Accuracy of self-reported adherence and therapeutic drug monitoring in a psychiatric emergency ward

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Abstract

The aims of the study were: 1) the evaluation of the agreement between therapeutic drug monitoring (TDM) and a self-assessment of adherence to psychopharmacological treatments; 2) the identification of predictors of TDM results.Adherence admitted into a psychiatric emergency service (PES) for a relapse of a schizophrenia spectrum disorder (SSD) or a bipolar disorder (BD; DSM-5) was assessed both directly with TDM and indirectly with a self-reported measure (Medication Adherence Report Scale -MARS- 10 items). The agreement between TDM and MARS was evaluated. Fifty-seven patients with SSD and 76 people with BD participated in the study. TDM was in range in about 50% of the global sample. No evidence of an association between MARS total scores and TDM results was found. Sensibility, specificity, positive and negative predictive values of almost all MARS total scores were near to 50%. Smoking was strongly associated with a reduction of TDM results within the reference range. In the BD group, female sex was a predictor of TDM in range. In this clinical setting, self-assessment of adherence is neither reliable nor predictive. Furthermore, smoking is a strong predictor of poor adherence to psychopharmacological therapy.

Keywords:

Medication Adherence Report Scale (MARS)

Therapeutic drug monitoring (TDM)

Schizophrenia Spectrum Disorders (SSD)

Bipolar Disorder (BD)

Smoking

Insight

Pseudo-resistance

Manuscript

1. Introduction

Adherence to treatments, defined as the extent to which a person's behavior (taking medication, following a diet, and/or executing lifestyle changes) corresponds with agreed recommendations from a health care provider, is often inadequate in chronic medical conditions as up to 50% of patients have no or only partial adherence (Sabaté,2003). In mental health, data are similar showing that up to 70% of people living with a mental disorder have an inadequate adherence to treatments (Haddad et al.,2014; Higashi et al.,2013; Murru et al.,2013). Adherence is a multidimensional phenomenon influenced by several elements: patient, illness, and treatment related factors, therapeutic alliance and engagement with health services, quality of mental health services, economic and social factors (Buchman-Wildbaum et al.,2020; Leclerc et al.,2013; Leucht e Heres, 2006; Kane e Correll, 2010; Velligan et al., 2017). In schizophrenia spectrum disorders (SSD) and bipolar disorders (BD), adherence appears to be negatively affected by cannabis (Schoeler et al., 2017), alcohol and substance use (Velligan et al.,2017), treatment-related side-effects (Pompili et al.,2013), impaired insight (Novick et al.,2015; Kim et al,2020; Velligan et al.,2017) cognitive deficits (Velligan et al.,2017), internalized stigma (Buchman-Wildbaum et al.,2020; Kamaradova et al.,2016: Verdoux et al., 2020), lower quality of life (Buchman-Wildbaum et al.,2020; Verdoux et al., 2020), stage of recovery, and mental well-being (Verdoux et al., 2020), and higher levels of hostility (Czbor et al.,2015;Novick et al.,2010). Conversely, it seems to be positively influenced by positive attitudes to medications (Sendt et al.,2015), therapeutic alliance (Novick et al.,2015; Pompili et al.,2013), and family support (Saba et al.,2019).

Partial or non-adherence to treatments negatively affects the evolution of SSD and BD, with greater frequency of relapses, reduction of response to psychopharmacological therapies, progressive chronicity of symptoms, higher suicide risk, and worsening of real-life functioning (Alvarez-Jimenez etal.,2012; Levin et al.,2016; Pompili et al.,2009). Poor adherence to treatments

is one of the only modifiable relapse risk factors (Emsley et al.,2013), therefore needs to be constantly monitored and addressed by acting on its determinants (Acosta et al.,2012; Kini e Ho,2018). Moreover, in case of relapse, it is crucial to differentiate between resistance to treatment and pseudo-resistance, due to inadequate adherence or substances interactions, as these two different scenarios could lead to different therapeutic choices (Dold e Leucht,2014; Fornaro et al., 2020; Kane et al., 2019).

Adherence can be measured by direct or indirect methods. Direct methods most widely applied are direct observed therapy and therapeutic drug monitoring (TDM). Indirect measures include objective and subjective evaluations. Objective methods are electronic drug monitoring, rate of prescriptions refill, clinical response evaluation, monitoring of markers of treatment effects. Subjective evaluations are represented by patients', caregivers', or health care professionals' estimate of adherence (Kane e Correll,2010, Osterberg e Blaschke,2005; Sajatovic et al.,2010, Velligan et al.,2020). Direct methods, in particular TDM, are generally more sensitive and specific than indirect ones but are not extensively adopted in everyday clinical practice for practical and economic reasons (Kane et al.,2019; Osterberg et Blaschke,2005; Velligan et al., 2020). On the contrary, self-assessment of adherence to therapy is one of the most used, practical, and cheap methods to evaluate compliance with psychopharmacological treatment but is often affected by patients' lack of awareness of the need of a continuous psychopharmacological treatment (Kane e Correll,2010; Kim et al.,2020; Novick et al. 2015; Sajatovic et al.,2010; Velligan et al.,2020). Indeed, insight deficit is a prevalent feature of SSD (Amador et al.,1994; Belvederi Murri e Amore,2019) also found in BD (Látalová,2012), and includes unawareness of symptoms, treatment need, and alterations in cognitive processes involved in the capacity for self-reflectiveness and self-evaluation (Dias et al., 2008; Elowe e Conus, 2017: Medalia e Thysen, 2010: Pini et al., 2001).

Following the World Health Organization recommendation to combine both direct and indirect methods to accurately assess adherence (Sabaté,2003), and the lack of scientific evidence of this

multimodal evaluation in a real word setting of emergency psychiatry, we decided to study the compliance with psychopharmacological therapy of patients with SSD and BD recently admitted in a psychiatric emergency service (PES). In particular, the aims of the present study are: 1) to evaluate the agreement between an objective (TDM) and a subjective (self-assessment) evaluation of adherence to the psychopharmacological treatments; 2) to assess which socio-demographic and clinical variables can predict treatment adherence determined with TDM.

2 Methods

The present work was conducted in the Psychiatric Emergency Service (PES) "Struttura Complessa Psichiatria – Servizio Psichiatrico di Diagnosi e Cura" (SPDC) of the Departmentof Neuroscience and Mental Health of "Città della Salute e della Scienza" hospital of Turin, Italy, in the period between February 2019 and November 2020.

2.1 Subjects

All patients consecutively admitted who fulfilled inclusion criteria were included in the study.

Inclusion criteria were the following: a) diagnosis of schizophrenia spectrum disorders (SSD) or diagnosis of bipolar and related disorders (BD), according to DSM-5 diagnostic criteria; b) age over 18 years; c) being in therapy, at the admission time, with a drug whose concentration in the serum could be evaluated at the hospital laboratory: lithium, sodium valproate, carbamazepine, haloperidol, clozapine, olanzapine, risperidone, paliperidone, quetiapine, aripiprazole. For patients with psychiatric polypharmacotherapy we measured only one drug: i.e., the only antipsychotic or mood stabilizer prescribed with a daily dosage indicated for the treatment of the SSD or of the BD according to the technical data sheet of that drug. When this selection of a single drug was not applicable, patients were not included in the study.

Exclusion criteria were the following: a) co-presence of a diagnosis of dementia, delirium or intellectual disability; b) standard informed consent to treatments and standard personal data

collection consent not provided by patient or his legal representative, c) concomitant treatment with a drug pharmacokinetically interacting with the drug assessed with TDM according to the technical data sheet of at least one of the two drugs; d) admission for psychotropic drug intoxication.

To avoid duplication, only data for the first hospitalization of patients who had multiple hospitalizations were included in this analysis.

The study was carried out in accordance with the principles of the Declaration of Helsinki (with amendments) and of the Good Clinical Practice and was approved by the Local Research Ethical Committee (LREC; in Italian Comitato Etico Interaziendale – CEI – n.185). The study protocol was integrated in the regular diagnostic assessment and did not imply any variation from standard care usually provided in the recruiting unit. Data were analyzed anonymously as all personally sensitive information was de-identified in the dataset, according to the Italian legislation. According to these characteristics of the study protocol, the LREC agreed that a study specific informed consent, additional to the standard ones used in the clinical practice of the PES, was not required.

2.2 Clinical assessment

Socio-demographic and clinical variables were assessed through a semi-structured interview. Psychiatric symptoms were rated with the Italian version of the Brief Psychiatric Rating Scale (BPRS) (Overall,1974) which encodes 5 sub-scales evaluating different psychopathological dimensions (Shafer,2005): BPRS-1, Affect (anxiety, guilt, depression, somatic symptoms); BPRS-2, Negative Symptoms (blunted affect, emotional withdrawal, motor retardation); BPRS-3, Positive Symptoms (unusual thought content, conceptual disorganization, hallucinatory behavior, grandiosity); BPRS-4, Activation (excitement, tension, mannerisms–posturing); BPRS-5, Resistance (hostility, uncooperativeness, suspiciousness). The global severity of symptoms was estimated with the Clinical Global Impression – Severity scale (CGI-S) (Guy,1976), the engagement with psychiatric services with the Services Engagement Scale (SES) where a higher total score indicates a lower engagement (Tait et al.,2004), the global functioning, prior to the clinical relapse that led to hospitalization, with

the Global Assessment of Functioning scale (GAF) (Goldman et al.,1992), and the psychopharmacological treatment side effects with the Udvalg for Kliniske Undersøgelser - Side Effect Rating Scale (UKU) (Lingjaerde et al.1987).

All assessments were performed by the same well-trained experienced interviewing psychiatrists (C.B. and F.P.). To reduce inter-rater variability, raters were trained to administer the psychometric tools according to common standards. Efforts were made to maintain inter-rater reliability across the entire study period, including careful standardization of the procedures and regular, in-depth review of a sample of interviews with the lead authors (P.R. and V.V.).

2.3 Evaluation of the adherence to the psychopharmacological treatment

An objective and a subjective self-evaluated measure of adherence to the psychopharmacological treatment were performed.

TDM has been performed at the admission in the unit or, when not possible, before the first assumption of the drug monitored. Ultra-high-performance liquid chromatography–tandem mass spectrometry (UHPLC-MS/MS) was used to assess serum drug concentration. The only exception was lithium ion whose concentration was measured with ion selective electrodes (ISE). According to the methods proposed by the Consensus Guidelines for Therapeutic Drug Monitoring in Neuropsychopharmacology: Update 2017 (Hiemke et al.,2018) dose-related reference range (DRRR) were calculated for each drug measured. Patients whose plasmatic drug concentration was within the DRRR have been classified in the group of TDM in range (TDM-iR), while those with drug concentration out of the DRRR have been divided into TDM below the range (TDM-bR) and TDM above the range (TDM-aR).

Subjective self-assessment of adherence to treatment was evaluated with the Medication Adherence Rating Scale (MARS); (Thompson et al. 2000). The MARS is a 10-item self-administered questionnaire designed to be simple and easy to complete in any clinical context. It assesses medication adherence behavior (items 1–4), attitude toward taking medication (items 5–8), and

negative side effects to psychotropic medication (items 9–10) (Verdoux et al., 2020). Total MARS score ranges between 0 and 10. Higher scores indicate better adherence.

2.4 Statistical analysis

Agreement between TDM and MARS total score was analyzed with point-biserial correlation (r_{pb}). Two ROC curves (SSD and BD groups) were built using TDM as gold standard and MARS total scores. Their areas under the curve (AUC) were compared with each other and with the random classification. Sensitivity (Sens), specificity (Spec), accuracy (Acc), positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (+LR), and negative likelihood ratio (-LR) with 95% confidence interval (95% CI) were calculated for each MARS total score value.

Univariate analyzes were carried out to compare the two clinical groups (SSD vs BD), and adherent and non-adherent patients according to the TDM (TDM-iR vs TDM-b/aR). TMD results were reported for each drug measured and a comparison between all antipsychotics and all mood stabilizers was performed. For these comparisons, analysis of variance (One-way ANOVA) for continuous variables and the χ^2 test for categorical variables were employed. A multivariate backward logistic regression was performed for each clinical group to assess which variables were most strongly associated with TDM-iR. Only the variables statistically different in univariate analyses were included in the two regression models. The amount of variation in the dependent variable explained by the model in terms of accuracy of the prediction was estimated with the Nagelkerke's pseudo-R^2 index.

Statistical analyses were performed using the Software System Statistical Package for the Social Sciences (SPSS), version 27 for Windows. Statistical significance was set at $p < .05$ for all analysis. Variables maintained in the regression models were consider significant if they were associated with a p-value < .1.

3. Results

3.1 Characteristics of participants and TDM results

Socio-demographic, clinical, psychopathological, and treatment-related variables of the two clinical groups are illustrated in table 1.

TDM was in range in about half of the global sample. No TDM result was above the DRRR, therefore all TDM results out of the DRRR were below the range (TDM-bR). The mean total score of the MARS was 5.6 in both clinical groups, meaning that, on average, patients self-assessed themselves as non-adherent to psychopharmacological treatment in 4 or 5 items of the scale.

TDM results for each drug monitored are shown in table 2. There was not statistically significant difference between adherence to antipsychotics and mood stabilizer ($\chi^2 = 1.095$; $p = .295$).

3.2 Agreement between direct (TDM) and indirect subjective (MARS) evaluation of adherence

No significant results were found with the point-biserial correlation in both clinical groups (SSD: $r_{pb} = .155$, $p = .250$; BD: $r_{pb} = .059$, $p = .613$). According to our data, there is no evidence of an association between the MARS total score and TDM results (fig. 1).

The ROC curves of the two clinical groups are displayed in figure 2. There was no statistical difference between the AUC of the two curves and the overall quality of two models was less than 0.5 (SSD = 0.43; DB = 0.41), meaning that the two models were not better than random prediction. Similarly, Acc, Sens, Spec, PPV, and NPP were near to 50 % (random prediction) for almost all values of MARS total score in both SDD and DB groups (tab .3). +LR and -LR were mostly near to 1, indicating poor performance of any score of the MARS in correctly identify patients' adherence.

3.3 Differences between subjects with TDM-iR and TDM-bR and predictors of adherence assessed with TDM

Sociodemographic, clinical, psychopathological, and psychopharmacological treatment related variables of the SDD and BD clinical groups divided into sub-groups according to TDM results (TDM-iR vs TDM-bR) are shown in table 4.

In the SSD group, the logistic regression model (tab. 5) was highly significant ($\chi^2 = 11.801$; p = .003). A lower engagement was associated with a small reduction (OR = .936; p = .077) of treatment adherence (TDM-iR) whereas cigarette smoking was strongly associated with a marked reduction of TDM-iR (OR = .196; p = .008). This model demonstrated a total accuracy in predicting TDM iR or bR of 64.9%, a greater ability in predicting TDM-bR (71.4%), and lower precision in the prediction of TDM-iR (58.6%). The amount of variation of TDM estimated with the Nagelkerke's pseudo-R^2 index was 24.9.

The logistic regression model of patients with BD (tab. 5) was highly significant ($\chi^2 = 12.134$; p = .002). Female sex was associated with an important increase (OR = 2.671; p = .055) of treatment adherence evaluated with TDM. Cigarette smoking was associated with a marked reduction of TDM-iR (OR = .273; p = .016). The total accuracy of the model in predicting TDM iR or bR was 65.8% with a greater ability in predicting TDM-iR (73.8%), and a lower precision in the prediction of TDM-bR (55.9%). The Nagelkerke's index was 19.7%.

4. Discussion

Main findings

To our knowledge, this the first study to evaluate the agreement between the results of an objective and reliable direct measure of adherence (ultra-sensitive TDM) with a self-assessed indirect one (MARS) in a real-world setting of psychiatric emergency ward, in both patients with SSD and BD, that was the first aim of the study. Furthermore, as second aim, this work tried to find out predictors of adherence evaluated with ultra-sensitive TDM.

Concerning the first aim, our results demonstrated poor concordance between self-reported and direct measures of adherence in both SSD and BD groups: as clearly graphically represented in figure 1, point-biserial correlation (r_{pb}) was not statistically significant. These data suggest that patients, during a relapse, have marked problems in reporting their adherence to the

psychopharmacological treatment. They also indicate that self-reporting is not informative irrespective of the direct measure of adherence (TDM) as shown in figure 1. This finding is in line with previous studies demonstrating that patients were inaccurate raters of their adherence to psychopharmacological therapy (Kane e Correll 2010; Velligan et al.,2017; Kim et al.,2020; Novick et al.,2015; Sajatovic et al.,2010; Velligan et al.,2020; Lopez et al.,2017). This difficulty in self-evaluation can have multiple reasons including metacognitive and insight deficits, misunderstanding the items on a rating scale, and inaccurately conceptualizing correct compliance with therapies. These types of errors could derive from cognitive deficits, from the severity of specific symptomatic dimensions, and from the socio-demographic characteristics of the patients. Focusing on the lack of insight, prior to the onset of the relapse, patients could underestimate the constant need of psychopharmacological therapy, even during a period of psychic wellbeing. Then, during the onset of the relapse a further reduction in the awareness of the need for proper treatment could induce an additional worsening of adherence, thus precipitating the clinical condition into a full-blown recurrence of illness. Finally, at the beginning of the hospitalization in the PES, mechanism other than insight reduction could influence the untrustworthiness of patients' self-assessment of adherence, e.g., an increase of psychotic or manic symptoms, and the fear to be blamed for poor compliance with therapies. In accordance with these suppositions, several studies attributed a central role to the insight in determining adherence to psychopharmacological therapies (Kane e Correll, 2017; Velligan et al.,2017; Kim et al.,2020; Novick et al.,2020; Sajatovic et al.,2010; Velligan et al.,2020).

As direct consequence of the mismatch found between direct and self-assessed evaluations of adherence, it was not possible to identify a reliable MARS threshold value suitable to identify subjects with TDM-uR or TDM-iR. Likewise, the ROC curves of the SSD and BD groups were similar and both close to random prediction. Consequently, almost all PPVs and NPVs were unreliable (about 50% of correct predictions) for any MARS score. Hence, according to our data, in the clinical setting of a PES, MARS is not a suitable instrument to evaluate adherence to psychopharmacological

treatment and consequently to distinguish between “actual” and pseudo-resistance.

Therefore, the evaluation of resistance to psychopharmacological therapy could be supported by TDM, which however entails costs and delays often not compatible with the clinical setting of and emergency psychiatry ward, where rapid and appropriate therapeutic decisions, frequently based on the distinction between “actual” and pseudo-resistance, are needed (Kane e Correll, 2010; Osterberg e Blaschke,2005; Velligan et al.,2020). These limits lead to the second objective of this work, namely the possibility of predicting, based on variables available at the admission into the PES, the result of the TDM and therefore to distinguish between “actual” and pseudo-resistance.

As regards the second aim, smoking more than 10 cigarettes a day was the strongest predictor of poor adherence evaluated with TDM in both SSD and BD groups. This negative association may have several explanations including: 1) smoking could increase the rate of metabolization of the drug by induction of cytochromes p-450 (CYPs) at liver level; 2) patients with more severe symptoms, such as during the onset of a relapse, might increase cigarette consumption with the aim of alleviating psychic suffering, thus increasing the induction of cytochromes; 3) an indirect relationship between smoking and the decrease in plasma concentrations of drugs. These three hypotheses can occur simultaneously and partly explain what is observed in our study. Concerning hypothesis 1 and 2, i.e., direct effect of cigarette smoking, polycyclic aromatic hydrocarbons found in tobacco induce CYP1A2. This enzyme metabolizes olanzapine and clozapine, thus reducing their serum concentration (Hiemke et al.,2018; Faber et al.,2005, Haslemo et al.,2006; Tsuda et al.,2014). Hypothesis 3, i.e., indirect relationship, can be explained with complex interplays among many different factors. Patients with more severe psychiatric disorders and symptoms tend to smoke more and vice versa. As compared to non-smokers leaving with a severe mental illness (SMI), smokers suffering from a SMI have poorer economic conditions, cognitive performance, prognosis, global functioning, quality of life, and subjective wellbeing (Caponnetto et al.,2020; Depp et al.,2015; Firth et al.,2020; Medeiros et al.,2018; Prochaska et al.,2017; Thomson et al.,2015; Wang et al.,2019). This illness- and patient-related characteristics could lead to a lower level of insight in terms of need for

treatment, thus facilitating the poor adherence. At the same time, this clinical population has a greater prevalence of unhealthy lifestyles habits as alcohol and substance use. This facilitates the prevalence of medical comorbidities and the need to take many different medications (Firth et al.,2020; Prochaska et al.,2017; Thomson et al.,2015). In this view, substance-drug or drug-drug pharmacokinetic interactions are more likely, resulting in sub-therapeutic serum concentration of psychopharmacological treatments.

In the SSD group, a higher SES score (i.e., lower service engagement) was associated with poor adherence (TDM-uR). This result agrees with the study of Kini et at al. 2018, according to which a good therapeutic alliance and a solid service engagement positively influence patients' compliance to treatments (Kini e Ho, 2018). Simultaneously, female sex in patients with BD was a strong predictor of good adherence (TDM-iR). This result is in line with previous findings that showed that women were more precise in taking the therapies prescribed (Gonzales-Pinto et al.,2006).

The two regression models were able to correctly classify as adherent or non-adherent, according to TDM results, about 65% of patients. This value is higher than random prediction, however far from a safe and certain forecast and in line with the relatively low psudo-R^2 indices (20-25%). Better prediction, over 70%, were found in predicting poor adherence in the SSD group and good adherence in the BD patients. The psudo-R^2 indices values could be partly explained by non-behavioral determinants of TDM-uR (Sutherland et al.,2018) like drug-drug interactions, not signaled in the technical data sheet or due to the interaction between more than two drugs, and patient related biological factors affecting pharmacokinetics of psychopharmacological treatment such as *CYPs* and ATP-binding cassette sub-family B member 1(*ABCB1*) genes, the formers coding for cytochromes P450 and the latter for permeability glycoprotein 1 (PGP1), also known as multidrug resistance protein 1 (MDR1).

Strengths and limitations

The main limitations of the present study are the lack of data that clearly explain the strong relationship between smoking and poor adherence, and the relatively small values of the pseudo-R^2 indices of the regression models.

Despite these limitations, this study has some important strengths: firstly, the naturalistic design in a real-world setting of psychiatric emergency focusing on a sample of acute inpatients, poorly represented in literature on adherence, which considers more frequently outpatients, and secondly the use of ultra-sensitive TDM for haloperidol and different second-generation antipsychotics, which is poorly studied and employed in clinical practice.

Future perspectives and implications

For further research, analysis of genes involved in pharmacokinetics, more in-depth methods to examine the influence of smoking on TDM, and simultaneous TDM of all drugs taken by the patients, should be performed. Moreover, new and larger studies investigating other variables that may affect TDM are needed to confirm and improve the predictive models proposed.

In conclusion, according to the results obtained, within inpatients admitted for a relapse of a SSD or a BD, smoking less than 10 cigarettes per day, valid alliance with mental health services (for SSD) and female sex (for BD) are strongly associated with good compliance with psychopharmacological therapy measured with TDM. Moreover, in this clinical setting, indirect self-assessed evaluation of adherence (MARS 10 items) is neither reliable nor predictive of compliance with therapies.

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Conflicts of Interest

None.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author, P.R. The data are not publicly available as they contain information that could compromise the privacy of research participants.

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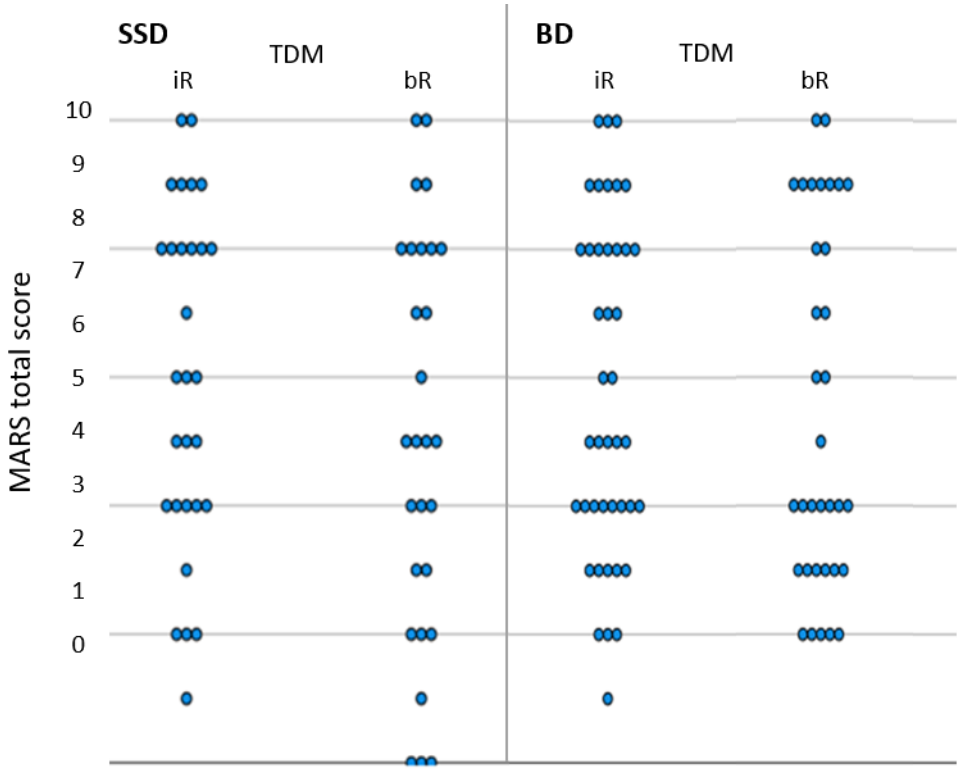
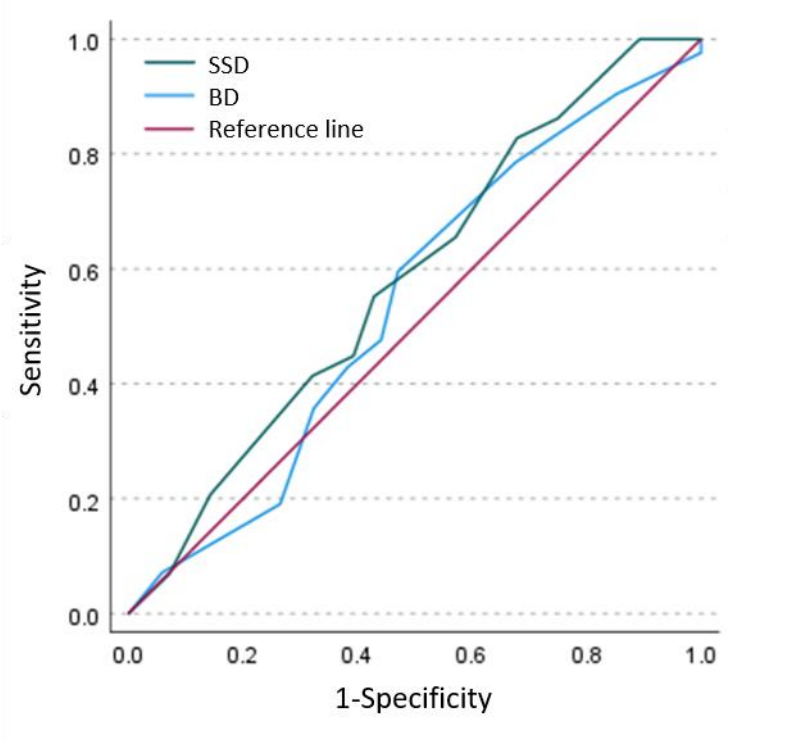
Figure 1 – MARS total scores subdivided according to TDM results.



MARS: Medication Adherence Report Scale; SSD: Schizophrenia Spectrum Disorders; BD: Bipolar and related Disorders; TDM: Therapeutic Drug Monitoring; iR: in Range; bR: below the Range.

Figure 2 – ROC Curves of MARS total scores using TDM as gold standard.



ROC: Receiver Operating Characteristic; MARS: Medication Adherence Report Scale; TDM: Therapeutic Drug Monitoring; SSD: Schizophrenia Spectrum Disorders; BD: Bipolar and related Disorders.

Table 1 - Sociodemographic, clinical, and psychopathological characteristics of the samples

	SSD (n = 57)	DB (n = 76)	F/χ^2	p-value†
Socio-demographic variables				
Gender, N of females (%)	19 (33.3)	34 (44.7)	1.940	.164
Age, years, mean (SD)	*43.1 (13.5)*	*51.9 (14.4)*	*12.795*	*<.001*
Married, N (%)	*9 (15.8)*	*36 (47.4)*	14.400	*<.001*
Working, N (%)	6 (10.5)	29 (38.2)	3.20	.074
Education, years, mean (SD)	*10.4 (3.2)*	*12.7 (3.7)*	*12.050*	*<.001*
Caucasic, N (%)	51 (89.5)	71 (93.4)	.431	.512
Clinical variables				
Duration of illness, mean (SD)	18.9 (11.7)	22.3 (12.3)	1.975	0.162
More than five prior hospitalizations for mental disorders, N (%)	35 (61.4)	38 (50.0)	3.15	.076
Compulsory admission for the present hospitalization, N (%)	11 (19.3)	15 (19.7)	.103	.749
Smoking (≥ 10 cigarettes/day), N (%)	34 (59.6)	47 (61.8)	.027	.870
Substance and alcohol abuse, N (%)	6 (10.5)	18 (23.7)	3.01	.083
Medical chronic comorbidities, N (%)	*24 (42.1)*	*44 (57.9)*	*3.92*	*.048*
Global Assessment of Functioning (GAF), mean (SD)*	*51.3 (10.2)*	*62.9 (12.2)*	*29.971*	*<.001*
Service engagement scale, mean (SD)	*19.7 (8.41)*	*16.5 (7.3)*	3.347	.065
Psychopathological variables				
BPRS-1, affect, mean (SD)	10.5 (4.1)	10.8 (4.7)	.171	.679
BPRS-2, negative symptoms, mean (SD)	*8.7 (3.6)*	*7.2 (4.2)*	*3.593*	*.025*
BPRS-3, positive symptoms, mean (SD)	10.6 (3.9)	9.7 (4.7)	1.129	.290
BPRS-4, activation, mean (SD)	*7.8 (3.3)*	*9.0 (3.2)*	*5.819*	*.017*
BPRS-5, resistance, mean (SD)	7.7 (4.5)	8.0 (4.8)	.582	.447
Clinical Global Impression (CGI), mean (SD)	4.6 (0.9)	4.5 (0.9)	.005	.942
Drug treatment at the moment of the hospitalization				
Haloperidol, N (%)	*16 (28.1)*	*7 (9.2)*	*8.10*	*.004*
Second generation antipsychotics, N (%)	35 (61.4)	58 (76.3)	2.89	.084
Both first- and second-generation antipsychotics, N (%)	6 (10.5)	-	NA	NA
Antidepressants, N (%)	10 (17.5)	13 (17.1)	.030	.862
Mood stabilizers, N (%)	*15 (26.3)*	*50 (65.8)*	*21.6*	*<.001*
Anxiolytics, N (%)	43 (75.4)	57 (75.0)	.002	.964
Polypharmacy, N (%)	47 (82.5)	70 (92.1)	2.22	.136
UKU gravity, mean (SD)	0.3 (1.3)	0.2 (0.5)	1.61	.206
Evaluation of psychopharmacological treatment adherence				
Therapeutic drug monitoring in range (TDM-iR), N (%)	29 (50.9)	42 (55.3)	.129	.719
Medication Adherence Report Scale (MARS), mean (SD)	5.6 (2.9)	5.6 (2.7)	.008	.928

SD: standard deviation; BPRS: Brief Psychiatric Rating Scale; UKU: Udvalg for Kliniske Undersøgelser - Side Effect Rating Scale; † uncorrected; * prior to hospitalization; NA: not applicable; Statistically significant different results are indicated in italics.

Table 2 - Therapeutic drug monitoring results for each drug measured

	TDM	
	iR	**bR**
Antipsychotics	37 (50.0%)	37 (50.0%)
Haloperidol [10.5%]	5 (35,7%)	9 (64.3%)
Aripiprazole [15.0%]	7 (35,0%)	13 (65,0%)
Clozapine [3.0%]	3 (75.0%)	1 (25.0%)
Olanzapine [8.3%]	6 (54,5%)	5 (45,5%)
Paliperidone [3.8%]	4 (80,0%)	1 (20,0%)
Quetiapine [8.3%]	7 (63.6%)	4 (36,4%)
Risperidone [6,8%]	5 (55.6%)	4 (44,4%)
Mood stabilizers	35 (59.3%)	24 (40,7%)
Lithium ion [21.1%]	12 (42.9%)	16 (57,1%)
Valproic acid [21.8%]	22 (75.9%)	7 (24.1%)
Carbamazepine [1.5%]	1 (50.0%)	1 (50%)

TDM: therapeutic drug monitoring; iR: in range; bR: below the range; (%): percentage of TDM in range or below the range; [%]: percentage of antipsychotics or mood stabilizer.

Schizophrenia Spectrum Disorders (n = 57)							
MARS ≥	**Sensitivity [%]**	**Specificity [%]**	**Accuracy [%]**	**PPV [%]**	**NPP [%]**	**+LR**	**-LR**
10	6.9 (0.9 - 22.8)	92.9 (76.5 - 99.1)	49.1 (35.6 - 62.7)	50.0 (13.1 - 86.9)	49.1 (45.5 - 52.6)	1.0 (0.2 - 6.4)	1.0 (0.9 - 1.2)
9	20.7 (8.1 - 39.7)	85.7 (67.3 - 96.0)	52.6 (39.1 - 66.0)	60.0 (32.1 - 82.6)	51.1 (45.1 - 57.0)	1.5 (0.5 - 4.6)	0.9 (0.7 - 1.2)
8	41.4 (23.5 - 61.1)	67.9 (47.7 - 84.1)	54.4 (40.7 - 67.6)	57.1 (40.1 - 72.7)	52.8 (42.9 - 62.5)	1.3 (0.7 - 2.6)	0.9 (0.6 - 1.3)
7	44.8 (26.5 - 64.1)	60.7 (40.6 - 78.5)	52.6 (39.0 - 66.0)	54.2 (39.1 - 68.6)	51.5 (40.6 - 62.3)	1.1 (0.6 - 2.1)	0.9 (0.6 - 1.4)
6	55.1 (35.7 - 73.6)	57.1 (37.2 - 75.5)	56.1 (42.4 - 69.3)	57.1 (43.8 - 69.6)	55.2 (42.4 - 67.3)	1.3 (0.8 - 2.2)	0.8 (0.5 - 1.3)
5	65.5 (45.7 - 82.1)	42.9 (24.5 - 62.8)	54.4 (40.7 - 67.6)	54.3 (43.9 - 64.3)	54.6 (38.3 - 69.9)	1.2 (0.8 - 1.7)	0.8 (0.4 - 1.6)
4	82.7 (64.2 - 94.2)	32.1 (15.9 - 52.4)	57.9 (44.1 - 70.9)	55.9 (48.2 - 63.1)	64.3 (40.8 - 82.5)	1.2 (0.9 - 1.7)	0.5 (0.2 - 1.4)
3	86.2 (68.3 - 96.1)	25.0 (10.7 - 44.9)	56.1 (42.4 - 69.3)	54.4 (47.9 - 60.7)	63.6 (36.5 - 84.2)	1.2 (0.9 - 1.5)	0.6 (0.2 - 1.7)
2	96.3 (81.0 - 99.9)	16.0 (4.5 - 36.1)	57.7 (43.2 - 71.3)	55.3 (50.7 - 59.9)	80.0 (32.4 - 97.1)	1.2 (1.0 - 1.4)	0.2 (0.0 - 1.9)
1	100.0 (88.1 - 100.0)	10.7 (2.3 - 28.2)	56.1 (42.4 - 69.3)	53.7 (50.5 - 56.9)	100.0 (NA)	1.12 (NA)	0.00 (NA)
0	100.0 (88.1 - 100.0)	0.0 (0.0 - 12.3)	50.9 (37.3 - 64.4)	50.9 (NA)	NA	1.00 (NA)	NA
Bipolar Disorders (n = 76)							
MARS ≥	**Sensitivity [%]**	**Specificity [%]**	**Accuracy [%]**	**PPV [%]**	**NPP [%]**	**+LR**	**-LR**
10	7.1(1.5 - 19.5)	94.1 (80.3 - 99.3)	46.1 (34.6 - 57.9)	60.0 (21.0 - 89.4)	45.1 (42.2 - 48.0)	1.2 (0.2 - 6.7)	1.0 (0.9 - 1.1)
9	19.1 (8.6 - 34.1)	73.5 (55.6 - 87.1)	43.4 (32.1 - 55.3)	47.1 (27.8 - 67.3)	42.4 (36.4 - 48.6)	0.7 (0.3 - 1.7)	1.1 (0.9 - 1.4)
8	35.7 (21.6 - 52.0)	67.7 (49.5 - 82.6)	50.0 (38.3 - 61.7)	57.7 (42.0 - 72.0)	46.0 (38.1 - 54.1)	1.1 (0.6 - 2.1)	1.0 (0.7 - 1.3)
7	42.9 (27.7 - 59.0)	61.8 (43.6 - 77.8)	51.3 (39.6 - 63.0)	58.1 (44.4 - 70.6)	46.7 (37.6 - 55.9)	1.1 (0.7 - 2.0)	0.9 (0.6 - 1.3)
6	47.6 (32.0 - 63.6)	55.9 (37.9 - 72.8)	51.3 (39.6 - 63.0)	57.1 (44.9 - 68.6)	46.3 (36.3 - 56.7)	1.1 (0.7 - 1.77)	0.9 (0.6 - 1.4)
5	59.5 (43.3 - 74.4)	52.9 (35.1 - 70.2)	56.6 (44.7 - 67.9)	61.0 (50.3 - 70.7)	51.4 (39.5 - 63.2)	1.3 (0.8 - 2.0)	0.8 (0.5 - 1.2)
4	78.6 (63.2 - 89.7)	32.4 (17.4 - 50.5)	57.9 (46.0 - 69.1)	58.9 (52.0 - 65.5)	55.0 (36.5 - 72.3)	1.2 (0.9 - 1.5)	0.7 (0.3 - 1.4)
3	90.5 (77.4 - 97.3)	14.7 (5.0 - 31-1)	56.6 (44.7 - 67.9)	56.7 (52.5 - 60.9)	55.6 (26.7 - 81.1)	1.1 (0.9 - 1.3)	0.7 (0.2 - 2.2)
2	97.6 (87.4 - 99.9)	0.0 (0.0 - 10.3)	54.4 (42.1 - 65.5)	54.6 (53.5 - 55.8)	NA	0.98 (NA)	NA
1	100.0 (91.6 - 100.0)	0.0 (0.0 - 10.3)	55.3 (43.4 - 66.7)	55.3 (NA)	NA	1.00 (NA)	NA
0	NA	NA	NA	NA	NA	NA	NA

Table 3 - Diagnostic characteristic of MARS total scores

Therapeutic drug monitoring results were used as gold standards. (95% CI), CI: confidence interval; PPV: positive predictive value; NVP: negative predictive value; +LR: positive likelihood ratio; -LR: negative likelihood.

Table 4 Comparison between TDM-iR and TDM-bR in SSD and BD clinical groups

	SSD				DB			
	TDM-iR (n = 29; 50.9%)	**TDM-bR (n = 28; 49.1%)**	**F/χ2**	**p-value†**	**TDM-iR (n = 42; 55.3%)**	**TDM-bR (n = 34; 44.7%)**	**F/χ2**	**p-value†**
Sociodemographic variables								
Gender, F/M, %	57.9/47.4	42.1/52.6	.219	.640	*70.6/42.9*	*29.4/57.1*	*4.777*	*.029*
Age, years, mean (SD)	40.9 (13.9)	45.4 (12.8)	1.602	.211	52.0 (15.3)	52.0 (15.3)	.001	.978
Married, Y/N, %	55.6/50.0	44.5/50.0	.000	1.000	58.3/52.5	41.7/47.5	.078	.780
Working, Y/N %	50.0/51.0	50.0/49.0	.000	1.000	*37.9/66.0*	*62.0/34.0*	*4.621*	*.032*
Education, years, mean (SD)	10.2 (3.1)	10.6 (3.4)	.213	.646	12.5 (3.7)	12.8 (3.7)	.127	.723
Caucasic, Y/N, %	49.0/66.6	51.0/33.3	.149	.699	54.9/60.0	45.0/40.0	.000	1.000
Clinical variables								
Duration of illness, mean (SD)	16.3 (12.4)	21.6 (10.4)	2.928	.092	22.7 (13.2)	21.8 (10.5)	.122	.728
More than five prior hospitalizations for mental disorder, Y/N, %	51.4/50.0	48.6/50.0	.000	1.000	57.9/52.6	42.1/47.4	.053	.082
Compulsory admission for the present hospitalization, Y/N, %	54.5/50.0	45.5/50.0	.000	1.000	66.7/52.5	33.3/47.4	.492	.483
Smoking, Y/N (%)	35.3/73.9	64.3/26.1	6.715	.010	*42.5/75.9*	*57.5/27.1*	*6.757*	*.009*
Substance and alcohol abuse, Y/N (%)	83.3/47.1	16.7/53.0	1.561	.211	55.6/55.2	44.4/44.8	.000	1.000
Medical chronic comorbidities, Y/N (%)	50.0/51.5	50.0/48.5	.000	1.000	54.6/56.3	45.5/43.8	.000	1.000
Global Assessment of Functioning (GAF), mean (SD)*	*54.3 (8.6)*	*48.3 (10.9)*	*5.467*	*.023*	62.4 (12.6)	63.6 (11.7)	.183	.670
Service engagement scale (SES), mean (SD)	*17.5 (8.3)*	*21.9 (8.1)*	*4.136*	*.047*	15.6 (7.7)	17.5 (6.6)	1.237	.270
Psychopathological variables								
BPRS-1, anxiety and depression, mean (SD)	11.1 (3.8)	9.8 (4.5)	1.448	.234	*11.7 (4.8)*	*9.5 (4.3)*	*4.176*	*.045*
BPRS-2, negative symptoms, mean (SD)	9.2 (3.5)	8.4 (3.7)	.745	.392	7.3 (4.0)	7.0 (4.4)	.080	.778
BPRS-3, though disorder, mean (SD)	9.7 (4.0)	11.5 (3.5)	3.141	.082	9.0 (4.6)	10.47 (4.7)	1.675	.200
BPRS-4, activation, mean (SD)	7.0 (3.3)	8.7 (3.1)	3.735	.058	8.9 (3.5)	9.2 (2.8)	.220	.640
BPRS-5, hostility and suspiciousness, mean (SD)	6.8 (3.7)	8.6 (5.0)	2.313	.134	8.1 (5.1)	7.9 (4.3)	.033	.856
Clinical Global Impression (CGI), mean (SD)	4.5 (0.7)	4.7 (1.0)	.954	.333	4.5 (0.9)	4.5 (0.9)	.000	1.000
Variables related to the psychopharmacological treatment								
Haloperidol, Y/N (%)	17.2/82.8	28.6/71.4	1.04	.308	42.9/56.2	57.1/43.5	.086	.769
Second generation antipsychotics, Y/N (%)	*89.3/10.7*	*53.6/46.4*	*9.74*	*.008*	58.6/44.4	41.4/55.6	.617	.432
Polypharmacy, Y/N (%)	75.9/24.1	89.3/10.7	1.77	.183	57.1/33.3	42.9/66.7	.487	.485
UKU gravity, mean (SD)	0.1 (0.3)	0.5 (1.8)	1.559	.217	0.3 (0.5)	0.2 (0.5)	.173	.678
Medication Adherence Rating Scale (MARS), Mean (SD)	6.0 (2.7)	5.1 (3.1)	1.350	.250	5.8 (2.6)	5.5 (2.8)	.258	.613

SD: standard deviation; Y/N: yes/no; BPRS: Brief Psychiatric Rating Scale; UKU: Udvalg for Kliniske Undersøgelser - Side Effect Rating Scale; † uncorrected; * prior to hospitalization; Statistically significant different results are indicated in italics.

Table 5 - Logistic regression

		Exp B	p-value
SSD	Smoking	.195	.008
	SES	.936	.077
BD	Smoking	.273	.016
	Sex	2.671	.055

SSD: schizophrenia spectrum disorders; BD: bipolar and related disorders; SES: service engagement scale; Smoking = smoking > 10 cigarettes a day.