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Duration of untreated psychosis: impact of the definition of treatment onset on its predictive value over three years of treatment.

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PG, LA and PC, contributed to the conception and design of the study.

LA and PB contributed to the acquisition of the data.

PG contributed to data analysis and interpretation of the data.

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ABSTRACT

Background: While reduction of DUP (Duration of Untreated Psychosis) is a key goal in early intervention strategies, the predictive value of DUP on outcome has been questioned. We planned this study in order to explore the impact of three different definition of “treatment initiation” on the predictive value of DUP on outcome in an early psychosis sample.

Methods: 221 early psychosis patients aged 18-35 were followed-up prospectively over 36 months. DUP was measured using three definitions for treatment onset: Initiation of antipsychotic medication (DUP1); engagement in a specialized programme (DUP2) and combination of engagement in a specialized programme and adherence to medication (DUP3).

Results: 10% of patients never reached criteria for DUP3 and therefore were never adequately treated over the 36-month period of care. While DUP1 and DUP2 had a limited predictive value on outcome, DUP3, based on a more restrictive definition for treatment onset, was a better predictor of positive and negative symptoms, as well as functional outcome at 12, 24 and 36 months. Globally, DUP3 explained 2 to 5 times more of the variance than DUP1 and DUP2, with effect sizes falling in the medium range according to Cohen.

Conclusions: The limited predictive value of DUP on outcome in previous studies may be linked to problems of definitions that do not take adherence to treatment into account. While they need replication, our results suggest effort to reduce DUP should continue and aim both at early detection and development of engagement strategies.

Key words: duration of untreated psychosis, early psychosis, first episode psychosis, treatment adherence

INTRODUCTION

Delay between psychosis onset and exposure to appropriate treatment or duration of untreated psychosis (DUP), has been identified as a key target in programs specialized in the treatment of the early phase of psychotic disorders, based on the rationale that it's reduction should have an impact on the course of symptoms and functioning (Melle et al. , 2008). While numerous papers have indeed shown DUP to be significantly associated with clinical and social outcomes (Malla et al. , 2014, Marshall et al. , 2005), this possible correlation was modest and has been a matter of an intense controversy (Craig et al. , 2000, Harrigan et al. , 2003, Ho and Andreasen, 2001).

Various factors may explain the contradictory nature of results in this domain and the only modest association found between DUP and outcomes in first episode psychosis (FEP) patients. First, in an extensive review, it has been suggested that considerable variability exists in the definition of both onset and endpoint of DUP (Compton et al. , 2007). In particular, the literature reveals significant differences between studies regarding the definition of treatment onset, hence "end" of DUP. In a previous paper, we reported that while considerable attention has been paid to the assessment of psychosis onset, resulting in a certain degree of consensus regarding its definition, this is not true for criteria applied to define the end of DUP: definitions applied ranged from "start of medication" to "hospitalization" and "entry to a specialized program", and were therefore based on many different conceptual levels (Polari et al. , 2009). Second, when definition of DUP's end is based on medication, various definitions have been considered, ranging from "initiation of medication", "start of any form of treatment", or "initiation of adequate treatment", to "time of first effective treatment" (Norman and Malla, 2001, Polari, Berk, 2009). Thirdly, when end of DUP is based on exposure to a certain level of medication, the definition of "adequate treatment" can be the matter of important debate, some authors requiring 12 weeks of medication (Loebel et al. , 1992) while 3 weeks were sufficient for others

(Larsen et al. , 1996). Globally, in a review of 16 FEP studies, Norman and Malla (2001) found that definition applied to identify initiation of treatment varied greatly. Fourthly, patients' adherence to the prescribed medication has not been taken into consideration in the majority of studies (Norman and Malla, 2001). Considering the high rate of non adherence to treatment in FEP patients, it is therefore likely that DUP may have been considered finished for many patients while they actually did not receive any adequate medication yet.

In this context, it can be argued that such a lack of consistency in definition could be one of the critical factors that so far limited the conclusiveness of studies exploring consequences of DUP (Polari, Berk, 2009). Indeed, when applying 3 possible definitions for treatment onset in a FEP sample, we confirmed that estimation of DUP could vary greatly, which in turn could significantly influence the measurement of its impact on outcome variables.

Considering that the existence or not of a correlation between DUP and outcome is critical when choosing strategies that should be applied in specialized programs for the early phase of psychosis, we designed the current study in order to compare different definitions of DUP in their ability to predict outcome in FEP patients. Our hypothesis was that when defining beginning of treatment in a restrictive manner on the basis of both engagement in a specialized program and adherence to adequate medication according to current guidelines, DUP would be significantly correlated to outcome. Considering some patients may never adhere to treatment despite our efforts (Lambert et al. , 2010) our secondary aim was to characterize patients who never met these restrictive criteria and could never be engaged into effective treatment within the 3-years of our program and therefore remained in a phase of “untreated psychosis”.

MATERIAL AND METHODS

Procedure and participants

TIPP (Treatment and early Intervention in Psychosis Program), a specialized early psychosis program, was launched in 2004 at the Department of Psychiatry CHUV, in Lausanne, Switzerland (Baumann et al. , 2013). Entry criteria to the program are: (I) age between 18 and 35; (II) residing in the catchment area (Lausanne and surroundings; population about 300'000); (III) meeting threshold criteria for psychosis, as defined by the 'Psychosis threshold' subscale of the Comprehensive Assessment of At Risk Mental States (CAARMS) scale (Yung et al. , 2005). Patients are referred to other treatment programs if they have psychosis related to intoxication or organic brain disease, or have an intelligence quotient below 70 or have been taking antipsychotic medication for more than a total of 6 months. This latter criteria, which allows admission of patients who would have been treated unsuccessfully for a limited amount of time explains why we refer to early psychosis rather than to first episode psychosis patients.

The Research and Ethics Committee of the Faculty of Biology and Medicine of Lausanne University granted access to TIPP clinical data for research purposes. Therefore all patients who take part in this program (who fulfil the inclusion criteria mentioned above) are automatically included in this study.

A specially designed questionnaire (the TIPP Initial Assessment Tool: TIAT, available upon request) is completed for all patients enrolled in the program by case managers who have up to one hundred contacts with patients during the three years of treatment. It allows assessment of demographic characteristics, past medical history, exposure to life events as well as symptoms and functioning. It is completed on the basis of information gathered from patients and their family over the first weeks of treatment and can be updated during follow up if new information emerges. Follow-up assessments exploring various aspects of treatment and co-morbidities as well as evolution of psychopathology and functional level are conducted by a psychologist and by case managers at baseline, after 2, 6, 12, 18, 24, 30 and 36 months in treatment. Symptoms assessment was conducted by a psychologist who was 100% independent of patients' treatment and had received standardized training prior to the study.

Inter rater reliability standards for the PANSS (Kay et al. , 1991) have been verified throughout the training using video-taped interviews and consensus reference ratings.

The current paper is based on the prospective follow-up of the first 229 patients who had been enrolled in TIPP and where 36 months had elapsed since entry to the program by January 2014. This study focused on assessments made 2 and 6, 12, 24 and 36 months after entry to the program. Eight patients were excluded because they were early drop-outs and for whom estimation of DUP was made impossible by the very short time spent in the program.

Measures

Diagnostic Assessment

Diagnosis is the result of an expert consensus and is based on the following elements: (1) Diagnosis reported by a treating psychiatrist in all medical documents and at the end of any hospitalization; (2) Longitudinal assessment by clinical case managers over the 3 years of treatment. The consensus diagnosis procedure is carried out by a senior psychiatrist and the senior psychologist who is in charge of scale based assessment over the treatment period. They both review the entire file once after 18 months and again after 36 months, or at the end of treatment. They then conduct a diagnostic process based on DSM-IV criteria (American Psychiatric Association, 1994) discussing any unclear issue with the clinical case managers. In this paper, only the final diagnosis, defined at the end of TIPP treatment period, was considered.

Duration of untreated psychosis (DUP)

DUP was measured using three progressively more stringent criteria to define treatment onset according to Polari et al. (2009): DUP1, DUP2 & DUP3 were obtained on the basis of an

expert consensus and were considered as the time between the time of onset of psychotic symptoms and the time where patient met 3 distinct definitions: (1) initiation of antipsychotic medication (DUP1), (2) enrolment into the TIPP programme (DUP2) (3) enrolment into the TIPP programme and adherence to adequate medication as defined by current clinical guidelines (DUP3). This latter definition was chosen in order to take into account international guidelines which suggest that adequate treatment is not limited to adherence to medication and should combine it with psychosocial intervention. Treatment adherence was assessed by the case managers during the follow-up with a Treatment Adherence Scale (TAS) that ranges from 0 to 2; 0 being non adherence; 1 partial adherence (from 25% to 75% of the time during the evaluation period); and 2 total adherence (from 75% to 100% of the time during the evaluation period).

Pre-treatment, baseline and outcome characteristics

(i) Pre-treatment characteristics: The premorbid functioning was assessed using the Premorbid Adjustment Scale (PAS; Cannon-Spoor et al. , 1982). It was delineated into the academic and social sub-scores and in childhood and early adolescence sub-scores (MacBeth and Gumley, 2008). Past psychiatric diagnoses were assessed according to DSM-IV criteria, and past suicide attempts according to ICD-10 classification (Dilling and Dittmann, 1990). Past history of trauma was assessed by case managers on the basis of the knowledge of history of patients in the frame of a 3 year's trusting relationship, and based on interviews with relatives (Alameda et al. , in press-a, Alameda et al. , in press-b). Socio-economic status (SES) was subdivided into high, intermediate and low according to others (Chandola and Jenkinson, 2000). Diagnosis of substance abuse or dependence before the disease was rated by case managers based on the DSM-IV (American Psychiatric Association, 1994).

(ii) Patients characteristics at baseline: Patients were rated as “working” at entry (baseline) on the basis of the Modified Vocational Status Index (MVSI; Tohen et al. , 2000): i.e., paid or unpaid full- or part-time employment, being an active student in school or university, or head of household with employed partner (homemaker), or full or part-time volunteer. Patients were rated as “living independently” on the basis of the Modified Location Code Index Independent living (MLCI; Tohen, Hennen, 2000): i.e., head of household, living alone, with partner, or with peers, and living with family with minimal supervision. The level of functioning at baseline was estimated by a composite overall score with the Global Assessment of Functioning (GAF; American Psychiatric Association, 1994) and with Social and Occupational Functioning Assessment Scale (SOFAS; American Psychiatric Association, 1994). A best lifetime score for the GAF and SOFAS was also estimated. While the SOFAS only takes the social and occupational functioning into account, the GAF also includes the intensity of symptoms. Baseline substance use was assessed with the Case Managers Rating Scale (CMRS; Drake et al. , 1990) that ranges from 1 to 5, 1 being absence of substance use and 5 very severe substance use. Insight into illness was assessed on the basis of one item with anchors ranging between absent, partial and complete (Conus et al. , 2007).

(iii) Outcome measures after 2, 6, 12, 24, and 36 months of follow-up: The functional measures with GAF and SOFAS and the percentage of patients with complete adherence (according to the TAS) were also assessed at each time point of the follow-up. Additionally the following psychopathological measures were assessed at each time point: 1) the level of positive and negative symptoms, using the total score of the positive and negative components of the Positive and Negative Syndrome Scale (PANSS; Kay et al. , 1987); 2) the level of depressive symptoms, using the total score of the Montgomery-Asberg Depression Rating Scale (MADRS; Montgomery and Asberg, 1979); 3) the level of manic symptoms, using the total score of the Young Mania Rating Scale (YMRS; Young et al. , 1978).

Outcomes definitions at discharge

Symptomatic remission at discharge was based on the Andreasen Criteria which is the simultaneous ratings of mild or less (≤3) on selected PANSS' items (delusion, unusual thought content, hallucinatory behaviour, conceptual disorganization, mannerisms, blunted affect, social withdrawal and lack of spontaneity) maintained over 6 months (Andreasen et al. , 2005). Functional recovery was operationalized as a final PAS score less than or equal to the premorbid rating on four of the five items of the PAS general scale (Strakowski et al. , 1998). Ratings on education and abruptness in the change in work were not included in this definition, as they could not have changed during the outcome period (Conus, Cotton, 2007).

Statistical analysis

Considering that many patients became compliant to medication only after some time in treatment, DUP3, which includes compliance to medication in its definition, could keep increasing over time. Accordingly, DUP3 values were computed at each time-point and were used with the outcomes measured of the exact same time. In consequence, the independent variable is always calculated in a timely manner with regards to the outcome variable of interest, which precisely prevents the assessment of the impact of this independent variable when that variable is not yet calculated at the time of the outcome variable. To evaluate to which extent each DUP definition could predict the different outcomes, we proceeded in two steps. First we used a series of linear regression where each of the three DUP value obtained on the basis of the 3 definitions was introduced as the only independent variable in order to determine whether each DUP could predict different outcomes. Second, in order to determine the best predictor for each outcome, a stepwise multiple regression was estimated with all DUP values as independent variables. Stepwise forward likelihood ratio logistic regressions were used for

analysis involving dichotomous outcomes (remission & recovery). Because DUP values were highly skewed, comparisons were performed using Wilcoxon Signed rank tests and DUP values were Log_{10} transformed prior to introduction into the regression and correlations (Gumley et al. , 2014, Hill et al. , 2012, Hui et al. , 2013, Marshall, Lewis, 2005). Characteristics of patients that met the restrictive criteria of adequate medication with good compliance at the end of the follow-up were compared to patients who did not. Differences between these two groups on demographic, premorbid, functional and clinical variables were compared with independent t-tests when the dependent variable was continuous and Chi squared test (or Fisher Exact tests when appropriate) when the dependent variable was categorical. Data are presented descriptively using mean (M) and standard deviation (SD) or median (Mdn) and interquartile range (IQR) for the DUP values. All statistical analyses were performed with IBM SPSS 22. All statistical tests were two-tailed and significance was determined at the .05 level.

RESULTS

Descriptive statistics for the three DUP are presented in Table 1. While DUP1 and DUP2 values did not vary over the time, DUP3 values could increase significantly during the follow-up ($Z = -8.823$, $p < .001$) considering the substantial number of patients who became adherent to medication only after a few weeks to months in treatment. It is worth noting that 9.1% patients never became adherent to medication, and therefore never met the definition of end of DUP3 (Figure 1). The most restrictive definitions were associated with considerably longer DUP values: at discharge, the median DUP3 (405.00 days) was significantly larger than the median DUP2 (127.00 days) which was also larger than the median DUP1 (19.00 days) (all $p<.001$; Table 1). Demographic, premorbid, functional and clinical characteristics of the 221 patients are presented in Table 2.

Prediction of symptomatic and functional outcomes

A summary of significant predictors of various symptomatic and functional outcomes is presented in Table 3. Results of the regression models revealed that except for the 2-month assessment (where no DUP definition was able to predict the PANSS positive score) DUP3 was systematically the best predictor of positive symptoms across 6 to 36 month with percent of explained variance (R^2) varying from 4.4% to 10.5%. For negative symptoms, only long term outcomes (24 and 36 months) could be predicted by DUP. Again, DUP3 showed to be the best predictor and accounted for between 3.9 to 6.0% of variance. Globally, whatever the definition, DUP never significantly predicted MADRS score (with the exception of DUP1 at the 12 month time-point). Results for the YMRS score were also less consistent than results for the PANSS score: YMRS score could only be predicted for the 6 and 12 month time-points by DUP2 and DUP3 scores; DUP3 showed to be the best predictor on both occasions (R^2 = 3.8% & R^2 = 7.7% respectively). Overall, DUP3 explained 2.4 times respectively 1.6 times more variance than DUP1 and DUP2 with symptomatic outcomes.

Regarding functional outcome, SOFAS and GAF scores were considered: DUP could only predict functional outcome in the long run (12, 24 & 36 months). Five out of 6 times, DUP3 showed to be the best predictor accounting for between 4.0% to 6.6% of the variance. It should be noted that in accordance to the most commonly used DUP criterion (DUP1), association between DUP and outcomes could only be described as very weak. Overall, DUP3 explained 1.6 times more variance than DUP1 and DUP2 with functional outcomes.

Results of symptomatic remission and functional recovery at discharge are presented in Table 4. Once again, the first definition (DUP1) greatly underestimated the relationship between DUP and important outcomes at discharge. Symptomatic remission (PANSS Andreasen criteria)

could be predicted by DUP2 and DUP3. However DUP3 was the best predictor (Odd ratio = .375, p = .001, R^2 = .183). All three DUP significantly predicted functional recovery (PAS Strakowski criteria) but DUP3 provided the best prediction (Odd ratio = .534, p = .003, R^2 = .098). For functional recovery as operationalized by MLCI and MVSI scales, results were more contrasted: DUP1 and DUP2 were not related to functional recovery for both the MLCI and MVSI while DUP3 could predict Independent Living (Odd ratio = .584, p = .006, R^2 = .063) but not Working (Odd ratio = .779, p = .161, R^2 = .015). Finally, only DUP3 was related to functional recovery using the combined criteria (MLCI and MVSI; Odd ratio = .610, p = .015, R^2 = .051). Overall, effect sizes for DUP3 were 5.3 times respectively 1.5 times larger than for DUP1 and DUP2 with symptomatic outcomes. Taken altogether, these results consistently depict DUP3 as a better predictor of important outcomes at discharge.

Characteristics of patients who remained on adherent to treatment and medication

Results are presented in 2 parts. First, baseline variables that are correlated with DUP3 are presented. Second, characteristics of patients that met DUP3 criteria by the end of the follow-up (N = 201; 90.9%) were compared to patients who did not (N = 20; 9.1%). Longer DUP3 were correlated with lower best lifetime GAF scores (r = -.209, p = .002, R^2 = .044), lower best lifetime SOFAS scores (r = -.195, p = .005, R^2 = .038), poorer PAS Academic scores (r = .151, p=.044, R^2 = .023) and younger age at psychosis onset (r = -.314, p <.001, R^2 = .097). Patients who never met criteria for DUP3 were more likely to have a lifetime diagnosis of cannabis abuse ($\chi^2(1)$ = 6.276, p = .012, Odd ratio = 3.48) or cannabis dependence ($\chi^2(1)$ = 8.078, p = .004, Odd ratio = 3.92), had higher cannabis use at baseline (t (219)= 2.199, p = .029), were more likely to have committed suicide attempts ($\chi^2(1)$ = 4.160, p = .041, Odd ratio = 2.89) and had lower insight at all assessment points (all p<.05).

DISCUSSION

To the best of our knowledge, this is the first prospective study in EP patients examining the impact of DUP on clinical and functional outcomes according to several definitions of treatment initiation.

Firstly, our results clearly show that defining end of DUP either on the basis of the date of "initiation of an antipsychotic medication" (DUP1) or on that of "entry to a specialized program" (DUP2) erroneously suggest that DUP has come to an end, since at each of these time points, an important proportion of patients are not yet engaged in treatment and/or do not take any medication. This issue is critical, considering that in the absence of sound evidence that treatment delay has an impact on outcome, the validity of the early intervention concepts can legitimately be questioned (Barnes et al. , 2000, Ho and Andreasen, 2001). While it seems obvious that a prerequisite for the assessment of the impact of delayed initiation of a treatment should be that this treatment has actually been initiated, most previous publications have not clearly taken this into account and it is likely that the contradictory and inconclusive nature of the results gathered so far in this domain may be linked to such a problem of definition.

This hypothesis seems to receive support from our study. While analyses based on less restrictive definitions for treatment onset (DUP1 and DUP2) were in line with previous papers and suggested that DUP was only marginally related to both symptomatic and functional outcome, the application of a more restrictive definition, based on both engagement in the TIPP program and adherence to medication (DUP3), revealed a stronger correlation between DUP and most aspects of outcome. Other studies have typically reported small effect sizes by traditional standards (Cohen, 1988) with around 5% of explained variance (Harrigan, McGorry, 2003, Schimmelmann et al. , 2008). In the present study, DUP3 effect sizes for some outcomes

(PANSS positive score and symptomatic remission) fall in the medium range (Cohen, 1988). More research is however needed to confirm these results in larger cohorts and in different settings.

Secondly, our data revealed that DUP, whatever the definition applied, was mainly correlated with longer term aspects of outcome (36 months): DUP3 was significantly correlated with most aspects of symptomatic and functional outcome at 12, 24 and 36 months, but not at 2 and 6 months and was a better predictor of symptomatic remission and functional recovery at discharge. This is in line with a study from Marshall et al. (2005) who found that correlations between DUP and outcome were small or not significant at first presentation but became statistically significant for most outcomes by 6- and 12-month follow-up. It is also congruent with a retrospective study conducted by Primavera et al. (2012) in a sample of patients with schizophrenia, where a shorter DUP was a significant predictor of outcome after 16 to 33 years of illness. Such data suggest that delayed treatment has limited impact on symptom intensity, but that it significantly influences potential for response to treatment and therefore hampers recovery.

Thirdly, we found that close to 10% of patients did never fulfil criteria for DUP3, and therefore were never exposed to adequate treatment of the 36 months of care in our specialized program. While this prevalence is about half of what Lambert et al. (2010) have reported in a retrospective study on a large sample of EP patients, the characteristics of these “medication refusers” are similar in both studies, and suggest that patients with poor premorbid adjustment, low level of insight and active substance abuse are at high risk not to be exposed to adequate treatment, and hence prolonged DUP. Specific strategies to facilitate engagement of such patients are therefore needed.

Some limitations of our study should be mentioned. First, even if a consensus exists regarding the definition and tools that can be applied to define psychosis onset, a precise dating of this event remains difficult. In the current study, a particular effort was made to update its evaluation throughout the treatment period whenever new information allowed a more precise estimation of this date. Second, because a small number of patients who were poorly engaged in treatment were excluded from the study due to lack of information, it could be argued that results of the current study are biased towards more compliant patients. However, the study being based on the clinical data gathered in the context of the prospective follow-up of all patients treated at our program who could be at least minimally assessed, the TIPP cohort is likely to be highly representative of EP patients in our catchment area. Thirdly, the definition of DUP3 is based on engagement in the TIPP program and adherence to medication; reaching these conditions may however coincide with other modifications such as interruption of substance abuse or acquisition of better coping strategies to face the illness, factors which may also play important roles regarding better outcome.

Conclusion

Despite these limitations, our study showed that when defined on the basis of engagement in a specialized treatment and adherence to medication, DUP is a significant predictor of outcome. While other studies based on a similar definition are needed in order to confirm our findings, these results suggest that early intervention and identification strategies are justified. They also suggest that additional effort should be put in the development of strategies facilitating engagement and adherence to treatment in patients with poor premorbid functioning, low level of insight and persistent substance abuse disorder, considering they may fail to be exposed to all the facets of treatment despite having been enrolled in a specialized program.

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Table 1. Duration of untreated psychosis (DUP).

DUP in days, Median (IQR)	computed at baseline	computed at discharge
DUP1	19.00 (153.50)	19.00 (153.50)
DUP2	127.00 (652.50)	127.00 (652.50)
DUP3	127.00 (652.50)	405.00 (1035.00)
Comparison of DUP values[a]	statistic	p-value
DUP3 computed at baseline vs DUP3 computed at discharge	Z = -8.823	<.001
DUP computed at discharge		
DUP1 vs DUP2	Z = -8.723	<.001
DUP1 vs DUP3	Z = -12.092	<.001
DUP2 vs DUP3	Z = -8.823	<.001

Note. IQR = Interquartile range. a = Wilcoxon Signed rank test.

Table 2. Patients demographic, premorbid, functional and clinical variables characteristics.

	Total patients N = 221
Age in y, Mean (SD)	24.17 (4.92)
Sex, male, % (N)	69.2 (153)
SES, % (N)	
Low	16.7 (37)
Intermediate	47.1 (104)
High	36.2 (80)
Trauma (non exposed), % (N)	63.3 (140)
Age at onset of psychosis, Mean (SD)	23.00 (5.31)
Diagnostic, % (N)	
Schizophrenia	62.0 (137)
Schizophreniform/brief psychotic episode	11.3 (25)
Schizoaffectif disorder	10.0 (22)
Major depression with psychotic features	3.6 (8)
Bipolar disorder	5.9 (13)
Others	7.2 (16)
PAS scores, Mean (SD)	
Childhood	0.31 (0.19)
Early adolescence	0.33 (0.18)
Social	0.29 (0.21)
Academic	0.36 (0.20)
Total	0.32 (0.17)
PANSS positive, Mean (SD)	13.33 (4.88)
PANSS negative, Mean (SD)	15.24 (5.91)
MADRS, Mean (SD)	14.76 (9.79)
YMRS, Mean (SD)	6.10 (5.70)
GAF Baseline, Mean (SD)	35.07 (15.67)
GAF Best Lifetime, Mean (SD)	74.21 (13.27)
SOFAS Baseline, Mean (SD)	38.13 (16.10)
SOFAS Best Lifetime, Mean (SD)	74.88 (12.77)

PANSS = Positive and Negative Syndrome Scale. MADRS = Montgomery Asberg Depression Rating Scale. YMRS = Young Mania Rating Scale. SOFAS = Social and Occupational Assessment of functioning Scale. GAF = Global Assessment of Functioning Scale.

Table 3. Summary of predictors of symptomatology and functioning during the follow-up.

	2 months			6 months			12 months			24 months			36 months		
	DUP1	DUP2	DUP3	DUP1	DUP2	DUP3	DUP1	DUP2	DUP3	DUP1	DUP2	DUP3	DUP1	DUP2	DUP3
PANSS positive					x	B		x	B	x	x	B	x	x	B
PANSS negative										x		B			B
MADRS							B								
YMRS					x	B		x	B						
SOFAS								x	B			B	x		B
GAF			B					x	B			B	B		x
Effect sizes R^2															
PANSS positive	.004	.001	.009	.007	.033	.044	.007	.052	.090	.033	.069	.075	.079	.074	.105
PANSS negative	.003	.000	.002	.002	.004	.000	.000	.004	.001	.033	.030	.039	.021	.028	.060
MADRS	.038	.008	.004	.001	.000	.001	.050	.037	.025	.005	.010	.006	.025	.000	.002
YMRS	.001	.000	.003	.013	.033	.038	.002	.025	.077	.018	.032	.028	.032	.020	.015
SOFAS	.004	.005	.012	.000	.000	.001	.014	.028	.054	.007	.005	.034	.027	.014	.047
GAF	.006	.009	.022	.002	.005	.013	.018	.040	.066	.010	.008	.036	.042	.016	.040

Note. x = significant predictor ($p<.05$). B = best significant predictor. PANSS = Positive and Negative Syndrome Scale. MADRS = Montgomery Asberg Depression Rating Scale. YMRS = Young Mania Rating Scale. SOFAS = Social and Occupational Assessment of functioning Scale. GAF = Global Assessment of Functioning Scale. Effect sizes are presented in bold when the predictor is statistically significant.

Table 4. Summary of predictors of symptomatic remission and functional recovery at discharge.

	36 months		
	DUP1	DUP2	DUP3
Symptomatic remission (PANSS)$_a$		x	B
Functional recovery (PAS)$_b$	x	x	B
Functional recovery – Living Independently (MLCI)			B
Functional recovery - Working (MVSI)			
Functional recovery – Combined (MLCI + MVSI)			B
Effect sizes Odds Ratios / Nagelkerke R^2			
Symptomatic remission (PANSS)$_a$	.859 / .010	.483 / .121	.375 / .183
Functional recovery (PAS)$_b$	.731 / .044	.543 / .092	.534 / .098
Functional recovery – Living Independently (MLCI)	.853 / .009	.732 / .022	.584 / .063
Functional recovery - Working (MVSI)	.871 / .009	.771 / .017	.779 / .015
Functional recovery – Combined (MLCI + MVSI)	.879 / .006	.756 / .016	.610 / .051

Note. x = significant predictor ($p<.05$). B = best significant predictor. a = based on the Andreasen criteria (PANSS). b = based on Strakowski criteria. PANSS = Positive and Negative Syndrom Scale. PAS = Premorbid Adjustment Scale. MLCI = Modified Location Code Index Independent living. MVSI = Modified Vocational Status Index. Effect sizes are presented in bold when the predictor is statistically significant.

Figure 1. Percentage of patients having received first antipsychotic medication and effective treatment (adequate medication with a good compliance) across 36 months.