T Expressing a choice |
|---|---|---|---|---|
| MMSE | 0.56** | 0.32** | 0.43** | 0.49** |
| MADRS | −0.12 | −0.27** | −0.14 | −0.16 |
| YMRS | −0.49** | −0.43** | −0.46** | −0.35** |
| BPRS | −0.48** | −0.35** | −0.44** | −0.33** |

Note. MMSE, Mini Mental State Examination; MADRS, Montgomery–Åsberg Depression Rating Scale; YMRS Young Mania Rating Scale; BPRS, Brief Psychiatric Rating Scale v 4.0; *p* values by Pearson's correlation coefficient. ** $p<0.001$.

**Table 4**
Individual capacity to understand an alternative future treatment.

| MacCAT-T alternative treatment | Total (*N*=100) | BD inpatients (*N*=53) | BD outpatients (*N*=47) | Test | *P* |
|---|---|---|---|---|---|
| MacCAT-AT treatment characteristics, mean (SD) | 1.6 (0.5) | 1.51 (0.5) | 1.79 (0.3) | *t*=-3.0 | <0.01 |
| MacCAT-AT risks/benefits, mean (SD) | 1.4 (0.6) | 1.32 (0.5) | 1.51 (0.6) | *t*=-1.5 | NS |
| MacCAT-AT composite score, mean (SD) | 3.0 (0.9) | 2.83 (0.9) | 3.30 (0.7) | *t*=-2.9 | <0.05 |

Note. BD, bipolar disorder; NS, not significant; SD, standard deviation, *t*, independent sample *t* test.

The comparison we did on a measure of understanding an alternative advance treatment, by the MacCAT-T AT, showed that outpatients proved more capable to understand its characteristics than their inpatient counterpart ($p<0.01$) (Table 4). No significant difference emerged between the study groups in their ability to understand risks and benefits of the proposed future alternative treatment. The same comparison using a sum score of understanding alternative treatment characteristics and risks and benefits showed a better total performance in BD outpatients. ($p<0.05$) (Table 4).

## Discussion

The results we found in the present study suggest that, during the acute phase of BD, patients present poorer capacity to consent to treatment than in stabilized BD. These data confirm an intuitive hypothesis, previously relatively lacking in empirical confirmation, based on a representative sample of patients. Nonetheless, we found no significant differences between the two study groups on the MacCAT-T appreciating subscale. Similar levels of diagnosis and treatment appreciation ability between the acute phase and the stabilized phase of BD, which we have found, could be firstly interpreted as due to only 5 involuntarily treated patients in the inpatients group. A sub-analysis comparing the MacCAT-T dimensions between voluntarily and involuntarily treated BD patients showed, in fact, that the latter achieved significantly lower scores on all subscales ($p<0.01$).

The appreciating MacCAT-T scale is basically associated with the level of agreement with the opinions of the attending physicians. A poor sensitivity in the MacCAT-T appreciation has been noted in other cross-sectional studies (Kennedy et al., 2009) and in some prospective measures of change (Dornan et al., 2015; Fernandez et al., 2017). In our sample, a medium-high level of agreement emerged regardless of the disorder phase, although the other TDMC facets were instead worse in the inpatient group. This result emphasizes the limited possibility of obtaining a valid TDMC evaluation by considering just patients' assent to treatment, particularly in BD patients.

Despite BD inpatients in our study presented significantly poorer cognitive functioning than outpatients, the two groups showed mean MMSE scores within the normality range. Since cognitive functioning is a well-known factor associated with poorer patients' capacity to provide informed consent (Palmer et al., 2004; Howe et al., 2005; Mandarelli et al., 2012), the fair mean MMSE scores allowed us to properly evaluate the impact of psychiatric symptoms on TDMC.

As concerning the impact of psychopathological symptoms, we focused on the manic and depressive dimensions, because they are the core features of BD. Manic symptom severity proved to be greatly associated with reduced patients' capacity to consent to treatment. In our study, those patients with higher YMRS scores performed poorly on ability to understand, appreciate, reason, and express a treatment choice (Table 3). This suggests a broad role of manic/hypomanic symptoms on TDMC, which seems to be in this specific population of patients as relevant as cognitive functioning, a well-known phenomenon (Vrabie et al., 2015). Mania is associated with possible optimistic bias, underestimation of the risks associated with choices, and disinhibition (Misra et al. 2008a).

Depressive symptoms proved to negatively affect only patients' ability to appreciate their clinical condition and treatment, while they did not impact the ability of understanding, reasoning and expressing a treatment choice. A possible interpretation of this results resides in the cognitive distortions and dysfunctional beliefs that are typically associated with depression (Beck, 2008).

The result of a generalized negative impact of psychiatric symptoms severity as measured by the BRPS on all the TDMC dimensions once again underlines the role of symptoms rather than diagnosis on patients' competency (Palmer et al., 2004: Howe et al., 2005; Mandarelli et al., 20142018, Rutledge et al., 2008). A similar consideration derives also from the poorer MacCAT-T scores we found in BD inpatients than outpatients.

Our study provides initial evidence that patients suffering from a mental disorder that is typically characterized by acute phases with possible consequent incapacity and long periods of symptom remission, show a better ability to understand possible alternative treatments in the remission phase. This preliminary empirical evidence calls for the opportunity to implement advance decision acquisition procedures that,

account for the level of therapeutic alliance – considered as an indispensable prerequisite – and allow to evaluate the presence of specific components that could negatively impact the patient's decision-making autonomy.

The advance treatment choices should be made in a remission phase to avoid collecting possibly incompetent patients' decision. On the other hand, an acute disease phase can present with irrational cognition or behavior, and in case of previous valid advance treatment decisions it would be appropriate to maintain that decision and override possible current different choices. This methodology could contribute in reducing a paternalistic medical approach to the patient.

### *Limitations*

The limitations of the present study include a cross-sectional design and recruitment from a single center. A longitudinal design is likely to provide stronger results, although capacity to consent has shown diachronic stability in populations comprising BD patients (Palmer et al., 2013).

### *Conclusions and future perspectives*

Patients diagnosed with BD present levels of TDMC that vary depending on the stage of bipolar disorder. During the phases of acute psychopathological decompensation, especially those associated with severe manifestation of manic symptoms and global symptom severity, the levels of TDMC are reduced, causing possible incapacity. The better TDMC we found during the compensation phase could constitute a precondition for the possibility to deposit Psychiatric Advance Directives.

## Declaration of Competing Interest

All authors declare no conflict of interests.

## CRediT authorship contribution statement

**Alexia Emilia Koukopoulos:** Conceptualization, Data curation, Formal analysis, Writing - original draft. **Gabriele Mandarelli:** Conceptualization, Data curation, Formal analysis, Writing - original draft. **Gino Maglio:** Data curation, Writing - review & editing. **Monica Macellaro:** Data curation, Writing - review & editing. **Mariarosaria Cifrodelli:** Data curation, Writing - review & editing. **Georgios D. Kotzalidis:** Data curation, Writing - review & editing. **Lorenzo Tarsitani:** Data curation, Writing - review & editing. **Massimo Biondi:** Data curation, Writing - review & editing. **Stefano Ferracuti:** Conceptualization, Data curation, Formal analysis, Writing - original draft.

## Acknowledgments

We appreciate the help of our secretary Ms. Tatiana Renzi for providing us useful tips for completing our manuscript. We are also grateful to Ms Mimma Ariano, Ms Ales Casciaro, Ms Teresa Prioreschi, and Ms Susanna Rospo, Librarians of the Sant'Andrea Hospital, School of Medicine and Psychology, Sapienza University, Rome, for rendering precious bibliographical material accessible.

## Ethical considerations

The study obtained ethical approval from the Ethics Committee of the Umberto I University Hospital, Rome. Consent to participate and Consent for publication were obtained from each patient. The study adhered to the Helsinki Principles of Human Rights as amended in 2013. All this has been duly specified in the text, as appropriately.

## Submission declaration

The work here described has not been published previously, either in the form of an abstract, lecture or academic thesis; it is not under consideration for publication elsewhere. Its publication is approved by all authors and tacitly or explicitly by the responsible authorities where the work was carried out. If accepted, it will not be published elsewhere in any form.

## Use of inclusive language

Used throughout the paper.

## Role of the funding source

This study has not been funded by public or private agencies and has not received grants.

## Research data and material availability

Through request to corresponding author.

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