A three-year prospective study

Correlates of full adherence to integrated treatment in early psychosis

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Summary

To the best of our knowledge, this is the first study to explore adherence to the combination of various recommended elements of specialised early psychosis programmes. This is astonishing, since all recommendations in this domain stress the importance, along with adapted medication, of other treatment components such as case management, psychosocial intervention, family intervention and supported employment. Various interesting elements stem from our data analysis. First, the vast majority of patients reach adherence to all elements of treatment at some point of the 3-year programme we propose. Second, lack of development of insight and persistence of substance abuse are the strongest correlates of failure to adhere to integrated treatment, along with the presence of a forensic history. Third, patients who fail to fully adhere to integrated treatment have poorer symptomatic remission and poorer insight after the entire treatment period. Finally, although some patients who never fully adhered to treatment over the entire 3 years reached a reasonable level of functioning, the vast majority did not and only 8% of them returned to independent work combined with independent living. Based on these results, it seems clear that promoting adherence to all the elements of specialised integrated treatment should be an aim with early psychosis patients.

Philippe Golay

Introduction

Over the last 30 years, the focus of interest on the early phase of psychosis has led to the development of specialised treatment programmes. The established international guidelines suggest that efficient treatment of this phase of psychotic disorders should include various components, ranging from medication to psychological and social interventions [1, 2] in an integrated fashion. Although each element of the treatment might per se have an impact on outcome, it is likely that combining all of them would increase the chances of recovery; the objective in early intervention programmes is therefore to engage patients through case management, in order to provide them with adequate medication, adapted psychological treatment and tailored social intervention.

In a recent paper [3], we argued that the definition of duration of untreated psychosis should be based on these principles. In other words, we proposed that the untreated phase of psychosis should be considered to be over only when patients are engaged in treatment, attend appointments and psychosocial interventions and take medication regularly. Such a stringent definition for the end of duration of untreated psychosis revealed even more clearly that treatment delay (long duration of untreated psychosis) is a determinant of outcome and that its reduction should therefore be an objective of mental health policies. Importantly, we showed that treatment delay is not limited to the time preceding access to specialised care, but that it often continues despite enrolment in an early intervention programme due to failure to adhere to the various proposed interventions. To our knowledge, the proportion of patients who fully engage in treatment over time and the impact of delayed engagement on outcome has, however, not been explored.

Therefore, we wanted to study the issue of the delay between entry to our early psychosis programme and full adherence to all aspects of treatment and its correlates regarding characteristics of patients at entry and at the end of the 3 years of treatment. Our first aim was to study the prevalence of failure to fully adhere to all elements of treatment 12, 24 and 36 months after enrolment in the Treatment and early Intervention in Psychosis Programme (TIPP), which is a specialised programme for the treatment of the early phase of psychotic disorders attached to the department of Psychiatry at Lausanne University Hospital, Switzerland [4]. The second aim was to identify the baseline characteristics of patients who fail to completely engage in treatment at each of these time points in order to identify subgroups who would benefit from adaptation of engagement strategies. Thirdly, we wanted to compare

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the 36-month outcome of these non-fully adherent patients with that of those who had eventually adhered to all treatment components after 12 months and 24 months, respectively. Finally, we wanted to see if some patients would do well despite never fully engaging in treatment and to identify factors that could predict such a favourable outcome in this patient subgroup.

Material and methods

Procedure

Patients are accepted in the TIPP if they are aged 18 to 35, live in the catchment area of about 350,000 inhabitants and if they have crossed the psychosis threshold as defined in the Comprehensive Assessment of At-Risk Mental States (CAARMS) instrument [5, 6]. Patients are referred to other treatment programmes if they have an IQ below 70, if they have been exposed to more than 6 months of antipsychotic treatment and if the psychotic symptoms are linked to either intoxication or organic brain disease.

All patients treated within the TIPP are fully assessed at baseline, after 2 months, 6 months and then prospectively every 6 months in order to monitor outcomes and adjust treatments. A specially designed questionnaire (the TIPP Initial Assessment Tool: TIAT, available upon request) is completed by case managers for all patients enrolled in the programme. It allows assessment of demographic characteristics, past medical history and exposure to life events, as well as symptoms and functioning. It is completed on the basis of information gathered from patients and their families over the first 12 weeks of treatment and can be updated during follow-up if new information emerges.

Over the three years of treatment, case managers are available to patients up to twice a week, and treatment can be intensified by the assertive case management team when necessary.

Follow-up assessments exploring various aspects of treatment and co-morbidities, as well as the evolution of psychopathology and functional level, are conducted by a trained psychologist and by case managers at baseline, and after 2, 6, 12, 18, 24, 30 and 36 months in treatment. Symptom assessments are conducted by a psychologist who is independent of patient's treatment and had received standard training. Over the three years of treatment, case managers are available to patients up to twice a week, and treatment can be intensified by the assertive case management team when necessary [7].

This study was conducted in accordance with the Declaration of Helsinki and was approved by the Human Research Ethics Committee of the Canton of Vaud (CER-VD; protocol #2020-00272). Access to clinical data was granted for research purposes, allowing the use of all data generated during patient follow-up. Consequently, all patients who received treatment within this programme could be included in this study, which is therefore based on a highly representative sample of early psychosis patients.

Measures

Case managers and an experienced psychologist performed detailed evaluations of patients' using interviews and the TIAT questionnaire. Case managers defined "full adherence to treatment" on the basis of regular attendance to appointments, engagement in the various clinical interventions (psycho-education, psychotherapy, appointments with social workers or supported employment professionals) and adherence to medication. This last element was assessed on the basis of the Treatment Adherence Scale [3], which ranges from 0 to 2, where 0 relates to nonadherence or medication refusal, 1 relates to partial adherence (from 25% to 75% of the time during the evaluation period); and 2 relates to complete adherence to medication (from 75% to 100% of the time during the evaluation period). In order to explore the progressive development of adherence to all elements of treatment and its correlates, the duration of untreated psychosis in this study was defined as the time elapsing between the onset of the psychotic symptoms as defined by the CAARMS psychosis threshold and admission to the TIPP. Patients' socioeconomic status was rated on three levels: low, intermediate and high [8]. Premorbid functional level was evaluated using the Premorbid Adjustment Scale (PAS; 9). The Global Assessment of Functioning (GAF; [10]) was used to assess functional levels at baseline. The Social and Occupational Functioning Assessment Scale (SOFAS) was also used in order to explore social and occupational functioning without considering the severity of symptoms. The best and lowest GAF and SOFAS levels over the entire lifetime were also estimated. Insight into the illness was categorised as complete, partial or absent [11]. Severity of illness at baseline was assessed using the Clinical Global Impression scale (CGI; 12). Diagnosis was based on DSM IV criteria and results from an expert consensus conducted after both 18 and 36 months in treatment, using all the elements stemming for medical records, as well as from the TIPP-assigned psychiatrist and case manager report. In this study, we used the latest consensus diagnosis available. Past diagnosis of substance

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abuse/dependence was rated according to DSM-IV criteria. Psychopathology and functional level were assessed at each assessment, with SOFAS, GAF, the Positive and Negative Syndrome Scale (PANSS; 13) and the Montgomery-Asberg Depression Rating Scale (MADRS; 14). A psychologist who was independent of patients' treatment and had received standard training prior to the study conducted the symptom assessment. Functional characteristics were assessed using the Modified Vocational Status Index and the Modified Location Code Index (MVSI and MLCI; 15). Patients were considered as *living independently* based on their MLCI score (head of household or living alone, living with a partner or peers, or living with their family with minimal supervision). Patients were considered as *working* based on the MVSI (in paid or unpaid, full- or part-time employment, being an active student in school or university, head of household with an employed partner (home-maker), or a full or part-time volunteer). Functional recovery was defined as a GAF score >60. Symptomatic remission was defined by the last PANSS score in the last year of the programme, following Andreasen's Criteria (mild or lower [≤3] score on the following items: delusion, unusual thought content, hallucinatory behaviour, conceptual disorganization, mannerisms, blunted affect, social withdrawal and lack of spontaneity; [16]). Insight into the illness over the treatment period was categorised as complete, partial or absent [11].

Statistical analysis

Patients were categorised into two groups depending on whether or not they reached full adherence to treatment after 12 months. To verify whether the same pattern of results was apparent, analyses were repeated by comparing patients who were not adherent after 24 months and 36 months with patients with "early adherence" (after 12 months). In order to check whether the demographic characteristics of patients in the groups were statistically different and to compare patients' profiles before entering the programme (premorbid characteristics), at the start of the programme (baseline) and after 36 months of treatment in the programme, we carried out chi-square tests for the categorical variables and analyses of variance (ANOVA) for the continuous variables. For variables with a highly skewed distribution, we used non-parametric Mann-Whitney U-tests. Mixed effects models repeated measures analysis of variance (MMRM) were used to determine differences between groups in symptomatology and functioning over time. Time was introduced as a within-group factor and treatment adherence as a between-group factor. The main effects of treatment adherence and time can be examined with these models, as well as the interaction between these two variables. Planned comparisons within MMRMs were also carried out by contrasting the first measure with the last programme endpoint. The selection of the optimal structure of the within-subject co-variance matrix was determined by the Akaike information criterion (AIC) coefficient. Different structures (unstructured, autoregressive, compound symmetry and Toeplitz) were tested. Because homogeneity of variances across measurement occasions was not guaranteed, we also included heterogeneous versions of these structures.

Mixed effects models repeated measures analysis of variance (MMRM) were used to determine differences between groups in symptomatology and functioning over time.

These results are based on the data stemming from the prospective follow-up of the 224 patients who had completed the three-year treatment period by the end of 2016.

In order to identify some factors among the patients that could predict a favourable outcome at the end of the study despite failing to fully engage in treatment, we also performed a series of exploratory simple linear regression analyses on the subgroup of nonadherent patients after 36 months. When the dependent variable was dichotomous, logistic regressions were used instead. All analyses were performed with IBM SPSS 23. All statistical tests were two-sided and significance was defined at $\alpha = 0.05$.

Ethics approval and consent to participate

This study was carried out in accordance with the Declaration of Helsinki and was approved by the Human Research Ethics Committee of the Canton of Vaud (CER-VD; protocol #2020-00272). Access to clinical data was granted for research purposes allowing the data generated during patient follow-up were used in the study. Consequently, all patients who received treatment within this programme could be included in this study.

Results

These results are based on the data stemming from the prospective follow-up of the 224 patients who had completed the three-year treatment period by the end of 2016. The average age of these patients was 23.9 years, and the majority were male (67.4%) from an intermedi-

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Table 1: Comparison between adherent and nonadherent patients after 12 months.

	Total (n = 224)	Nonadherent (n = 59, 26.3%)	Adherent (n = 165, 73.7%)	Statistic	p-value
Gender (male), % (n)	67.4 (151)	69.5 (41)	66.7 (110)	$\chi^2(1) = 0.158$	0.691
Age, mean (SD)	23.9 (4.68)	23.1 (4.4)	24.2 (4.7)	$t(222) = -1.463$	0.145
Socioeconomic level, % (n)				$\chi^2(2) = 4.356$	0.113
– Low	18.3 (41)	25.4 (15)	15.8 (26)		
– Intermediate	44.2 (99)	33.9 (20)	47.9 (79)		
– High	37.5 (84)	40.7 (24)	36.4 (60)		
Educations in years, mean (SD)	9.67 (2.7)	10.0 (2.52)	9.5 (2.8)	$t(197) = 1.040$	0.300
Familial history of psychiatric disorders, % (n)	66.0 (136)	63.5 (33)	66.9 (103)	$\chi^2(1) = 0.203$	0.652
Familial history of schizophrenia, % (n)	26.4 (46)	27.3(12)	26.2 (34)	$\chi^2(1) = 0.021$	0.884
History of trauma, % (n)	26.3 (59)	16.9 (10)	29.7 (49)	$\chi^2(1) = 3.640$	0.056
Age at onset, mean (SD)	22.38 (5.11)	21.3 (5.1)	22.8 (5.1)	$t(222) = -1.975$	0.050
Forensic history, % (n)	12.8 (25)	20.0 (11)	10.0 (14)	$\chi^2(1) = 3.533$	0.060
Medication before treatment, % (n)				$\chi^2(2) = 0.544$	0.762
– Without	56.7 (123)	58.9 (33)	55.9 (90)		
– Partial	25.8 (56)	26.8 (15)	25.5 (41)		
– Complete	17.5 (38)	14.3 (8)	18.6 (30)		
Duration of untreated psychosis, median (IQR)	121.50 (581.5)	228 (790)	99 (477.5)	U = 4050.0	0.056
History of psychiatric disorders, % (n)	64.9 (144)	64.9 (37)	64.8 (107)	$\chi^2(1) = 0.000$	0.993
Lifetime substance abuse (DSM), % (n)					
– Alcohol	27.6 (59)	31.5 (17)	26.3 (42)	$\chi^2(1) = 0.553$	0.457
– Cannabis	40.9 (88)	62.5 (35)	33.3 (53)	$\chi^2(1) = 14.57$	<0.001
– Other substances	13.5 (30)	17.5 (10)	12.1 (20)	$\chi^2(1) = 1.066$	0.302
Lifetime substance dependence (DSM), % (n)					
– Alcohol	9.8 (21)	11.1(6)	9.4 (15)	$\chi^2(1) = 0.138$	0.711
– Cannabis	33.6 (72)	55.4 (31)	25.9 (41)	$\chi^2(1) = 16.016$	<0.001
– Other substances	7.7 (17)	10.5 (6)	6.7 (11)	Fisher exact test	0.388
Diagnosis, % (n)				Fisher exact test	0.665
– Schizophrenia	62.1 (139)	64.4 (38)	61.2 (101)		
– Brief schizophreniform disorder	8.0 (18)	5.1 (3)	9.1 (15)		
– Schizoaffective disorder	10.3 (23)	11.9 (7)	9.7 (16)		
– Major depression	2.7 (6)	5.1 (3)	1.8 (3)		
– Bipolar disorder	8.5 (19)	6.8 (4)	9.1 (15)		
– Other	8.5 (19)	6.8 (4)	9.1 (15)		
Insight at baseline, % (n)				$\chi^2(2) = 16.061$	<0.001
– Absent	38.9 (84)	55.2 (32)	32.9 (52)		
– Partial	44.4 (96)	43.1 (25)	44.9 (71)		
– Complete	16.7 (36)	1.7 (1)	22.2 (35)		
GAF, mean (SD)					
– Lifetime best	74.09 (13.30)	73.23 (12.8)	74.40 (13.5)	$t(211) = -0.564$	0.573
– Lifetime worst	25.59 (10.46)	26.04 (9.57)	25.45 (10.76)	$t(194) = -0.334$	0.739
– Baseline	35.33 (15.50)	34.51 (14.07)	35.62 (15.1)	$t(209) = -0.455$	0.650
Work activity (MVSI) at entry, % (n)	33.6 (75)	32.2 (19)	34.1 (56)	$\chi^2(1) = 0.073$	0.786
Living independently (MLCI) at entry, % (n)	66.8 (149)	66.1 (39)	67.1 (110)	$\chi^2(1) = 0.018$	0.892
Family environment, % (n)					
– Presence of father	77.9 (173)	71.2 (42)	80.4 (131)	$\chi^2(1) = 2.123$	0.145
– Presence of mother	91.4 (202)	86.4 (51)	93.2 (151)	$\chi^2(1) = 2.522$	0.112
Past suicide attempt, % (n)	15.4 (33)	18.2 (10)	14.5 (23)	$\chi^2(1) = 0.433$	0.511
CGI, mean (SD)					
– Baseline	5.05 (1.31)	4.89 (1.3)	5.10 (1.326)	$t(186) = -0.958$	0.339
– Worst	5.89 (0.783)	5.70 (0.795)	5.95 (0.773)	$t(188) = -1.850$	0.066
PAS, mean (SD)					
– Childhood	0.31 (0.18)	0.31 (0.20)	0.31 (0.18)	$t(175) = 0.099$	0.921
– Early adolescence	0.33 (0.17)	0.31 (0.18)	0.33 (0.17)	$t(177) = -0.631$	0.529
– Social	0.29 (0.20)	0.29 (0.22)	0.29 (0.20)	$t(174) = 0.002$	0.998
– Academic	0.36 (0.20)	0.36 (0.22)	0.36 (0.19)	$t(177) = 0.060$	0.952
– Total	0.32 (0.16)	0.30 (0.17)	0.32 (0.16)	$t(162) = -0.616$	0.539

CGI: Clinical Global Impression; GAF: Global Assessment of Functioning; IQR: interquartile range; MLCI: Modified Location Code Index; MVSI: Modified Vocational Status Index; PAS: Premorbid Adjustment Scale; SD: standard deviation

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ate socioeconomic background (44.2%). On average, they had gone to school for 9.6 years and 26.3% had been exposed to sexual or physical abuse. The median duration of untreated psychosis was 121 days or 17 weeks.

Based on case managers' assessment, 26.3% of patients failed to fully adhere to treatment after 12 months, 17.0% after 24 months and 12.1% after 36 months of enrolment in our specialised programme.

The characteristics of patients who failed to adhere to all elements of treatment after 12 months in the programme are reported in table 1. Data analysis showed that these patients displayed a significantly higher rate of cannabis abuse and lower level of insight than patients who had fully engaged in all aspects of treatment by that time (early adherent patients). The pattern of results for patients with nonadherence after 24 and 36 months was very similar, with the exception of forensic history, which was higher for patients nonadherent after 24 months (p = 0.049) and 36 months (p = 0.021) than patients with early (12 months) adherence. The only other difference was for insight, where patients nonadherent after 36 months no longer differed from adherent patients (p = 0.076).

At the end of the three-year treatment period, patients who were fully adherent to treatment after 12 months were significantly more likely to display complete insight and had a lower prevalence of cannabis use (see table 2). They were also more likely to achieve symptomatic remission. The pattern of results was identical when comparing adherent and non-adherent patients after 24 months.

Regarding the evolution of positive symptomatology (PANSS positive), MMRM models revealed that nonadherent patients after 12 months had greater symptoms throughout the follow-up ($F_{1,198.547}$ = 12.422, p <0.001). However, there was no difference in improvement between the 2-month marker and programme exit. Regarding general symptomatology (general PANSS), we found that the treatment group had overall lower symptoms ($F_{1,200.309}$ = 15.446, p <0.001). We observed a very similar pattern of results for these two variables using nonadherent patients after 24 and 36 months for the comparison. Regarding depressive symptomatology (MADRS), we observed that nonadherent patients had overall higher symptoms ($F_{1,212650}$ = 4.499, p = o.035). However, this was no longer the case when nonadherence was defined at 24 and 36 months. Regarding the evolution of functioning (GAF), we found that nonadherent patients after 12 months had lower functioning throughout the follow-up ($F_{1,233.134}$ = 11.360, p = 0.001). This was similar when non-adherent patients after 24 and 36 months were used for the comparison.

Our fourth objective was to find out the characteristics of patients who recovered well despite never fully adhering to treatment over the entire 36-month treatment period. Our analysis showed that 27.8% of these patients reached GAF levels greater than 60, an outcome that was linked to lower level of cannabis use at the entry in the programme (B = -1.823, odds ratio = 0.162, p = 0.027). However, only 8.3% of the patients who never fully adhered to treatment managed to return to work and to live independently (compared with 21.8% for patients who developed adherence). Patients who

Table 2: Outcomes at the end of the programme with regard to treatment adherence after 12 months.

	Total (n = 224)	Nonadherent (n = 59, 26.3%)	Adherent (n = 165, 73.7%)	Statistic	p-value
Functional recovery, % (n)					
– Work activity (MVSI)	23.6 (48)	16.7 (9)	26.2 (39)	$\chi^2(1) = 1.985$	0.159
– Living independently (MLCI)	57.4 (116)	50.0 (27)	60.1 (89)	$\chi^2(1) = 1.662$	0.197
– Living combined	20.2 (41)	13.0 (7)	22.8 (34)	$\chi^2(1) = 2.389$	0.122
Functional recovery, GAF, % (n)	50.0 (94)	48.9 (23)	50.4 (71)	$\chi^2(1) = 0.028$	0.866
Symptomatic remission (Andreasen), % (n)	49.7 (76)	22.6 (7)	56.6 (69)	$\chi^2(1) = 11.415$	0.001
Insight at the end of the programme, % (n)				f	<0.001
– Absent	7.6 (14)	17.8 (8)	4.3 (6)		
– Partial	39.1 (72)	55.6 (25)	33.8 (47)		
– Complete	53.3 (98)	26.7 (12)	61.9 (86)		
CMRS at the end of the programme, median (IQR)					
– Alcohol	2.0 (1)	1 (1)	2 (0)	U = 3673.5	0.202
– Cannabis	1.0 (1.0)	1 (1)	1(0)	U = 3409.5	0.016
– Other substances	1.0 (0)	1 (0)	1(0)	U = 3915,5	0.964

CMRS: ; GAF: Global Assessment of Functioning; IQR: interquartile range; MLCI: Modified Location Code Index; MVSI: Modified Vocational Status Index

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developed full insight at the end of the treatment period were more likely to have been exposed to trauma (B = 0.786, p = 0.007) and to have displayed insight at baseline (B = 0.611, p = 0.044) and have used alcohol at baseline (B = 0.301, p = 0.041).

Disscusion

To the best of our knowledge, this is the first study to explore adherence to the combination of the various recommended elements of specialised early psychosis programmes. This is astonishing, considering that all recommendations in this domain stress the importance, along with adapted medication, of other treatment components such as case management, psychosocial intervention, family intervention and supported employment. Various interesting elements stem from our data analysis. First, the vast majority of patients reach adherence to all elements of treatment at some point of the three-year programme we propose. Second, lack of development of insight and persistence of substance abuse are the strongest correlates of failure to adhere to integrated treatment, along with the presence of a forensic history. Third, patients who fail to fully adhere to integrated treatment have poorer symptomatic remission and poorer insight after the entire treatment period. Finally, although some patients who never fully adhered to treatment over the entire 3 years reached a reasonable level of functioning, the vast majority did not and only 8% of them returned to independent work combined with independent living. Based on these results, it seems clear that promoting adherence to all the elements of specialised integrated treatment should be an aim with early psychosis patients.

Failure to eventually fully adhere to all treatment components was correlated principally with two characteristics: first with persistent cannabis abuse and second with a low degree of insight.

Our data showed that rate of full adherence to integrated treatment progressed over time, starting from 73% after 12 months and reaching 87% by 36 months in treatment. This is consistent with our observation in a previous paper that only 6% of patients disengage from treatment over the 3 years of the TIPP [17], and confirms that strategies applied in specialised early intervention programmes have a major impact on engagement in treatment. Indeed, while we found in a previous study [18] that in the same catchment area, before the implementation of TIPP, 50% of patients disengaged, often as early as immediately after discharge from a first hospital admission, we observed after its implementation a major drop in treatment interruption [17] in the frame of the combination of assertive case management and intermittent assertive outreach [7, 19].

Failure to eventually fully adhere to all treatment components was correlated principally with two characteristics: first with persistent cannabis abuse and second with a low degree of insight. This is in line with previous observations that complete disengagement from treatment in early psychosis is linked mainly with long duration of untreated psychosis, symptom severity at baseline, insight, substance abuse and dependence and lack involvement of a family members in treatment [20–23]. It is interesting to see that failure to ever adhere to all elements of treatment, which is different from complete disengagement, is driven by similar variables. The deleterious impact of cannabis and other substance abuse on the recovery process and on adherence to treatment has already been identified by others [24–26]. However, the observation that interruption of cannabis use is related to a large improvement in outcome [24] should be a motivation for clinicians to maintain their efforts in this domain: various approaches such as motivational interviews and group treatment should therefore be part of all early intervention programmes and clinicians should not give up despite the size of the challenge. Although it may seem trivial that lack of insight is correlated with failure to fully engage in treatment, it is interesting to note that patients who never fully adhered to treatment over the entire 36 months had nevertheless a rate of insight that was similar to that of patients who had become fully adherent after 12 months. This illustrates the complexity and the multifaceted nature of insight and may suggest that psychoeducation in itself is maybe not sufficient to motivate patients to get involved in treatment.

Taken together, these elements add support to the hypothesis that the sooner patients adhere to all elements of treatment, the better.

It is worth noting that patients who failed to fully adhere to treatment at 24 and 36 months had the additional characteristic of a higher rate of forensic history. In a previous study we observed that this characteristic was correlated with a higher risk of treatment disengagement [23], which may be linked to an aversion to institutions when having had to deal with judiciary situations at a young age.

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Regarding the correlates of failure to fully engage in treatment with outcome, our analysis showed that it is linked with a lower rate of symptoms remission, which suggests that promotion of engagement into all elements of treatment is a useful aim. Moreover, the assessment of symptom progression over the treatment period revealed that nonadherent patients had higher levels of positive and general symptoms on the PANNS. This was also true for depressive symptoms and for global level of functioning. Taken together, these elements add support to the hypothesis that the sooner patients adhere to all elements of treatment, the better. Indeed, although the recovery model suggests that reduction of symptoms may not be the only valid aim of treatment, the persistence of positive and general symptoms certainly does not favour recovery and the continuous presence of depression symptoms contributes to a higher risk of poor functioning and suicide. Nevertheless, because we did not find significant differences in the rate of improvement over the 3 years, we cannot rule out that possibility patients who achieved early adherence were also less severely ill from the start.

Finally, we observed that a small proportion of patients had a favourable outcome despite never adhering to all elements of treatment. This was, however, true only for a minority of them who reached a GAF level equal or superior to 60, and for an even smaller number of them when considering return to work or studies and living independently. Although this subgroup may be identified by low level of cannabis use and better insight at baseline, it seems difficult to identify patients for whom failure to engage in treatment would be without consequences; in consequence, our data suggest that promotion of full adherence to treatment should be an aim with all patients who present with a first episode of psychosis.

These results should, however, be considered with caution because of various limitations. First, the case managers are asked to record, for each patient, the date when they fully adhere to all elements of treatment; it is possible that some patients might have later become nonadherent to some aspects of treatment, which may blur the results. Second, the sample size is relatively limited and these results should be reproduced in larger samples of patients. Third, adherence to medication, one of the elements considered to define full adherence to all aspects of treatment, was not based on blood tests or pill counts. However, the prospective follow-up of metabolic side effects of medication allows regular assessment of blood levels of medication, therefore at least excluding patients who do not take any medication at all. Moreover, the quality of the interaction with case managers and the collaborative approach proposed to patients creates a context where they are usually open about their nonadherence to medication. Fourth, patients who had received antipsychotic treatment for longer than 6 months were not included in the TIPP. It is difficult to assess whether this may have had an impact on the results. Fifth, the naturalistic nature of the cohort prevented us from including all sample individuals at each assessment as some patients either refused or did not attend assessment at various time points. Very few patients have 100% complete data and we considered that the study would be less representative if based on them alone.

Despite these limitations, our data suggest that in the specialised context of our early psychosis programme, the great majority of patients eventually engage in all the treatment elements that we propose. They show that persistence of substance abuse, as well a delayed development of insight and past forensic history are correlated with delayed engagement in the proposed treatment. Clinicians must therefore adapt their approach to these challenges, as failure to engage in all aspects of treatment is linked to poorer symptomatic remission and poorer insight after the entire treatment period.

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Author contributions
PG and PC designed this research. PG and DE analysed and interpreted the data. PG and DE drafted the first version of the manuscript. PC critically revised the manuscript for important intellectual content. All authors have read and approved the manuscript.

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